Monitoring

Rheumatoid Arthritis

Emilia Gvozdenović

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Promotores

Prof. dr. D.M.F.M. van der Heijde

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Prof. dr. R.G.H.H. Nelissen

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Chapter 1

General introduction

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic inflammatory disease that mostly affects peripheral joints but may have systemic manifestations, potentially resulting in irreversible joint damage.[1,2] RA may present at any age, and the disease is more common in women than in men. The global prevalence of RA is estimated to be rather stable during the past decades, ranging from 0.5-1%.[1,3] A few decades ago, many patients had prognostically unfavourable disease, were continuously suffering from pain and stiffness, and faced functional disability and progressive joint destruction. Extra-articular manifestations of the disease included involvement of internal organs, which interfered with general wellbeing and resulted in frequent hospitalisations and increased mortality.[4-6] During the last decades, major changes have impacted the global severity of RA. The disease is often recognized earlier nowadays, and effective treatment often starts before joint destruction has occurred.[7,8] In 2010 new criteria by ACR and EULAR were released, pertaining to patients with more recent RA.[9] Treatment strategies, aiming at low disease activity assessed by recently developed and validated scores, exploiting combinations of antirheumatic drugs, corticosteroids and/or biologic therapies, have together resulted in a more effective suppression of inflammation and radiographic progression. To date, RA is a far more manageable disease than decades ago, and severe damage to joints and internal organs has become rather rare. RA is to some extent comparable to other chronic conditions, such as diabetes, where patients are frequently monitored and therapy is adjusted according to laboratory tests, in order to prevent the future risk of organ damage.[10,11] As a relative novelty in the field of rheumatology, treatment decisions may now include decisions about tapering medication when the disease has been adequately suppressed, and long-term drug-free remission seems to become a feasible reality.[12-14]

THEAPIES AND TREATMENT MANAGEMENT

Rheumatologists may use three types of antirheumatic disease modifying drugs (DMARDs): 1. classical or conventional synthetic (cs) DMARDs, 2.biologic (b) DMARDs and 3. corticosteroids. Of the csDMARDs methotrexate (MTX) is most often used, and may be most effective. MTX is considered to be the ‘anchor drug’, is well tolerated but rather slow acting and may need several months to fully exert its efficacy.[15] MTX can be used as monotherapy but is claimed to be more effective in combination with other DMARDs. Up to two-third of

all RA patients does not achieve a low disease activity state with methotrexate alone and other csDMARDs such as sulfasalazine[16] and leflunomide[17,18] can be chosen as monotherapy or added to MTX.[19] Also bDMARDs and oral corticosteroids are most effective in combination with csDMARDs, preferably MTX. Several studies have shown that a bDMARD plus a csDMARD, as well as csDMARDs in combination with oral corticosteroids,[20-22] are more effective than monotherapy with csDMARDs.[23,24]

The third category of DMARDs is glucocorticoids. Glucocorticoids differ from csDMARDs in that they usually act very rapidly. Their long term use is disputed because of the fear of adverse events, and glucocorticoids are often prescribed only for short periods of time. Glucocorticoids can be used orally, but also locally in the form of intra articular injections. The main purpose of glucocorticoids is symptom relief by suppression of inflammation, but glucocorticoids have also been demonstrated to inhibit radiographic progression, which effectively makes them DMARDs.[25]

Recommendations management RA

The changes in treatments and treatment approaches during the recent years have resulted in new strategies to manage RA. In 2010 collaborating international rheumatologists have released a set of recommendations for the management of RA for patients with bDMARDs and csDMARDs, to be used in all-day clinical practice.[11] In these recommendations the values of an early diagnosis, of an early treatment start and of setting treatment goals and monitoring them meticulously, have been stipulated. Of note, a shared treatment decision between patient and physician, emphasising mutual responsibility for the treatment outcome, was considered very important. Also, stepwise algorithms have been developed for the start of medication in newly diagnosed patients, with treatment adjustments based on measured clinical responses. The procedures also include tapering of medication for patients in sustained remission or in a low disease activity state. It is recommended that DMARD medication should be intensified or changed if a predefined treatment target was not met within a time frame of 3-6 months.[10] Such a time frame was not (yet) specified for tapering medication in patients with longstanding remission, since patients may flare and therefore tapering should be performed cautiously.[11] In an attempt to further emphasize the importance of meticulous monitoring and guided decisions about treatment intensification, the treat-to-target (T2T) initiative has formulated recommendations to stimulate rheumatologists to set and aim at achieving treatment goals.[25] In 2013 the 2010 EULAR recommendations were

updated including improved treatment strategies for which scientific proof has become available.[26] The ultimate goal to achieve in an individual patient with RA is a (long-standing) state of remission. To date, a significant proportion of the patients have still not reached this target of remission or even a more lenient target of low disease activity.[11] This implies that the care for RA can still be improved. While improvement of care often has a connotation of 'developing better drugs', in the field of RA a better implementation of existing recommendations in daily practice may be similarly effective in achieving this goal.

Treat to target

As mentioned before, a treat-to-target approach has been formulated to provide guidance for the management of RA in clinical practice. It describes definitions for achieving a clinical state of remission, and the frequency (every three months in patients with active RA and every six months in patients with low disease activity or remission) of patient monitoring using validated composite measures.[25,27]

Both the EULAR and treat-to-target recommendations have been recognized by experts to be associated with better functional and radiographic outcomes.[28] Patients agree with these recommendations,[29] but may experience and interpret symptoms differently than their physicians.[30-32] Here, a trained nurse could be instrumental in helping patients understand why clinicians want to follow a treat-to-target approach.[33]

Implementation of recommendations in clinical practice

As mentioned above, better implementation of recommendations in clinical practice is important to improve care for RA. In general, increasing numbers of recommendations for clinicians have been developed during the past decade. Recommendations seek to improve the quality of care, and are thought to have an impact on patient outcomes, and there is a need to disseminate and implement them in clinical practice. Implementation of recommendations is not easy and not well understood. Strategies of dissemination are important, but previous studies have shown that it is not clear which strategy is most appropriate.[34,35]

Another factor of importance is related to how physicians interpret the content of recommendations: Physicians tend to follow recommendations according to their own interpretation, especially if the text of recommendations leaves room for alternative interpretations. Another well-known factor interfering with an appropriate implementation is the presence of significant comorbidities that may or may not interfere with a correct follow

up of recommendations (that often do not specifically include guidance about specific co-morbidities). Lack of awareness on -and agreement with- therapies are also reasons for not implementing them in clinical practice.[36-38]

CLINICAL OUTCOMES

Disease activity

Inherent to the treat-to-target strategy is the use of composite scores to evaluate disease activity and treatment success. A high score implies high disease activity and a need to intensify treatment. During the 1990s these scores have been developed, based on physicians' and patients' judgement of disease activity, primarily to study the efficacy of treatments in clinical trials,[39] and later to assess variation of disease activity over time in individual patients. The first composite score was the Disease Activity Score (DAS). This measure includes the Ritchie Articular Index (RAI) for the assessment of tenderness in 53 joints, the number of swollen joints among 44 joints, the erythrocyte sedimentation rate (ESR in mm/hr.) and the visual analogue scale (VAS) for patient's assessment of global health (ranging from 0-100 with 0=best and 100=worst). All together, these components form the following DAS formula: $0.54 * \sqrt{RAI} + 0.0065 * SJC + 0.33 * \ln(ESR) + 0.007 * VAS\text{-}GH$ (Patient's assessment of global health, or alternatively, patients' assessment of global disease activity, rated on a 100 mm visual analogue scale, with 0 mm as best and 100 mm as worst possible).[40] The regression coefficients and the mathematical transformations, which are incompletely understood and inappropriately valued by many as being too laborious, serve in reality to optimize the performance of the DAS in groups of patients and in individuals.

EULAR has formulated criteria with which patients can be classified as having high (DAS>3.7), moderate (DAS: 2.4-3.7) or low disease activity (DAS: 1.6-2.4) or remission (DAS<1.6). A clinical improvement is defined when the DAS is 0.6 points lower than at the previous visit.[41, 42] Later, modifications of the DAS have been developed, such as the DAS28 including only 28 joint counts for swelling and tenderness.[43] Another modification includes C-reactive peptide (CRP) instead of ESR. In addition, indices with a far simpler metric have been developed to measure disease activity: the Clinical Disease Activity Index (CDAI) and the Simplified Disease Activity Index (SDAI).[44,45] Theoretically, these simplifications have gone at the cost of performance of the indices: At the group level they still work; at the individual patient level they may fall short.

Nowadays, the DAS (actually often its 28-joint modification with CRP instead of ESR) is one of the most used composite scores worldwide. In clinical trials it has been proven that adjustment of treatment intensity based on the DAS results in better clinical and radiographic outcomes.[46-48] However, in terms of implementation, a lot is still to gain: Several studies have suggested that DAS-steered therapy is not yet widely applied in clinical practice.[49-54] Among the multiple alternative explanations, the following two are relevant for the discussion here: 1. Physicians may put more value on certain components of the DAS than on the DAS itself, and use for instance ESR or swollen joint count rather than DAS to decide about treatment; and 2.[55] Differences between the patient's and the physician's perception of the level of disease activity may be at the basis of a patient's refusal to follow up a DAS-based advice by the physician.

Physical functioning

In addition to disease activity, measures for functional disability have been developed in order to score how well patients were able to perform daily activities. The most widely used measure is the Health Assessment Questionnaire (HAQ). The HAQ consists of 24 questions regarding eight distinct categories: dressing, arising, eating, walking, hygiene, reach, grip and usual activities.[56] The HAQ reflects disability in daily activities. With disability either related to actual disease activity or to damage due to previous disease activity, the HAQ can be seen as consisting of two components, the reversible and the irreversible HAQ.[57] Medication changes that suppress actual disease activity may decrease the total HAQ only to the extent where sustained damage has a permanent impact on functional ability.[57,58] Thus, to avoid irreversible disability, disease activity has to be suppressed early, in order to prevent the occurrence of joint damage.

Radiologic joint damage

Earlier treatment initiation and the use of combinations of therapies including oral corticosteroids or the newer bDMARDs have resulted in fewer patients developing severe joint damage. Ideally, clinical remission (no symptoms of RA activity) is accompanied by radiographic remission (absence of joint damage, or no progression from baseline). Joint damage can be assessed with several scoring methods.[59] For the small joints of hands and feet the modified Sharp van der Heijde Score (SHS) is often used, which scores the number and severity of erosions and the severity of joint space narrowing in 44 joints of the wrists, hands

and feet, resulting in a possible maximum score of 448.[60] The SHS is usually applied in clinical trials, because it is too comprehensive to apply in individual patients in clinical practice, and requires special training. In research, SHS is still considered very important because it may reflect the level of disease activity, both in terms of extent and duration. Often, (partially) patient-reported outcomes such as DAS and HAQ are tested against the external standard of joint damage, quantified by SHS. The Larsen score is most often used to score the severity of damage in the large joints (shoulders, elbows, wrists, hips, knees and ankles), and has a range from 0 to 5 per joint.[61]

TREAT TO TARGET: FROM TRIALS TO DAILY PRACTICE

Many trials have proven the efficacy of targeted treatment with regard to clinical outcomes. The TICORA study was the first to demonstrate that targeted treatment aiming at low disease activity results in better clinical and radiological outcomes than 'routine' interview-based care.[46] Other trials demonstrating that a treat to target approach may result in remarkable clinical and radiological improvement were FINRA-Co,[62] CAMERA,[63] and the BeSt study.[64] The BeSt study, discussed in some more detail here since data from this study will feature in this thesis, has started as a multicentre randomised clinical trial consisting of four treatment arms and aimed at effective disease suppression using principles of targeted treatment in patients with recently diagnosed active RA. Between 2000 and 2002, 508 patients were randomised to: 1) sequential monotherapy of csDMARDs, 2) step-up therapy of csDMARDs, 3) initial combination therapy of csDMARDs with tapered high-dose prednisone or 4) initial combination therapy including infliximab. In addition, intra articular corticosteroid injections were allowed at the rheumatologists' discretion. Every three months, protocolled treatment adjustments were made based on the DAS. The HAQ was also completed at each visit. The Best study was one of the trials that have shown that DAS-steered treatment may result in better long-term clinical outcome, such as functional ability,[64] and in less progression of joint damage.

METEOR and other databases

The benefits of DAS-steered therapy have been studied in clinical trials[46-48,65,66] including optimal protocols, motivated rheumatologists and nurses, and relatively healthy (trial) patients. Whether or not treat-to-target is feasible and practiced in common daily clinics,

however, was not well known. The Measurement of Efficacy of Treatment in the 'Era of Outcome' in Rheumatology (METEOR) database has been developed to help clinicians implementing strategies such as treat-to-target in their routine clinical care. The database serves as an online software tool for rheumatologists to encourage frequent monitoring, subsequent treatment adjustments, and registration of disease activity and physical functioning in patients with RA. The METEOR initiative has been started by rheumatologists and has been developed for rheumatologists worldwide. Besides composite measures and functional ability data, rheumatologists can add information on medication use and other patient- and physician- reported outcomes. METEOR can also provide benchmarks to the rheumatologist that allows him to compare his performance with that of other rheumatologists. This may lead to research comparing data of clinical outcomes in RA care within and between countries.[67] Apart from METEOR, other international initiatives (registers, databases or cohorts) promote T2T in clinical practice and advocate comparing clinical outcomes between countries.[68,69] Many of these initiatives exploit a rather small database and although they may overlap in design and registration, it appears to be difficult to combine data for integrated analyses. To improve the quality of research EULAR has published a repository of databases in which researchers can collaborate and share information on databases, which will be further discussed in this thesis.

International Recommendation Implementation Study (IRIS)

To study the incorporation of the EULAR and the treat to target recommendations for RA in clinical practice and to identify how application of these recommendations by rheumatologists could be further enhanced, the International Recommendation Implementation Study (IRIS) was started. In the IRIS a survey was established to study whether rheumatologists apply the recommendations in clinical practice. A well-recognized pitfall of surveys is that we do not know if the outcome of the survey truly reflects daily practice: responses might be influenced by 'desirable' answers that participants may give.[29,50,52,54]

For the IRIS study, rheumatologists worldwide were contacted via their national rheumatology societies and asked to participate, and 132 rheumatologists from many countries agreed. These were asked to follow an educational program, which included reading two scientific papers on treat to target therapy, and watching an educational video. Before the educational training they were asked to fill in a questionnaire on their awareness on the EULAR and treat to target recommendations. After the educational program, the participating

rheumatologists were asked to each include 5-10 newly diagnosed RA patients, which were then followed up for one or two years.

OUTLINE OF THIS THESIS

Main Aims

- Compare rheumatologists' agreement with - and their actual performance of - treat-to-target recommendations in daily clinical practice.
- Investigating (cultural) differences in perceptions of both the RA-patient and the treating physician in rating the global disease activity of the patient

The main focus of this thesis is on treat-to-target therapy and improving care in RA, in particular on rheumatologists' awareness and the implementation of treat-to-target recommendations in daily clinical practice. In **Chapter 2** we focused on existing databases in the field of rheumatoid arthritis. Here we have described the results of a systematic literature review in which we were aiming to provide an overview of the existing European (international and national) databases in RA. In four international- and 30 national databases we described characteristics, such as the aims, funding, size, year of inception, collection of clinical data and participation in the repository of databases. The latter database was set up by the EULAR to stimulate collaboration between European researchers. In the context of a DAS steered trial (the Best-trial database) we have further investigated the use and the benefits of intra articular injections on local inflammation, which includes swollen and tender joints over 3 months (short term). Over a longer period, intermediate (until 1 year after injection) and long term (until 8 years after injection) we investigated the association between intra articular injections and systemic clinical outcomes, such as the DAS and HAQ (**chapter 3**).

In **chapter 4 and 5** we focused on the patient- versus the physician-reported outcomes in RA in the METEOR database, since they may have different perceptions of patients' disease activity. We investigated differences in assessments of the patients' global disease activity by patient and physician, and explored which determinants influenced both patients' and physicians' assessments. We also investigated which determinants were associated with a difference (>20mm) in global disease activity score of the patient and the physician.

In **chapter 5** we investigate whether differences between patients' and physicians' assessment of global disease activity are dependent on the country of residence, as language, patient-

physician interaction or other cultural differences may affect how patients and physicians perceive this subjective outcome.

In **chapter 6** we focussed on whether DAS steered therapy has been applied in clinical practice. Questionnaire-based research suggests that rheumatologists apply T2T on a daily basis, while on the other hand some observational studies have suggested that DAS steered therapy is infrequently practiced. Therefore we have investigated whether - and if yes: to what extent - DAS steered therapy has been applied in a clinical practice database (METEOR). The association between level of DAS and treatment adjustments was compared in various DAS-classification groups.

In **chapter 7** we showed the first results of the IRIS study. This study compared rheumatologists' willingness to use a T2T approach, as based on the results of a questionnaire, with subsequent data from the METEOR database showing how T2T is implemented by these rheumatologists in daily practice. Since the questionnaire was followed up by an educational program on the EULAR and T2T recommendations, we will be able to give an impression on whether such an educational program is useful in the process of implementing recommendations in clinical practice.

In **chapter 8** we summarized and discussed the results of the studies reported in the thesis. Also we will give a future perspective on recommended research in this field.

REFERENCE LIST

1 Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. *Semin Arthritis Rheum* 2006;36:182-188.

2 Grassi W, De AR, Lamanna G, et al. The clinical features of rheumatoid arthritis. *Eur J Radiol* 1998;27 Suppl 1:S18-S24.

3 Cross M, Smith E, Hoy D, et al. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis* 2014;73:1316-1322.

4 Pincus T, Sokka T, Kautiainen H. Patients seen for standard rheumatoid arthritis care have significantly better articular, radiographic, laboratory, and functional status in 2000 than in 1985. *Arthritis Rheum* 2005;52:1009-1019.

5 Pincus T, Sokka T, Chung CP, et al. Declines in number of tender and swollen joints in patients with rheumatoid arthritis seen in standard care in 1985 versus 2001: possible considerations for revision of inclusion criteria for clinical trials. *Ann Rheum Dis* 2006;65:878-883.

6 Wolfe F, Mitchell DM, Sibley JT, et al. The mortality of rheumatoid arthritis. *Arthritis* Rheum 1994; 37: 481-494

7 Silman AJ. Trends in the incidence and severity of rheumatoid arthritis. *J Rheumatol Suppl* 1992;32:71-73.

8 Uhlig T, Heiberg T, Mowinckel P, et al. Rheumatoid arthritis is milder in the new millennium: health status in patients with rheumatoid arthritis 1994-2004. *Ann Rheum Dis* 2008;67:1710-1715.

9 Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/ European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010;69:1580-1588.

10 Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia* 2009;52:17-30.

11 Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2010;69:964-975.

12 van den Broek M, Klarenbeek NB, Dirven L, et al. Discontinuation of infliximab and potential predictors of persistent low disease activity in patients with early rheumatoid arthritis and disease activity score-steered therapy: subanalysis of the BeSt study. *Ann Rheum Dis* 2011;70:1389-1394.

13 O'Mahony R, Richards A, Deighton C, et al. Withdrawal of disease-modifying antirheumatic drugs in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Ann Rheum Dis* 2010;69:1823-1826.

14 Klarenbeek NB, van der Kooij SM, et al. Discontinuing treatment in patients with rheumatoid arthritis in sustained clinical remission: exploratory analyses from the BeSt study. *Ann Rheum Dis* 2011;70:315-319.

15 Pincus T, Yazici Y, Sokka T, et al. Methotrexate as the "anchor drug" for the treatment of early rheumatoid arthritis. *Clin Exp Rheumatol* 2003;21:S179-S185.

16 Suarez-Almazor ME, Belseck E, Shea B, et al. Sulfasalazine for rheumatoid arthritis. *Cochrane Database Syst Rev* 2000; CD000958.

17 Prakash A, Jarvis B. Leflunomide: a review of its use in active rheumatoid arthritis. *Drugs* 1999;58:1137-1164.

18 Li EK, Tam LS, Tomlinson B. Leflunomide in the treatment of rheumatoid arthritis. *Clin Ther* 2004;26:447-459.

19 van der Kooij SM, de Vries-Bouwstra JK, Goekoop-Ruiterman YP, et al. Limited efficacy of conventional DMARDs after initial methotrexate failure in patients with recent onset rheumatoid arthritis treated according to the disease activity score. *Ann Rheum Dis* 2007;66:1356-1362.

20 Bakker MF, Jacobs JW, Welsing PM, et al. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2012;156:329-339.

21 Svensson B, Boonen A, Albertsson K, et al. Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: a two-year randomized trial. *Arthritis Rheum* 2005; 52:3360-3370.

22 Wassenberg S, Rau R, Steinfeld P, et al. Very low-dose prednisolone in early rheumatoid arthritis retards radiographic progression over two years: a multicenter, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2005;52:3371-3380.

23 Keystone EC, Curtis JR, Fleischmann RM, et al. Rapid improvement in the signs and symptoms of rheumatoid arthritis following certolizumab pegol treatment predicts better longterm outcomes: post-hoc analysis of a randomized controlled trial. *J Rheumatol* 2011;38:990-996.

24 Emery P, Fleischmann R, van der Heijde D, et al. The effects of golimumab on radiographic progression in rheumatoid arthritis: results of randomized controlled studies of golimumab before methotrexate therapy and golimumab after methotrexate therapy. *Arthritis Rheum* 2011;63:1200-1210.

25 Da Silva JA, Jacobs JW, Kirwan JR, et al. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. *Ann Rheum Dis* 2006;65:285-293.

26 Smolen JS, Aletaha D, Bijlsma JW, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010;69:631-637.

27 Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014;73:492-509.

28 Smolen JS, Aletaha D. Monitoring rheumatoid arthritis. *Curr Opin Rheumatol* 2011;23:252-258.

29 Schoels M, Smolen JS. Treating rheumatoid arthritis to target: evidence-based recommendations for enhanced disease management. *Reumatol Clin* 2012;8:1-2.

30 Haraoui B, Bensen W, Bessette L, et al. Treating rheumatoid arthritis to target: a Canadian physician survey. *J Rheumatol* 2012;39:949-953.

31 Studenic P, Radner H, Smolen JS, et al. Discrepancies between patients and physicians in their perceptions of rheumatoid arthritis disease activity. *Arthritis Rheum* 2012;64:2814-2823.

32 Nicolau G, Yogui MM, Vallochi TL, et al. Sources of discrepancy in patient and physician global assessments of rheumatoid arthritis disease activity. *J Rheumatol* 2004;31:1293-1296.

33 Khan NA, Spencer HJ, Abda E, et al. Determinants of discordance in patients' and physicians' rating of rheumatoid arthritis disease activity. *Arthritis Care Res* (*Hoboken*) 2012;64:206-214.

34 de Wit MP, Smolen JS, Gossec L, et al. Treating rheumatoid arthritis to target: the patient version of the international recommendations. *Ann Rheum Dis* 2011;70:891-895.

35 Brusamento S, Legido-Quigley H, Panteli D, et al. Assessing the effectiveness of strategies to implement clinical guidelines for the management of chronic diseases at primary care level in EU Member States: a systematic review. *Health Policy* 2012;107:168-183.

36 Francke AL, Smit MC, de Veer AJ, et al. Factors influencing the implementation of clinical guidelines for health care professionals: a systematic meta-review. *BMC Med Inform Decis Mak* 2008;8:38.

37 Rashidian A, Eccles MP, Russell I. Falling on stony ground? A qualitative study of implementation of clinical guidelines' prescribing recommendations in primary care. *Health Policy* 2008;85:148-161.

38 Michie S. Changing behavior: theoretical development needs protocol adherence. *Health Psychol* 2005;24:439.

39 Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999;282:1458-1465.

40 van der Heijde DM, van 't HM, van Riel PL, et al. Development of a disease activity score based on judgment in clinical practice by rheumatologists. *J Rheumatol* 1993;20:579-581.

41 Koevoets R, Klarenbeek NB, Guler-Yuksel M, et al. Simplified versions of the original disease activity score: validation in the BeSt trial. *Ann Rheum Dis* 2011;70:1471-1474.

42 van Gestel AM, Prevoo ML, Van 't Hof MA, et al. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. *Arthritis Rheum* 1996;39:34-40.

43 Prevoo ML, van Gestel AM, van THM, et al. Remission in a prospective study of patients with rheumatoid arthritis. American

Rheumatism Association preliminary remission criteria in relation to the disease activity score. *Br J Rheumatol* 1996; 35:1101-1105.

44 Prevoo ML, Van 't Hof MA, Kuper HH, et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995;38:44-48.

45 Smolen JS, Breedveld FC, Schiff MH, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. *Rheumatology* (*Oxford*) 2003; 42:244-257.

46 Aletaha D, Nell VP, Stamm T, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. *Arthritis Res Ther* 2005;7:R796-R806.

47 Grigor C, Capell H, Stirling A, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 2004;364:263-269.

48 Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Kerstens PJ, et al. DAS-driven therapy versus routine care in patients with recent-onset active rheumatoid arthritis. *Ann Rheum Dis* 2010;69:65-69.

49 Castrejon I, Pincus T, Soubrier M, et al. GUEPARD treat-to-target strategy is significantly more efficacious than ESPOIR routine care in early rheumatoid arthritis according to patient-reported outcomes and physician global estimate. *Rheumatology* (*Oxford*) 2013;52:1890-1897.

50 van Hulst LT, Creemers MC, Fransen J, et al. How to improve DAS28 use in daily clinical practice?--a pilot study of a nurse-led intervention. *Rheumatology* (*Oxford*) 2010;49:741-748.

51 Park YB, Koh EM, Kim HY, et al.Treating rheumatoid arthritis to target: recommendations assessment questionnaire in Korea. *Clin Rheumatol* 2013;32:1791-1797.

52 Littlejohn G, Roberts L, Arnold M, et al. A multi-center, observational study shows high proportion of Australian rheumatoid arthritis patients have inadequate disease control. Int *J Rheum Dis* 2013;16:532-538.

53 Kruger K, Karberg K. [Treat-to-target from the perspective of office-based rheumatology]. *Z Rheumatol* 2011;70:664-669.

54 Haraoui B, Smolen JS, Aletaha D, et al. Treating Rheumatoid Arthritis to Target: multinational recommendations assessment questionnaire. *Ann Rheum Dis* 2011; 70:1999-2002.

55 Schoels M, Aletaha D, Smolen JS, et al. Follow-up standards and treatment targets in rheumatoid arthritis: results of a questionnaire at the EULAR 2008. *Ann Rheum Dis* 2010;69:575-578.

56 Pyne L, Bykerk VP, Boire G, et al. Increasing treatment in early rheumatoid arthritis is not determined by the disease activity score but by physician global assessment: results from the CATCH study. *J Rheumatol* 2012;39:2081-2087.

57 Siegert CE, Vleming LJ, Vandenbroucke JP, et al. Measurement of disability in Dutch

rheumatoid arthritis patients. *Clin Rheumatol* 1984;3:305-309.

58 Wolfe F. Which HAQ is best? A comparison of the HAQ, MHAQ and RA-HAQ, a difficult 8 item HAQ (DHAQ), and a rescored 20 item HAQ (HAQ20): analyses in 2,491 rheumatoid arthritis patients following leflunomide initiation. *J Rheumatol* 2001;28:982-989.

59 Bombardier C, Barbieri M, Parthan A, et al. The relationship between joint damage and functional disability in rheumatoid arthritis: a systematic review. *Ann Rheum Dis* 2012;71:836-844.

60 Aletaha D, Smolen J, Ward MM. Measuring function in rheumatoid arthritis: Identifying reversible and irreversible components. Arthritis Rheum 2006;54:2784-2792.

61 van der Heijde DM. Plain X-rays in rheumatoid arthritis: overview of scoring methods, their reliability and applicability. Baillieres Clin Rheumatol 1996;10:435-453.

62 van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 2000;27:261-263.

63 Larsen A. A radiological method for grading the severity of rheumatoid arthritis. *Scand J Rheumatol* 1975;4:225-233.

64 Rantalaiho V, Kautiainen H, Korpela M, et al. Targeted treatment with a combination of traditional DMARDs produces excellent clinical and radiographic long-term outcomes in early rheumatoid arthritis regardless of initial infliximab. The 5-year follow-up results of a randomised clinical trial, the NEO-RACo trial. *Ann Rheum Dis* 2014;73:1954-1961.

65 Verstappen SM, Jacobs JW, van der Veen MJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). *Ann Rheum Dis* 2007;66:1443-1449.

66 van der Kooij SM, de Vries-Bouwstra JK, Goekoop-Ruiterman YP, et al. Patient-reported outcomes in a randomized trial comparing four different treatment strategies in recent-onset rheumatoid arthritis. *Arthritis Rheum* 2009;61:4-12.

67 Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2007;146:406-415.

68 Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): A randomized, controlled trial. *Arthritis Rheum* 2008;58:S126-S135.

69 Schipper LG, Vermeer M, Kuper HH, et al. A tight control treatment strategy aiming for remission in early rheumatoid arthritis is more effective than usual care treatment in daily clinical practice: a study of two cohorts in the Dutch Rheumatoid Arthritis Monitoring registry. *Ann Rheum Dis* 2012;71:845-850.

70 Soubrier M, Lukas C, Sibilia J, et al. Disease activity score-driven therapy versus routine care in patients with recent-onset active rheumatoid arthritis: data from the GUEPARD trial and ESPOIR cohort. Ann Rheum Dis 2011;70:611-615.

71 Koevoets R, Allaart CF, van der Heijde DM, et al. Disease activity monitoring in rheumatoid arthritis in daily practice: experiences with METEOR, a free online tool. *J Rheumatol* 2010;37:2632-2633.

72 Sokka T, Kautiainen H, Toloza S, et al. QUEST-RA: quantitative clinical assessment of patients with rheumatoid arthritis seen in standard rheumatology care in 15 countries. *Ann Rheum Dis* 2007;66:1491-1496.

73 Chatzidionysiou K, Lie E, Nasonov E, et al. Highest clinical effectiveness of rituximab in autoantibody-positive patients with rheumatoid arthritis and in those for whom no more than one previous TNF antagonist has failed: pooled data from 10 European registries. *Ann Rheum Dis* 2011;70:1575-1580.

Chapter 2

Comparison of characteristics of (inter)national databases in rheumatoid arthritis: a systematic review

E. Gvozdenović, R. Koevoets, J.M. Langenhoff, C.F. Allaart, R. Landewé

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ABSTRACT

Objective

To evaluate current (inter)national registers and observational cohorts in Europe, and to compare inclusion criteria, aims, collected data and participation in the EULAR repository.

Methods

We performed a systematic search strategy in six literature databases. Publications reporting European (inter)national prospective registers/cohorts including >200 RA patients with at least half a year of follow-up were selected.

Results

In total, 417 articles and abstracts were included, which described 4 international databases and 39 national databases/cohorts. International databases were of roughly similar design, frequency of data collection and selection criteria and are mostly initiated to monitor and compare clinical patient care among countries. National databases/cohorts vary in aims and inclusion criteria. Half of the national registers are connected to the EULAR repository of databases.

Conclusion

Our findings may indicate that among researchers there is little awareness of recommendations to set up registers or cohorts and of the existence of the database collaboration network of EULAR.

INTRODUCTION

The development of treatment care in rheumatoid arthritis (RA) is usually studied in randomized clinical trials (RCTs). However, it is well known that patients included in clinical trials often differ from patients in standard care due to specific inclusion criteria.[1,2] Patients in RCTs in general have higher disease activity and less or no co-morbidities compared to patients in cohorts.[3]

More valuable 'daily practice'-based information may be found in large representative long-term registries that have been established to monitor patients specifically in clinical practice.[4] Already some reviews compared characteristics of various registries to investigate differences between treatment results in clinical practice and RCTs.[5,6]

It appears that despite the availability of international recommendations on management of RA and similar access to the same drug therapies, important differences in outcomes remain. This may be due to variations in defining outcomes, or differences in local culture or variability in the use of biological agents (e.g. invoked by reimbursement policies or access to health care). In addition, the inclusion criteria, design and purpose of such registries may greatly influence the results of a database analysis. To improve collaboration between European rheumatologists, the European League Against Rheumatism (EULAR) has recently started a repository of databases, which can be used as a platform for researchers to start collaborative projects.

In this article we aim to give a complete overview of the existing large registers and cohorts in Europe (international, national, regional and local), to inform on participation of these databases in the EULAR repository and to provide details on inclusion criteria, aim of the registry and its data collection.

METHODS

Retrieval of possibly relevant references

A literature search was performed according to the PRISMA statement[7,8] for cohorts, registries and databases on of three types: international (more than one European country captured), national (captured centers in all parts of the country), regional (captured centers in more than one city in the same region) and local (captured one or more centers in a city). We searched in six databases; PubMed, Embassy, Web of Science (WOS), Academic Search Premier, Wiley-Blackwell and LWW. In collaboration with a trained librarian (JL), an

extensive search strategy was formulated (Attachment I). Search strategies for the other databases were formulated similarly but adjusted to the specific database. References were stored and deduplicated in a Reference Manager database. While recognizing the existence of numerous RA registries, we identified publications that were best served for our aims.

Selection of references

Criteria to include a reference or an article were:
1) The disease studied was at least RA
2) The database/study was prospective and longitudinal
3) The study was initiated in Europe
4) The study included more than 200 study participants
5) The study had at least half a year of follow-up.

Articles or abstracts were excluded if they described:
Cohorts/databases that also studied patients with non-rheumatologic diseases (such as studies based on hospital discharge registers, health service registers, and population based cohorts)
Case control studies.

The selection procedure consisted of 2 phases:
Two independent investigators (EG and RK) screened the references by title or abstract for selection. Differences were resolved by agreement. After this, the full text of the remaining articles and abstracts was read and reviewed extensively by one investigator (EG).
Additionally, a questionnaire was sent to 47 national societies of rheumatology connected to the EULAR asking for the presence and features of any RA or arthritis databases in their country. Both the questionnaire and the literature search were used to select the databases and cohorts for our study.

RESULTS

In total 5078 references were found with our systematic literature search (figure 1).

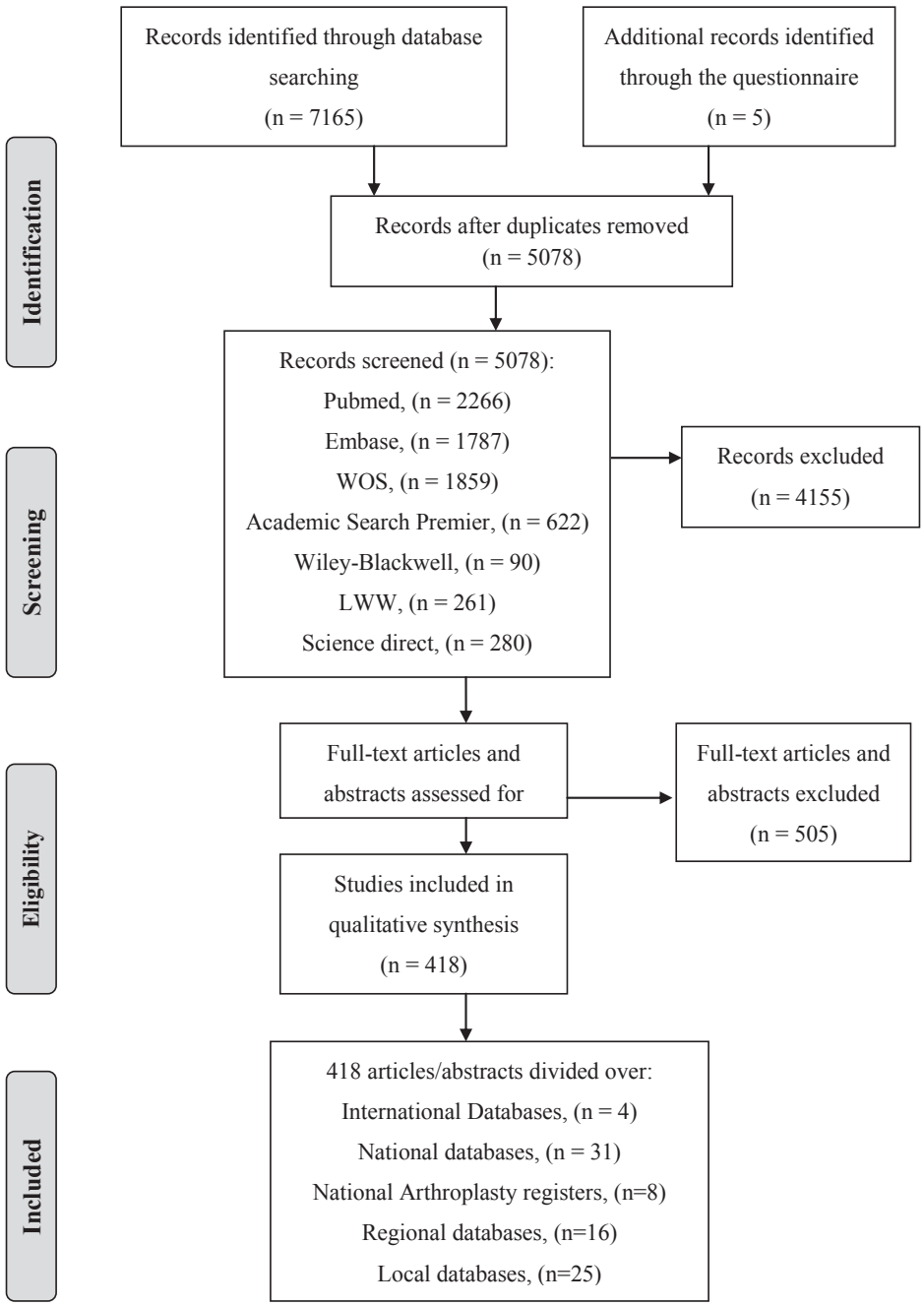

Figure 1. PRISMA Flow chart inclusion.

4155 references were excluded after screening of the titles and abstracts, which left us with 923 references. After reading the full text of the publications, another 506 references were excluded, resulting in a final set of 417 articles and abstracts for inclusion. The response rate of the questionnaire was 32/47 (68%) which provided us with 5 additional databases, of which no publications were found identified in the literature search. We identified combining both strategies 4 international databases, 39 national databases (7 of which were left out when they proved to be arthroplasty registers), 16 regional databases and 25 local databases. For some databases, more than one publication was available to describe all features. Approximately half of the databases were described once (n=33) or twice (n=12) but 5 databases were described in more than 20 publications (table 1).

The characteristics of the 4 international and the 32 national registers were further described and summarized in the tables, with focus on the following features: funding, aims, number of patients, year of inception, clinical evaluation of the physician, patient reported outcomes, laboratory information, radiographic imaging, drug treatment, frequency of data collection, selection criteria for enrolment into the registry, control groups, rheumatic diseases captured, connection to the EULAR repository of databases and the number of publications. Not all features we aimed to describe were reported in the publications, and we refer to them as 'not reported'.

International databases

Table 2 describes the four international databases that we have found: METEOR (Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology), GoTreatIt, Quest-RA (Quantitative Patient Questionnaires in Standard Monitoring of Patients with Rheumatoid Arthritis) and Cererra (the European Collaborative Registries for the Evaluation of Rituximab in Rheumatoid Arthritis).[4,9,10]

All databases are practice-based registers, collecting clinical information on RA patients. The purpose of these databases is mostly to monitor clinical patient care and comparing patient care among countries. The available clinical collected outcomes are roughly similar in the four databases: DAS, HAQ and erosions.

METEOR and GoTreatIt are both internet-based instruments to monitor disease activity in RA and response to treatment.

Table 1. The number of publications per database.

Publications	**National/ international (n=43)**	**Regional (n=16)**	**Local (n=25)**	**Total (n=8)**
Databases not described in publications, n*	3	0	1	5
databases described in:				
1 publication, n	9	9	15	33
2 publications, n	8	1	3	12
3 publications, n	1	2	1	4
4 publications, n	3	1	1	5
5 publications, n	2	0	1	3
6 publications, n	3	0	0	3
7 publications, n	3	0	1	4
10 publications, n	1	0	0	1
11 publications, n	1	1	0	2
12 publications, n	1	0	0	1
13 publications, n	1	0	0	1
14 publications, n	1	0	0	1
16 publications, n	0	1	0	1
17 publications, n	0	0	1	1
18 publications, n	0	0	1	1
19 publications, n	0	1	0	1
≤20 publications, n	5	0	0	5

*5 databases were not described in the publications, they were found via the questionnaire, n=number.

They are based on and aim to promote using composite scores as tools to monitor disease activity.[10] Quest-RA is a monitoring program for standard care in RA.[4] Cererra is a drug-safety register with a fixed (every 0, 3, 6, 9 and 12 month's patients are seen) monitoring protocol the efficacy of rituximab in RA.[9] METEOR, QUEST-RA and GoTreatIt follow patients without fixed monitoring time points. The largest database is METEOR with more than 17.000 patients registered including at least one entry of disease activity; the database covering the highest number of countries (N=20) is QUEST-RA. METEOR, Quest-RA and Cererra are funded by pharmaceutical industry and GoTreatIt by the government.

Table 2. Characteristics of international databases/cohorts.

International database	*Funding*	*Aims*	*RA patients (n)*	*Year of inception*	*Physician/ clinical evaluation*	*Patient reported outcomes*	*Additional (labs/ radiographies/ imaging)*	*Drug treatment recorded*	*Articles/ abstracts published (n)*
METEOR (Measurement of Efficacy of Treatment in the 'Era of outcome' in Rheumatology)[1]	3	3	Ongoing, 17.700	2008	DAS, SJC, TJC, VAS (global), SDAI, CDAI	HAQ, VAS pain/global	Erosions, RF, CCP, ESR, CRP	b and csDMARDs, NSAIDs, glucocorticoids	1
Quest-RA (Quantitative Patient Questionnaire Monitoring in Standard Clinical Care of Patients with Rheumatoid Arthritis)[4]	3	3	Ongoing, 7.568	2005	DAS, SJC, TJC, VAS (global)	HAQ, RADAI, ROAD, VAS pain/global	Erosions, RF, ESR, CRP	b and csDMARDs, NSAIDs, glucocorticoids	6
Cererra (European Collaborative Registries for the Evaluation of Rituximab in Rheumatoid Arthritis)[9]	3	1	Ongoing/ Closed, is not reported 2.019	Not reported	DAS, SJC, TJC, VAS (global)	HAQ, VAS pain/global	Erosions, RF, CCP, ESR, CRP	b and csDMARDs, glucocorticoids	4
GoTreatIt	1	3	Ongoing, ~8.000	2004	DAS, SJC, TJC, VAS (global)	HAQ, VAS pain/global	Erosions, RF/CCP factor, ESR/CRP	b and csDMARDs, NSAIDs, glucocorticoids	0

Table 2 (continued). Characteristics of international databases/cohorts.

International database	*Frequency of Data collection (mo)*	*Selection criteria for enrolment*	*Control group*	*Rheumatologic Diseases captured*	*European countries captured (n)*	*Connected to the EULAR*
METEOR (Measurement of Efficacy of Treatment in the 'Era of outcome' in Rheumatology)[10]	Continuous	RA patients Spa at all stages	No	Early and established RA	16	No
Quest-RA (Quantitative Patient Questionnaire Monitoring in Standard Clinical Care of Patients with Rheumatoid Arthritis)[4]	Continuous	RA patients, usual patient care	No	Early and established RA	20	No
Cererra (European Collaborative Registries for the Evaluation of Rituximab in Rheumatoid Arthritis)[9]	Fixed protocol, Every 0,3,6,9,12	RA patients treated with rituximab	No	Early and established RA	10	No
GoTreatIt	Continuous	All patients with rheumatic diseases	No	All rheumatic diseases	2	No

Funding: 1) government 3) Pharmaceutical industry, Aims: 1) efficacy and safety of biological or other treatments 3) monitoring/ benchmarking (disease activity) for clinical practice, DAS=Disease Activity Score, HAQ=Health Assessment Questionnaire, SJC=swollen joint count, TJC=tender joint count, VAS=visual analogue scale, ESR=erythrocyte sedimentation rate, CCP=anti-cyclic citrullinated peptide, CRP=C-recreative proteïne, RF=rheumatoid factor, DMARDs=disease-modifying anti rheumatic drugs (b=biological, cs=conventional), n=number, mo=months, NSAIDs=nonsteroidal anti-inflammatory drugs, RA=rheumatoid arthritis.

National databases/cohorts

Distribution: Attachment II; table 1 shows the national databases and cohorts in Europe. 16 European countries have nationally based databases or cohorts. Most of them were found in France (n=4), Spain (n=4) and the United Kingdom (n=4). However, the largest registers were found in the United Kingdom, Germany and Denmark.

Size/number of publications: The largest registers with more than 10.000 patients are the British Society for Rheumatology Rheumatoid Arthritis Register (BSRBR) (N≈20.000, 44 publications), the German Collaborative Arthritis Centers (N≈15-17,000, 26 publications), the Danish Registry for Biologic Therapies in Rheumatology (DANBIO) (N≈10.000, 14 publications) and the German biologics register (RABBIT) (N≈12.303, 20 publications). DANBIO, BSRBR and Rabbit are aiming at efficacy of the biologic drugs and all include early and established RA patients, while the German Collaborative Arthritis Centers is established for epidemiologic purposes and includes all RA patients, without restriction of drug use.[11-14] Eleven databases are currently closed, 15 are ongoing and for six databases the size was not reported (Attachment II; table 1).

Year of inception: The inception of the cohorts and registers varies between 1986 and 2011. The largest registers were not all the oldest registers. The oldest cohort is the Early Rheumatoid Arthritis study (ERAS) which started in the United Kingdom, in 1986. Also long running are the Norfolk Arthritis Register (NOAR, 1989), the national database of the German Collaborative Arthritis Centers (since 1993), the Early Swedish Rheumatoid Arthritis Register (RAMONA) (since 1995) and the Swiss Clinical Quality Management program for RA (SCQM-RA) (since 1997). These older databases differed in aims and inclusion criteria. ERAS and RAMONA primarily aimed at monitoring clinical disease activity and included only early RA patients.[15,16] NOAR, SCQM-RA and the German Collaborative Arthritis Center have different purposes (predictive, monitoring and epidemiologic respectively) but similar inclusion criteria.[13,17,18]

Diseases captured: 23 databases described both early and established RA, 6 only early RA and 2 only established RA. Approximately half of the databases are covering more rheumatologic diseases besides RA such as Spondyloarthritis or Psoriatic Arthritis (Attachment II; table 1).

Selection criteria for enrolment into the registry: selection criteria vary with the main aims of the registry. We divided the registries in two sections based on aims as described in the publications: Fifteen registries have as primary aim to investigate efficacy and safety of biologic (or other) treatments. Inclusion criteria for these registers were for 14/15 both early and established RA. Most (11/15) of the efficacy registers were biologic registers. 8 of the registers aim at monitoring disease activity and benchmarking for clinical practice purposes. Inclusion criteria were for 4/6 both early an established RA patients, for 1 register established and for 3 registers early RA patients. Half of the latter register types are not connected to the EULAR repository of databases. Four registries serve epidemiological purposes, studying the prediction of outcome and aetiology. Inclusion criteria varied from established RA (n=1) to both established and early RA (n=3). Four registers aimed at monitoring one (biologic) drug in particular (Autoimmunity and Rituximab in RA cohort, MAbThera registry in RA, Orencia and RA study, medico-economic evaluation of infliximab study.[19-21]

Therapies: DMARDs and/or biologic agents are registered in 31/32 databases.

Frequency of data collection: In 11 of the databases, data collection is performed on a continuous basis, each time the patient visits the physician and not only at predefined time points. For the fixed protocols, seven databases include data collected every 3 months and 7 databases collected data every 6 months (Attachment II; table 1).

Physician/clinical evaluation: 31 registries collect Disease Activity Score (DAS) and/or DAS components, 19 of the registers use the DAS28 score. 4 registers report CDAI and SDAI and four registries also report morning stiffness.[11,14,16,19, 22-24]

Patient reported outcomes (PROs): 25 registries report results of the Health Assessment Questionnaire (HAQ), or alternatives/derivatives of the HAQ such as the Functional Status Questionnaire Hannover (FFbH). Results of the short-form-36 health survey questionnaires (SF-36) was reported in the BSRBR, the Early Rheumatoid Arthritis Network cohort (ERAN), the Gruppo Italiano Artrite Reumatoide Aggressiva (GIARA)-registry, the Norwegian disease-modifying antirheumatic drug register (NOR-DMARD) registry, study for the medico-economic evaluation of infliximab (EMER study), NOAR and the rheumatic diseases Portuguese register (Reumapt).[12,17,20,25-28] The RADAI (self-administered

rheumatoid arthritis disease activity index) was reported in the Swiss SCQM-RA and in the Belgian MIRA register.[18,21]

Additional (Labs/radiographies/imaging): All registries report CRP or ESR as acute phase reactants; radiographic information was collected in 50% of the registers, however for biological databases radiological measures (such as x-rays) were not always done or reported (Attachment II; table 1).

Funding: 16 of the databases are funded by pharmaceutical industries; also government, charity, health care, private sources and rheumatologic associations are funding registers. Most (11/14) of the biologic registers were funded by pharmaceutical companies (Attachment II: table 1).

Connection to EULAR: 16 of the 32 databases were connected to the EULAR repository of databases.[11-15,17-19,22,27-33]

Main differences: databases were distributed over 16 national countries, which shows that the population is various. The smallest database was Iceland's biologics register containing 214 subjects and the largest was BSRBR, with approximately 20.000 subjects.[12] A wide range between years of inception (24 years between the youngest (Biologic register Austria) and the oldest (ERAS) cohort) shows that there is a continuous need, and apparently renewal of funds, to start these registries and databases. Furthermore there are differences in inclusion criteria (only RA or also other diseases, only early RA, or also established RA, only one biologic therapy or all treatments), and in timing and regulation of data collection.

Main similarities: almost all databases collected similar drug information and clinical outcomes (patient reported outcomes and physicians evaluation).

DISCUSSION

In this systematic review we described four international and 32 national RA databases and cohorts of rheumatoid arthritis patients. The international initiatives have roughly similar aims, unrestricted inclusion criteria and continuous data collection, enabling comparisons of patients in daily practice between countries. The included patients have various degrees of disease severity, and are treated with a wide range of synthetic and biologic DMARDs.[4,9,10] It is not clear which percentages of eligible patients are included, and by what selection criteria this is determined. Thus, the included patients appear to represent patients from

normal daily practice, but may still present a selected population. Having been initiated relatively recently (between 2004 and 2008), these databases are mostly still collecting data and have not led to many publications, in comparison to some of the national databases .All four international initiatives are funded by pharmaceutical industry or the government and they are not connected to the EULAR repository of databases.

The national RA databases were set up between 1986 and 2010; approximately half of them are still ongoing.[11-40] 16 of these national databases were mentioned in the EULAR repository for databases. Although there are differences in inclusion criteria, aim, frequency of data collection and distribution among countries in Europe, the national databases generally collect similar patient reported outcomes, physician clinical evaluation and medication. This may stem from government requirements to monitor safety of recently introduced therapies, which may also explain involvement of sponsors from the pharmaceutical industry. Four databases appear to have been initiated to monitor patients treated with one (biologic) drug in particular.[19-21] The similarities also may indicate that there is not so much a need for new data, but a desire to 'own' one's own data to do research and write scientific papers. However, research on individual databases may be hampered by small numbers, but the (small) differences among the registries make the data of various databases difficult to compare or pool with others. This itself may be a reason to start yet again a new (large and/or international) database or registry. Curtis et al. and Zink et al. focused on biological registers while comparing characteristics of international databases. They found in concordance to our results that there is heterogeneity among databases, which Zink et al. suggest may lead to further analyses and new information.[5, 6]

Mostly the oldest and largest national databases are connected to the EULAR repository of databases.[11-18] It appears not all researchers are aware of or follow recommendations to set up registries or cohorts, nor aware of the EULAR network and database repository that aims to support collaboration between database researchers. Since databases and registries mostly have been initiated to provide information that may be missed in RCTs, it is relevant to identify if the results of these initiatives have been published in medical journals. Without publication, the effort of building the database may not be matched by the output of little information to few direct users. We found that in particular results from older and larger databases have been published. Some registers had few or no publications, which might be

due to difficulties in retrieving information from the registry, possibly due to the size and set up of the registry, incomplete data collection or poor IT support. These problems could be prevented when researchers connect their registers to the EULAR repository of databases. It has to be kept in mind that despite resembling daily practice, intentional or unintentional selection of patients whose data will enter the database may compromise generalizability of the database results.

In conclusion, through a systematic literature search and an additional inventory by questionnaire we found four international RA databases with similar inclusion criteria and content and frequency of data collection, and 32 national RA databases or registries, which differ substantially. Half of these databases, the oldest and largest with most publications, are connected to the EULAR repository of databases. It may be worthwhile for the others to join initiatives such as the EULAR repository for databases for collaboration between cohorts, to decrease differences in database structure and content and to improve quality of research and output. Since half of the databases is not joining the EULAR repository of databases, our results provide a more complete overview of the current present databases than the EULAR repository of databases. This overview is useful for researchers that want to start collaborations with researchers of databases that answer their research questions. Also researchers of existing databases can collaborate and compare data. Via this overview they can easily find the aims, inclusion and data collection of existing databases.

REFERENCE LIST

1. Gogus F, Yazici Y, Yazici H. Inclusion criteria as widely used for rheumatoid arthritis clinical trials: patient eligibility in a Turkish cohort. Clin Exp *Rheumatol* 2005;23(5):681.
2. Sokka T, Pincus T. Eligibility of patients in routine care for major clinical trials of antitumor necrosis factor agents in rheumatoid arthritis. *Arthritis & Rheumatism* 2003;48(2):313-8.
3. Sokka T, Pincus T. Most patients receiving routine care for rheumatoid arthritis in 2001 did not meet inclusion criteria for most recent clinical trials or american college of rheumatology criteria for remission. *J rheumatol* 2003;30:1138-1146.
4. Sokka T, Kautiainen H, Toloza S , et al: QUEST-RA: quantitative clinical assessment of patients with rheumatoid arthritis seen in standard rheumatology care in 15 countries. *Ann Rheum Dis* 2007;66:1491-1496.
5. Curtis JR, Jain A, Askling J, et al: A Comparison of Patient Characteristics and Outcomes in Selected European and US Rheumatoid Arthritis Registries; *Elsevier* 2010; 40: 2-14.
6. Zink A, Askling J, Dixon WG, et al. European biologicals registers: methodology, selected results and perspectives. *Ann Rheum* Dis 2009;68:1240-1246.
7. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151(4):264-269
8. Man JP, Weinkauf JG, Tsang M, et al. Why do some countries publish more than others? An international comparison of research funding, English proficiency and publication output in highly ranked general medical journals. *J Clin Epidemiol* 2004;19:811-817.
9. Chatzidionysiou K, Lie E, Nasonov E, et al. Highest clinical effectiveness of rituximab in autoantibody-positive patients with rheumatoid arthritis and in those for whom no more than one previous TNF antagonist has failed: pooled data from 10 European registries. *Ann Rheum Dis* 2011;70:1575-1580.
10. Koevoets R, Allaart CF, van der Heijde et al. Disease activity monitoring in rheumatoid arthritis in daily practice: experiences with METEOR, a free online tool. *J Rheumatol* 2010;37:2632-2633.
11. Hetland ML. DANBIO. powerful research database and electronic patient record. *Rheumatology* (*Oxford*) 2011 Jan;50(1):69-77.
12 Watson K, Symmons D, Griffiths I, et al. The British Society for Rheumatology biologics register. *Ann Rheum.Dis* 2005 Nov;64 Suppl 4:iv42-iv43.
13. Zink A, Listing J, Klindworth C, et al. The national database of the German Collaborative Arthritis Centres: I. Structure, aims, and patients. Ann *Rheum.Dis* 2001 Mar;60(3):199-206.
14. Zink A, Listing J, Strangfeld A, et al. [Dose adjustment in patients treated with infliximab in routine rheumatologic care in Germany. Results from the Biologics Register RABBIT]. *Z.Rheumatol*. 2006 Sep;65(5):441-6.

15. van Vollenhoven RF, Askling J. Rheumatoid arthritis registries in Sweden. *Clin Exp.Rheumatol*. 2005 Sep;23(5 Suppl 39):S195-S200.
16. Young A, Dixey J, Williams P, et al. An evaluation of the strengths and weaknesses of a register of newly diagnosed rheumatoid arthritis, 1986-2010. *Rheumatology* (*Oxford*) 2011 Jan;50(1):176-83.
17. Symmons DP, Silman AJ. The Norfolk Arthritis Register (NOAR). Clin *Exp.Rheumatol*. 2003 Sep;21(5 Suppl 31):S94-S99.
18. Langenegger T, Fransen J, Forster A, et al. [Clinical quality management in rheumatoid arthritis]. *Z.Rheumatol*. 2001 Oct;60(5):333-41.
19. Combe B. The French early arthritis registry. *Clin Exp.Rheumatol*. 2003 Sep;21(5 Suppl 31):S123-S128.
20 Sany J, Cohen JD, Combescure C, et al. Medico-economic evaluation of infliximab in rheumatoid arthritis--prospective French study of a cohort of 635 patients monitored for two years. *Rheumatology* (*Oxford*) 2009 Oct;48(10):1236-41.
21. Van Der Cruyssen B, Westhovens R, Durez P, et al. The belgian MIRA (Mabthera in rheumatoid arthritis) registry: Clues for the optimization of rituximab treatment strategies. *Arthritis and Rheumatism* 2009; Conference: American College of Rheumatology/ Association of Rheumatology Health Professionals Annual Scientific Meeting:2009.
22 Carbonell J, Cobo T, Balsa A, et al. The incidence of rheumatoid arthritis in Spain: results from a nationwide primary care registry. *Rheumatology* (*Oxford*) 2008 Jul;47(7):1088-92.
23 Dostal C, Pavelka K, Zvarova J, et al. Some principles of the development of a clinical database/national register of selected inflammatory rheumatic diseases in the Czech Republic. *Int J Med Inform*. 2006 Mar;75(3-4):216-23.
24. Grigor C, Porter D, et al. Clinical audit of care in rheumatoid arthritis (CARA). *Rheumatology* 2010 Apr;Conference: Rheumatology 2010 - British Society for Rheumatology:April 2010..
25. Canhao H, Faustino A, Martins F, et al. Reuma.pt - the rheumatic diseases portuguese register. Acta *Reumatol.Port*. 2011 Jan;(1):45-56.
26. Nikolaisen C, Kvien TK, Mikkelsen K, et al. Contemporary use of disease-modifying drugs in the management of patients with early rheumatoid arthritis in Norway. *Scand J Rheumatol.* 2009;38(4):240-5.
27. Kiely P, Williams R, Walsh D, et al. Contemporary patterns of care and disease activity outcome in early rheumatoid arthritis: the ERAN cohort. *Rheumatology (Oxford)* 2009 Jan;48(1):57-60.
28. Marchesoni A, Govoni M, Valentini G, et al. The Italian registry of aggressive rheumatoid arthritis -- the GIARA project. *J Rheumatol*. 2007 Dec;34(12):2374-81.
29. Ferraz-Amaro I, Machin S, Carmona L, et al. Pattern of use and safety of non-steroidal anti-inflammatory drugs in rheumatoid arthritis patients. A prospective analysis from clinical practice. *Reumatol.Clin* 2009 Nov;5(6):252-8.
30. Gomez-Reino JJ, Rodriguez-Lozano C, Campos-Fernandez C, et al. Change in the discontinuation pattern of tumour necrosis factor antagonists in rheumatoid arthritis over 10 years: data from the Spanish

registry BIOBADASER 2.0. *Ann Rheum Dis* 2012 Mar;71(3):382-5.

31. Neovius M, Simard J, Sundstrom A, et al. Generalisability of clinical registers used for drug safety and comparative effectiveness research: coverage of the Swedish Biologics Register. *Ann Rheum.Dis* 2011 Mar;70(3):516-9.
32. Virkki LM, Valleala H, Takakubo Y, et al. Outcomes of switching anti-TNF drugs in rheumatoid arthritis-a study based on observational data from the Finnish Register of Biological Treatment (ROB-FIN). *Clin Rheumatol*. 2011 Jun 7.
33. Young A, Dixey J, Cox N, et al. How does functional disability in early rheumatoid arthritis (RA) affect patients and their lives? Results of 5 years of follow-up in 732 patients from the Early RA Study (ERAS). *Rheumatology* (*Oxford*). 2000 Jun;39(6):603-11.
34. Gudbjrnsson B. Scandinavian arthritis registries - Iceland. *Scandinavian Journal of Rheumatology* 1933; Conference: 33rd Scandinavian Congress of Rheumatology: 2010.
35. Kvien TK, Heiberg, Lie E, et al. A Norwegian DMARD register: prescriptions of DMARDs and biological agents to patients with inflammatory rheumatic diseases. *Clin Exp.Rheumatol*. 2005 Sep;23(Suppl 5 39):S188-S194.
36. Lapadula G, Ferraccioli G, Ferri C, et al. an Italian biological agents registry in rheumatology.*Reumatismo* 2011;63(3):155-64.
37. Mariette X, Gottenberg JE, Ravaud P, et al. Registries in rheumatoid arthritis and autoimmune diseases: data from the French registries. *Rheumatology* (Oxford) 2011 Jan;50(1):222-9.
38. Naredo E, Moller I, Cruz A, et al. Power Doppler ultrasonographic monitoring of response to anti-tumor necrosis factor therapy in patients with rheumatoid arthritis. *Arthritis Rheum*. 2008 Aug;58(8):2248-56.
39. Sidiropoulos P, Flouri I, Drosos A, et al. Long-term follow-up of RA patients of the Hellenic biologies registry: Comparison of first versus second anti-TNF-alpha therapy. *Clinical and Experimental Rheumatology* 2009; Conference: 13th Mediterranean Congress of Rheumatology Cavtat Croatia. Conference Start: 20091118 Conference End: 2009 1121. Conference Publication: (var.pagings):708.
40. Vander CB, Durez P, Westhovens R, et al. Seven-year follow-up of infliximab therapy in rheumatoid arthritis patients with severe long-standing refractory disease: attrition rate and evolution of disease activity. *Arthritis Res Ther* 2010;12(3):R77.

Attachment I. Full search strategy for PubMed.

("Arthritis, Rheumatoid"[mesh] OR "Rheumatoid Arthritis"[all fields] OR ra[ti] OR "Rheumatoid Nodule"[all fields] OR "Rheumatoid Vasculitis"[all fields]) AND ("Databases, Factual"[Mesh] OR "database"[all fields] OR "databases"[all fields] OR "Registries"[Mesh] OR "registry"[all fields] OR "registries"[all fields] OR "register"[all fields] OR "internet"[Mesh] OR "internet"[all fields] OR "software"[mesh] OR "software"[all fields] OR "Cohort Studies"[Mesh] OR "cohort"[tiab]) AND (“international”[tiab] OR “national”[tiab] OR "Europe"[Mesh] OR "europe"[tiab] OR "european"[tiab] OR "Andorra"[tiab] OR "Andorran"[tiab] OR "Austria"[tiab] OR "Austrian"[tiab] OR "Belgium"[tiab] OR "Belgian"[tiab] OR "Albania"[tiab] OR "Albanian"[tiab] OR "Estonia"[tiab] OR "Estonian"[tiab] OR "Latvia"[tiab] OR "Latvian"[tiab] OR "Lithuania"[tiab] OR "Lithuanian"[tiab] OR "Baltic"[tiab] OR "Bosnia-Herzegovina"[tiab] OR "Bosnian"[tiab] OR "herzegovinian"[tiab] OR "Bulgaria"[tiab] OR "Bulgarian"[tiab] OR "Croatia"[tiab] OR "Croatian"[tiab] OR "Czech"[tiab] OR "Hungary"[tiab] OR "Hungarian"[tiab] OR "Macedonia"[tiab] OR "Macedonian"[tiab] OR "Moldova"[tiab] OR "Moldovian"[tiab] OR "Montenegro"[tiab] OR "Montenegran"[tiab] OR "Poland"[tiab] OR "Polish"[tiab] OR "Republic of Belarus"[tiab] OR "belarian"[tiab] OR "Romania"[tiab] OR "Romanian"[tiab] OR "Russia"[tiab] OR "Russian"[tiab] OR "Serbia"[tiab] OR "Serbian"[tiab] OR "Slovakia"[tiab] OR "Slovakian"[tiab] OR "Slovenia"[tiab] OR "Slovenian"[tiab] OR "Ukraine"[tiab] OR "Ukrainian"[tiab] OR "Yugoslavia"[tiab] OR "Yugoslavian"[tiab] OR "Finland"[tiab] OR "Finnish"[tiab] OR "France"[tiab] OR "French"[tiab] OR "Germany"[tiab] OR "German"[tiab] OR "Gibraltar"[tiab] OR "Gibraltarian"[tiab] OR "Great Britain"[tiab] OR "British"[tiab] OR "United Kingdom"[tiab] OR "Greece"[tiab] OR "Greek"[tiab] OR "Iceland"[tiab] OR "Icelandic"[tiab] OR "Ireland"[tiab] OR "Irish"[tiab] OR "Italy"[tiab] OR "Italian"[tiab] OR "Liechtenstein"[tiab] OR "Luxembourg"[tiab] OR "Luxembourgian"[tiab] OR "Monaco"[tiab] OR "Monegasque"[tiab] OR "Netherlands"[tiab] OR "dutch"[tiab] OR "Portugal"[tiab] OR "Portuguese"[tiab]

Attachment II: Table 1. Characteristics national databases/cohorts.

National databases by country	Funding	Aims Primary	Aims Secondary	Size, RA patients (N)	Year of inception	Physician/clinical evaluation	Patient reported outcomes	Articles/ abstracts published (N)	Connected to the EULAR
Germany									
Rabbit (German Biologics Register)[14]	3	1		Ongoing, 12.303	2001	DAS28, SJC28, TJC28, morning stiffness	FFbH, VAS (general health, pain, fatigue)	20	Yes
National database of the German Collaborative Arthritis Centers[13]	1	2	9, 3, 10	Ongoing 5-17.000 py	1993	Severity of disease, VAS (global), DAS28, SJC28, TJC28	FFbH, VAS (pain, global)	26	Yes
United Kingdom									
BSRBR (British Society for Rheumatology RA Register)[12]	3	1	9, 7	Ongoing ~ 20.000	2001	DAS28, SJC28, TJC28, clinical questionnaire	HAQ, SF-36, patient questionnaire	44	Yes
ERAN (Early RA Network cohort)[27]	5	3	10, 1	Ongoing, 1.180	2002	DAS28, SJC28, TJC28, VAS (global), morning stiffness	HAQ, SF-36, VAS (global)	5	Yes
ERAS (Early RA Study)[33]	2	3	2, 4, 9, 7	Ongoing, 1.460	1986	SJC, TJC, RAI	HAQ, VAS (pain, global)	12	Yes
Norfolk ArthritisRegister(NOAR)[17]	2	4	2, 6	ongoing, 1.745	1989	SJC, TJC, DAS, DAS28, TJC28, SJC28	HAQ, SF-36	32	Yes
Scotland									
Sera (Studies of the Etiology of RA)	4	7		Ongoing, 1.800	2010/ 2011	DAS, SJC, TJC, VAS (global)	HAQ, VAS (pain, global)	0	No

National databases by country	Additional (labs/ radiographies/ imaging)	Drug treatment recorded	Frequency of data collection (mo)	Selection criteria for enrollment into registry	Control group	Rheumatic diseases captured
Germany						
Rabbit (German Biologics Register)[14]	ESR, CRP, RF	cs or bDMARDs NSAIDs, glucocorticoids	Every 0, 3, 6, 12, until 120	RA, start bDMARDs	conventional DMARD	Early and established RA, AS, PsA
National database of the German Collaborative Arthritis Centers[13]	ESR/CRP, RF	cs or bDMARDs Glucocorticoids	continuous	inflammatory rheumatic disease in daily practice	General population/ patients of same Rheumatology unit	Early/ established RA, other rheumatologic diseases
United Kingdom						
BSRBR (British Society for Rheumatology RA Register)[12]	ESR/CRP	cs or bDMARDs NSAIDs	Every 0, 6, 12, 18, 24, 30, 36, then annually	RA starting b or csDMARD.	Active RA patients treated with csDMARDs.	Early/ established RA and other rheumatologic diseases
ERAN (Early RA Network cohort)[27]	RF, erosions, X-rays, ESR/CRP	DMARDs	Every 0,3, 6, then annually	Newly diagnosed RA patients in routine care	General population/ patients of same Rheumatology unit	Early RA
ERAS (Early RA Study) [33]	ESR, RF erosions	Second line drugs or DMARDs	Annually	RA symptom > 2yr, no use of second line drugs	Patients not fulfilling 1987 revised ACR criteria for RA	Early RA
Norfolk Arthritis Register (NOAR)[17]	X-rays, Larsen, CRP, RF, CCP	-	Annually	Patient ≥16 years, ≥2 inflamed joints ≥4weeks.	Not reported	Early/ established RA
Scotland						
Sera (Studies of the Etiology of RA)	ESR/CRP, laboratory serum	Not reported	Not reported	Newly diagnosed RA/UA	Not reported	Early RA/UA

National databases by country	Funding	Aims Primary	Aims Secondary	Size, RA patients (N)	Year of inception	Physician/ clinical evaluation	Patient reported outcomes	Connected to the EULAR	Articles/ abstracts published (N)
Portugal									
Reumapt. (Rheumatic Diseases Portuguese Register)[25]	3	3		Ongoing, ~2.500	2008	DAS28, SJC28, TJC28, VAS (global)	VAS (pain, global), SF-36, HAQ	No	1
Finland									
rob-fin (National Register of Biological Treatment in Finland)[32]	3	1	9	Ongoing, <1.688	1999	TJC, SCJ, VAS (global)	HAQ, VAS (general, pain, global)	Yes	7
Sweden									
ARTIS (Swedish Biologics Register)[31]	3	1		Closed, 7.354	1998	DAS28, SJC28, TJC28, VAS	VAS (global, pain), HAQ	Yes	11
RAMONA (Swedish early RA register)[15]	1	3	2, 7	Closed, 6.745	1995	DAS28, SJC28, TJC28	HAQ	Yes	7
Swiss									
SCQM-RA (Swiss Clinical Quality Management program for RA)[18]	6	3	1, 7	Ongoing, 6.300	1997	DAS28, SJC28, TJC28	HAQ, RADAI	Yes	11

National databases by country	Additional (labs/ radiographies/ imaging)	Drug treatment recorded	Frequency of data collection (mo)	Selection criteria for enrollment into registry	Control group	Rheumatic diseases captured
Scotland						
Sera (Studies of the Etiology of RA)	ESR/CRP, laboratory serum	Not reported	Not reported	Newly diagnosed RA/UA	Not reported	Early RA/UA
Portugal						
Reumapt. (Rheumatic Diseases Portuguese Register)[25]	ESR/CRP, X-ray, SHS,CCP	cs or bDMARDs	Continuous	rheumatic patients receiving cs or bDMARDs	Not reported	Early RA/ established RA, AS, SPA and JIA
Finland						
rob-fin (National Register of Biological Treatment in Finland)[32]	ESR/CRP	cs or bDMARDs glucocorticoids,	Every 6	Active RA, DMARDs response not satisfied, start TNF blocker	RA patient using DMARD	Early/ established RA
Sweden						
ARTIS (Swedish Biologics Register)[31]	ESR/CRP	cs or bDMARDs NSAIDs, corticoids	Every 0, 3, 6, 12, 18, 24 after start bDMARD	RA patients starting biologics	Patients with RA/ comorbidity	Early/ established RA
RAMONA (Swedish early RA register)[15]	RF, ESR/CRP	DMARDs	Every 0, 3, 6, 12, 18 , 24 after start bDMARD	Diagnosis of RA < 12 mo after symptom onset	Patients with RA/ comorbidity	Early RA
Swiss						
SCQM-RA (Swiss Clinical Quality Management program for RA)[18]	ESR/CRP, radiograpy	cs or b DMARDs glucocorticoids	Continuous	patients receiving cs or bDMARDs	Patients receiving other drugs	Early/ established RA, AS, PsA

National databases by country	Funding	Aims Primary	Aims Secondary	Size, RA patients (N)	Year of inception	Physician/ clinical evaluation	Patient reported outcomes	Connected to the EULAR	Articles/abstracts published (N)
France									
ORA (Orencia and RA) [37]	3	1		Closed, 1.000	2008	DAS28,SJC28, TJC28	Not reported	No	1
ESPOIR (French Early Arthritis Cohort) [19]	5	4	5, 7, 9	Closed, 813	2002	TJC28, SJC28, DAS28, morning stiffness	HAQ	Yes	21
EMER study (medico-economic evaluation of infliximab)[20]	5	9		Not reported, 635	2001	VAS (global), DAS28, SJC28, TJC28	VAS (pain, global), HAQ, SF-36	No	1
AIR RA (autoimmunity and Rituximab in RA)[37]	3	4	2	Closed, 2.000	2005	DAS28, SJC28, TJC28	Not reported	No	2
Spain									
BIOBADASER (Spanish Registry of biological therapies in rheumatic diseases)[30]	5	1	2, 10	Closed, ~ 6.000	2000	Not reported	Not reported	Yes	10
EMECAR (Spanish RA Registry Cohort Study)[29]	5	8	2, 4	Closed, 789	1999	DAS28, SJC28, TJC28	MHAQ	Yes	6
SERAP (Evaluation of a Model for Arthritis Care in Spain)[22]	3	1	2, 5	Closed, 777	2004	DAS28, SJC28, TJC28, morning stiffness	HAQ	Yes	2

National databases by country	Additional (labs/ radiographies/ Imaging)	Drug treatment recorded	Frequency of data collection (mo)	Selection criteria for enrollment into registry	Control group	Rheumatic diseases captured
France						
ORA (Orencia and RA)[37]	ESR/CRP	cs or bDMARDs,	Every 0, 3, 6, then every 6	RA patients	Not reported	Early/ established RA
ESPOIR (French Early Arthritis Cohort)[19]	RF, erosions, CRP, CCP, immunologic/ biologic data	DMARDs	Every 0,6 and 12 for 10 years	Age 18-70, <2 TJC/SJC, 6 weeks to 6 mo RA or suspected RA, DMARD naïve	Not reported	Early RA
EMER study (medico-economic evaluation of infliximab)[20]	ESR/CRP	bDMARDs	2 years, Continuous	RA patients	Not reported	Early/established RA
AIR RA (autoimmunity and Rituximab in RA)[37]	RF, ESR/CRP	bDMARDs	<2 years, 7 treatments	RA patients	Not reported	Early/ established RA, SLE
Spain						
BIOBADASER (Spanish Registry of biological therapies in rheumatic diseases)[30]	ESR/CRP	cs or bDMARDs, NSAID	continuous	bDMARD users	EMECAR cohort	Early/ established RA and other rheumatic diseases
EMECAR (Spanish RA Registry Cohort Study)[29]	ESR/CRP, RF erosions, radiology	bDMARD, NSAID, glucocorticoids	continuous	RA patients	BIOBADASER cohort	Early RA
SERAP (Evaluation of a Model for Arthritis Care in Spain)[22]	CRP, ESR, RF factor	Not reported	Every 6	Suspected RA (<1 SJC; pain, morning stiffness <30 minutes), >16 years, first joint manifestation <6 months before study	Non RA patients	Early RA

National Databases by country	Funding	Aims Primary	Aims Secondary	Size, RA patients (N)	Year of inception	Physician/ clinical evaluation	Patient reported outcomes	Connected to the EULAR	Articles/ abstracts published (N)
Study of Ultrasound Group of the Spanish Society of Rheumatology [38]	3	3		Not reported, 367	2004	SJC28, TJC28, DAS28	HAQ, VAS (pain)	No	1
Denmark									
DANBIO (Danish Registry for Biologic Therapies in Rheumatology)[11]	3	1	4, 3	Closed, ~10.000	2000	DAS28, SJC28, TJC28, CDAI	HAQ, HR-QoL, VAS (pain, fatigue, global)	Yes	14
Norway									
Nor-DMARD (Norwegian register of DMARD prescriptions for patients with inflammatory arthropathies)[35]	5	1	3, 7	Closed, ~3.000	2000	DA2S28, SJC28, TJC28	VAS (pain, global, fatigue), HAQ, SF-36	No	4
Biorheuma (Biologic treatment of patients suffering from inflammatory Rheumatic disorders in Norway)	1	1		Closed, ~12.000	Not reported	DAS, SJC, TJC	VAS (pain, global)	No	0
Belgium/Luxembourg									
Mira registry Belgium/Luxembourg (MabThera In RA)[21]	3	1		Ongoing, approx. 40% of centers in Lux/Belg	2006	DAS28, SJC28, TJC28	VAS (global) HAQ, RADAI	No	2

National Databases by country	Additional (labs/radiographies/ Imaging	Drug treatment recorded	Frequency of data collection (mo)	Selection criteria for enrollment into registry	Control group	Rheumatic diseases captured
Study of Ultrasound Group of the Spanish Society of Rheumatology[38]	RF, ESR, CRP	cs or bDMARDs	Every 0, 3, 6 and 12	RA according to the 1987 criteria	Not reported	Early/ established RA
Denmark						
DANBIO (Danish Registry for Biologic Therapies in Rheumatology)[11]	Erosions, CRP, x-ray, sharp score	cs or bDMARDs	Continuous	rheumatic patients using bDMARDs	Rheumatic patients from the same department of rheumatology	Early/ established RA, AS, PsA
Norway						
Nor-DMARD (Norwegian register of DMARD prescriptions for patients with inflammatory arthropathies)[35]	CRP, ESR, IgM RF factor, erosions	cs or bDMARDs NSAIDs, glucocorticoids	Every 0, 3, 6, 12, then annually	All consecutive DMARD prescriptions in adult patients (³ 18 years) with inflammatory arthropathies	Not reported	Early/ established RA and other inflammatory arthropaties
Biorheuma (Biologic treatment of patients suffering from inflammatory Rheumatic disorders in Norway)	CRP/ESR	bDMARDs	Not reported	bDMARD users	Not reported	Early/ established RA and other inflammatory rheumatic disorders
Belgium/Luxembourg						
Mira registry Belgium/Luxembourg (MabThera In RA)21	ESR, RF, CCP	bDMARDs	Every 8 weeks	RA patients	Not reported	Early/ established RA

National Databases by country	Funding	Aims Primary	Aims Secondary	Size, RA patients (N)	Year of inception	Physician/ clinical evaluation	Patient reported outcomes	Connected to the EULAR	Articles/ abstracts published (N)
Belgium EAP (Belgian Expanded Access Program RA Study)[40]	3	3	1	Not reported, 511	2000	VAS (global), DAS28, SJC28, TJC28	HAQ, VAS (global)	No	1
Greece									
Hellenic biologic register[39]	3	1	3	Ongoing, ~ 1.100	2003	DAS, TJC, SJC	HAQ	No	3
Czech Republic									
Attra (Czech National Registry of biological treatments)[23]	1	1		Not reported, 1.700	2002	DAS, TJC, SJC, CDAI, VAS (global)	VAS (global)	No	7
Iceland									
Icebio (Iceland's biologics register)[34]	3	1	7	Ongoing, 214	Not reported	DAS, VAS (global), SJC, TJC	HAQ, VAS (global, pain)	No	2
Austria									
CARAbase (care for RA database)[24]	Not reported	3		Not reported	2002	DAS, CDAI, SDAI, TJC, SJC, VAS (global)	VAS (global)	No	0
Bio-reg (biologic register)	3	1	9	Not reported	2010	DAS, TJC, SJC, CDAI, VAS (global)	VAS (global) HAQ	No	0

National Databases by country	Additional (labs/ radiographies /imaging	Drug treatment recorded	Frequency of data collection (mo)	Selection criteria for enrollment into registry	Control group	Rheumatic diseases captured
Belgium EAP (Belgian Expanded Access Program RA Study)[40]	CRP, ESR, RF	cs or bDMARDs	Every 0, 2,6 weeks, then every 8 weeks	RA patients	Not reported	Established RA
Greece						
Hellenic biologic register[39]	ESR/CRP	bDMARDs	Continuous	RA, Spa patients	Not reported	Early/established RA, SPA
Czech Republic						
Attra (Czech National Registry of biological treatments)[23]	X-rays, CRP	cs or bDMARDs,	Continuous	Failure of 1 DMARD, DAS 28 > 5.1, no contraindication TNF	Not reported	Early/established RA, AS, PSA, JIA
Iceland						
Icebio (Iceland's biologics register)[34]	ESR/CRP, RF	bDMARDs	Continuous	Rheumatic diseases	Not reported	Early/established RA, PsA, SPA, SLE
Austria						
CARAbase (care for RA database)[24]	ESR,CRP	Cs or bDMARD	Continuous	RA	Not reported	Early/ established RA
Bio-reg (biologic register)	Radiologic progression, RF factor, CCP, CRP	bDMARDs	Every 6	Patients with inflammatory diseases	Not reported	Early/ established RA and other Inflammatory diseases

National Databases by country	Funding	Aims Primary	Aims Secondary	Size, RA patients (N)	Year of inception	Physician/clinical evaluation	Patient reported outcomes	Connected to the EULAR	Articles/ abstracts published (N)
Italy									
GISEA (Italian Group for the Study of Early Arthritis)[36]	4	1	2, 3	Ongoing, ~ 1.000	2003	DAS, SJC, TJC, (VAS global)	VAS (global)	No	1
GIARA (Italian registry of aggressive RA)[28]	3	2	3	Ongoing, 1.218	2001	DAS, SJC, TJC, VAS (global)	HAQ, VAS (global), SF-36	Yes	2

National Databases by country	Additional (labs/ radiographies/ imaging	Drug treatment recorded	Frequency of data collection (mo)	Selection criteria for enrollment into registry	Control group	Rheumatic diseases captured
Italy						
GISEA (Italian Group for the Study of Early Arthritis)[36]	ESR/CRP	bDMARDs	Every 6	Patients aged above 18	Not reported	Early/ established RA and other rheumatologic diseases
GIARA (Italian registry of aggressive RA)[28]	RF, CRP/ESR, erosions	DMARDs, NSAIDs, glucocorticoids,	Every 6	RA<5 years classified as having established RA	Not reported	Established RA

Funding: 1) government; 2) charity; 3) pharmaceutical industry; 4) other private sources; 5) Mixed, Aims 1) efficacy and safety of biological (or other) treatments; 2) determining epidemiological core data (Incidence or prevalence); 3) monitoring/benchmarking (disease activity) for clinical practice; 4) research aiming at outcome and prediction of outcome; 5) Registration of diagnoses, 6) registries aiming at natural course of the disease; 7) Research aiming to investigate causal mechanisms; 8) Study comorbidities; 9 Medio economic evaluation 10) Educational studies (e.g. implementation or recommendations), DAS=Disease Activity Score, HAQ=Health Assessment Questionnaire, SJC=swollen joint count, TJC=tender joint count, VAS=visual analogue scale, ESR=erythrocyte sedimentation rate, CRP=C-reactive protein, RF=Rheumatoid Factor, CCP=anti-cyclic citrullinated peptide, DMARDs=disease-modifying anti rheumatic drugs (b=biologic, cs=conventional), NSAIDs=nonsteroidal anti-inflammatory drugs, RA=rheumatoid arthritis, CDAI= Clinical Disease Activity Index, SDAI= Simplified Disease Activity Index.

Chapter 3

Intra articular injection with corticosteroids in patients with recent onset rheumatoid arthritis: subanalyses from the BeSt study

E. Gvozdenović, L. Dirven, M. van den Broek, K.H. Han, E.T.H. Molenaar, R. Landewé, W.F. Lems and C.F. Allaart.

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ABSTRACT

Objective

To investigate the association between intra-articular (IA) large joint corticosteroid injections and clinical outcomes in patients with recent onset rheumatoid arthritis (RA).

Methods

We compared pain (visual analogue scale (VAS)), the Disease Activity Score (44 joints) (DAS) and swollen and tender joint counts before and after IA injection. Using linear mixed models (LMM) the DAS and the Health Assessment Questionnaire (HAQ) score over time were compared in IA injected versus non-injected patients.

Results

In year 1, 93 joints were injected in 44 patients treated with initial methotrexate monotherapy, and 16 in patients treated with initial combination therapy ($p<0.01$). Three months later, swelling and tenderness were resolved in 50-58% of the injected joints but within 12 months after the injection, swelling recurred in 14% and tenderness in 41% of the injected joints. Mean (SD) DAS decreased from 4.0 (1.4) before to 3.2 (1.2) 3 months after injection ($p<0.01$) and VAS for pain from 49 (26) to 40 (27) ($p<0.01$). LMM showed a higher DAS and HAQ in patients injected in year 0-1 compared to those not injected, but no difference in subsequent years, and similar treatment adjustments. Eight year radiographs showed similar damage in injected joints (17%) and non-injected joints (14%).

Conclusion

IA corticosteroid injections are associated with symptom relief, sometimes only temporarily, in 50% of the cases. Initially DAS significantly improved, but over time DAS and HAQ were similar in injected versus non-injected patients. After 8 years there was no difference in joint damage.

INTRODUCTION

Inflammation of joints in rheumatoid arthritis (RA) causes pain and loss of physical function and eventually may result in joint destruction. Current treatment consist of disease-modifying anti rheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs (NSAIDs), biological agents and oral corticosteroids.[1] In addition, intra articular (IA) corticosteroid injections are given, mostly in the large joints, as local therapy to reduce pain and swelling.[2-6] In daily practice short term effect varies per patient due to accuracy and needle placement, type of corticosteroid, misdiagnosis of inflammation.[5,7,8] Long term, IA-injections in combination with DMARDs are suggested to have a positive effect on inflammation in RA. [9]

In the BeSt study, which compares 4 different treatment strategies aimed at a Disease Activity Score (DAS) =<2.4 in patients with recent onset RA, we investigated the association of IA-injections in the large joints with disease activity and functional ability in the first year and over 8 years of treatment including number of treatment adjustments and radiological damage at year 8.

METHODS

Patients

The BeSt is a multicenter trial including 508 patients with recent onset RA (1987 classification criteria) between April 2000 and August 2002. More details are described elsewhere.[10] In all four groups, IA injections were allowed at the rheumatologists' discretion. Intra muscular injections were not allowed. For the current analysis patients who received IA injections in the large joints during the first year, and patients who did not were compared. Early (3 months after IA injection), short term (from t=1 year to t=2 years) and long term (between t=2 years and t=8 years) outcomes were measured every three months using the three monthly swollen and tender joint counts, a visual analogue scale (VAS in mm, 0=best, 100=worst) for pain, the DAS, with local swelling (based on a 44 joint count) and tenderness (measured in 51 joints with the Ritchie Articular Index), and functional ability (Health Assessment Questionnaire HAQ).[11] Radiological damage defined as a Larsen score >=1 and the number of treatment adjustments (made when three monthly DAS as measured by trained nurses was >=2.4) were used as secondary outcome measure in the analyses.

Statistical analyses

Descriptive analyses using X^2-test for categorical data and analysis of variance (ANOVA) or Kruskal-Wallis test for continuous data were performed, depending on normal distribution of the tested variable. Short term associations of IA injections were tested with a paired T-test. Aiming to correct for patient selection resulting in IA injected patients being more likely have more active RA, we used propensity scoring.[12] The propensity model included the following covariates: gender, age at inclusion, body mass index (BMI), rheumatoid factor (RF) status; anti-cyclic citrullinated peptide (ACPA) status; baseline total Sharp van der Heijde Score (SHS), DAS, HAQ, treatment strategy, swollen joint count, tender joint count, patient's assessments of global disease activity and pain on a visual analogue scale (VAS) and doctor's VAS for disease activity. The propensity score showed moderate to good discrimination, the area under the receiver operating characteristic (ROC) curvewas 0.73 (95% confidence interval 0.67-0.80). HAQ and DAS over time in injected and non-injected patients, adjusted for propensity score and follow-up time, were compared using a linear mixed-effects model (LMM) analysis. Logistic regression was performed to analyze the association of IA injections on radiological damage after 8 years, corrected for the propensity score. Univariate linear model building was used to measure the association between injections (yes/no) on the number of high DAS44 steered treatment adjustments within the treatment arms (post-hoc test). Software program SPSS version 17.0 was used for the analyses; p-values were reported two-sided and p-values smaller than 0.05 were considered statistically significant.

RESULTS

Of the 508 patients, 60 patients (12%) were injected in one or more large joints (n=93) during the first year of treatment, 42 (60%) of whom were women. At baseline, patients who would receive IA injections had a significantly higher mean DAS, HAQ, number of swollen and tender joints than the non-injected patients (table 1).

Of the injected joints, 32 (34%) were knees, 29 (31%) shoulders, 19 (20%) wrists, 7 (8%) ankles, 5 (5%) elbows and 1 (1%) hip. Depending on preference in the participating hospitals, 47 (52%) joints were injected with triamcinolonacetonide (Kenacort), 12 with methylprednisolone (Depo-medrol) (13%) and 32 (35%) with triamcinolonhexacetonide (Lederspan).

Table 1. Baseline characteristics in injected patients versus the rest of the patients.

	IA-injection during first year, n=60	**No IA injection during first year, n=447**	**p-value**
Women, n (%)	42 (60)	301 (67)	0.66
Age (years), mean (SD)	55 (14)	54 (13)	0.64
BMI, mean (SD)	26 (4)	26 (4)	0.37
Symptom duration (wks) median (IQR)	21 (12 to 57)	24 (14 to 53)	0.46
ACPA positive, n (%)	34 (57)	266 (62)	0.15
RF positive, n(%)	39 (65)	290 (65)	0.97
Smoking, n (%)	35 (58)	292 (66)	0.26
Alcohol, n (%)	33 (55)	229 (52)	0.64
DAS_{44}, mean (SD)	4.7 (0.8)	4.4 (0.9)	<0.01
HAQ, mean (SD)	1.6 (0.6)	1.4 (0.7)	<0.01
VAS pain, mean (SD)	58 (25)	53 (21)	0.10
VAS disease activity (patient) mean (SD)	65 (21)	59 (22)	0.07
VAS morning stiffness, mean (SD)	62 (23)	59 (24)	0.48
VAS general well-being, mean (SD)	55 (19)	52 (20)	0.19
Swollen joint count large joints, mean (SD)	3.7 (1.9)	3.0 (1.9)	<0.01
Tender joint count large joints, mean (SD)	5.4 (2.6)	4.7 (2.7)	0.05
VAS disease activity (physician), mean (SD)	62 (17)	56 (18)	0.06
Treatment strategy, n (%)			<0.01
Sequential monotherapy	21 (35)	105 (23)	
Step-up combination therapy	23 (38)	98 (22)	
Initial combination with prednisone	5 (8)	128 (29)	
Initial combination with infliximab	11 (18)	111 (25)	

n=number, SD=standard deviation, IQR = interquartile range, BMI= body mass index, ACPA = anti−citrullinated protein antibody, RF = rheumatoid factor, DAS44= Disease Activity Score in 44 joints, HAQ= Health Assessment Questionnaire, VAS = visual analogue scale

Recurrence of symptoms was similar after these types of injections (data not shown). Significantly ($p<0.01$) more injected patients, n=44, had been allocated to initial monotherapy in strategy arms 1 and 2 than to the initial combination therapy in strategy arms 3 and 4 (n=16) (Figure1).

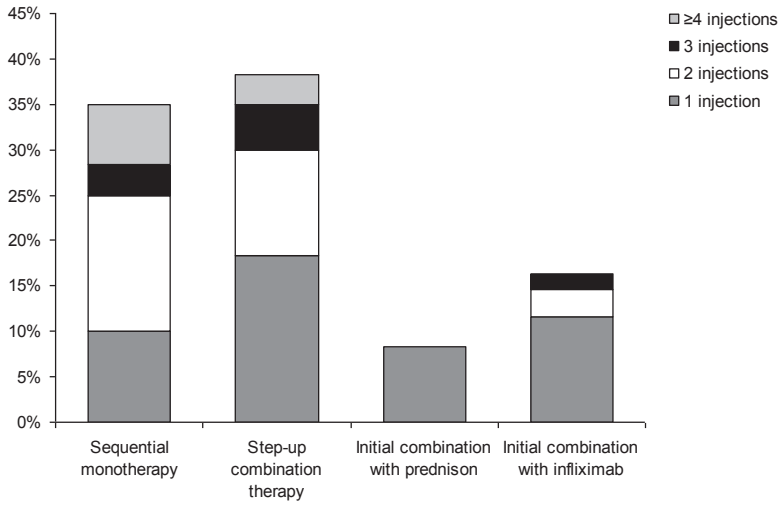

Figure 1. Percentage of injected joints in patients per treatment group.

Pre-injection, local joint swelling as assessed by the study nurses was present in 41 (46%) of injected joints, local tenderness in 56 (63%), and both local tenderness and joint swelling in 31 (36%) of the injected joints. 24 joints were deemed by the research nurse to be neither swollen nor tender. Three months after the first injection, 27(50%) of the swollen joints were no longer swollen and 23 (58%) of the tender joints were no longer tender. Mean (SD) DAS before and 3 months after IA injection was 4.0 (1.4) and 3.2 (1.2), respectively ($p<0.01$) and VAS for pain before and 3 months after IA injection was 49 (26) and 40 (27), respectively ($p<0.01$).

Within 12 months after the injection, swelling recurred in 3/12 (14%) of the resolved swollen joints after injection and tenderness recurred in 11/27 (41%) of the resolved tender joints after injection.

Seventeen joints were injected twice in the first year of treatment. Three months after the second injection, 3/9 of the tender joints were no longer tender, and 2/6 of the swollen joints were no longer swollen. Five joints were injected a third time, resulting in non-tenderness three months later in 1/5. In 10 (38%) of the injected patients that reached a DAS44 =<2.4 in the first year, no systemic treatment adjustment occurred. During year 0-1, IA injected patients had a higher DAS44 than non-injected patients, mean (95% CI) 3.66 (3.48 to 3.84) versus 2.80 (2.73 to 2.87) and higher HAQ 0.96 (0.84 to 1.08) versus 0.78 (0.74 to 0.82)

($p<0.01$), after propensity scoring. However these were less than the minimal clinically significant difference.[13, 14] Between t=1 year and t=2 years, and between t=2 years and t=8 years, there were no significant differences in DAS and HAQ over time between injected and non-injected patients (Figure 2).

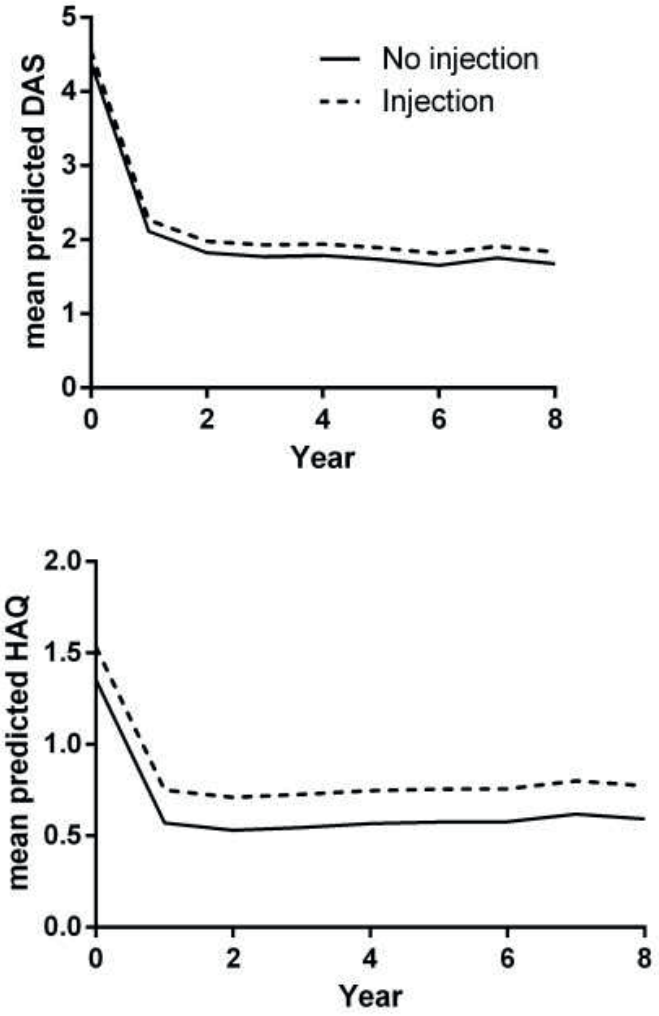

Figure 2. Predicted mean HAQ (Health Assessment Questionnaire and mean DAS44 (Disease activity score in 44 joints) based on a linear mixed models analysis in injected patients versus non injected patients during the eight years of follow-up.

From baseline until year 8, the number of treatment steps taken in the four strategy groups was similar in the injected patients and the non-injected patients (table 2).

Radiographs, assessed at t=8 years in the BeSt protocol, were available for 51% (n=46) of the injected joints, and 53% (n=3179) of the non-injected joints, in 28 (47%) injected and 262 (58%) non-injected patients.

Radiological damage was present in 17% (n=8) of the radiographs of injected joints, and in 14% (n=453) of the radiographs of non-injected joints. Since there were no baseline radiographs, progression could not be scored. On patient level, no significant (p=0.67) association between IA injection and damage was present, adjusted for propensity score (OR: 0.82, 95% CI 0.33 to 2.03).

Table 2. Univariate linear model showing number of treatment steps after 8 years for injected versus non injected patients, per treatment strategy.

	Injected in the first year (yes/no)		
	Yes	**No**	**p-value**
Sequential monotherapy,	3.7	2.3	0.10
mean (95% CI)	(2.02 to 4.43)	(1.38 to 3.35)	
Step-up combination therapy,	3.5	2.4	0.12
mean (95% CI)	(1.99 to 5.08)	(1.40 to 3.46)	
Initial combination with prednisone, mean	1.0	1.7	0.49
(95% CI)	(-0.99 to 2.98)	(1.10 to 2.30)	
Initial combination with infliximab,	1.0	2.2	0.14
mean (95% CI)	(-0.50 to 2,47)	(1.66 to 2.76)	

CI=confidence interval.

DISCUSSION

In recent onset RA patients, randomized in the BeSt study to start treatment with either methotrexate mono-or with combination therapy, intra-articular corticosteroid injections were allowed at the discretion of the rheumatologists. Joint swelling and tenderness outcomes were assessed at 3-monthly intervals by trained nurses who calculated the Disease Activity Score (DAS). The 12% injected patients improved in clinical outcomes (VAS pain, DAS, HAQ)

after three months and a year after injection. Local swelling resolved in 50% and tenderness in 58% of injected joints, but within 12 months recurred in 14% of previously swollen and 41% of previously tender injected joints. Injected patients had a higher baseline DAS and HAQ, and were more often randomized to the initial monotherapy arms of the BeSt trial. These arms overall required more treatment adjustments than the initial combination therapy arms in year 1. After propensity scoring to correct for differences between the injected and non-injected patients using, we found that in the years following the injections there were no significant differences in DAS and HAQ over time between injected and non-injected patients. Also number of three-monthly treatment adjustments that were required if DAS was >=2.4 were similar between injected and non-injected patients within the treatment strategies over 8 years. In the linear mixed model analysis, IA injections were not associated with DAS and HAQ reduction in the subsequent years after IA injection.

Our data suggest that IA injections are associated with short term symptom relief in patients with early RA. Assuming that injected patients had more active disease than non-injected patients, IA injections in year 1 also seem to be associated with suppression of disease activity in the longer term, as injected and non-injected patients had over time similar disease activity and functional ability, required similar number of systemic treatment adjustments and had similar prevalent local joint damage at t=8 years.

One may argue that an early success rate of 50% to 58% of a local anti-inflammatory treatment is disappointing, in particular when symptoms sometimes rapidly return. Although previously described[15] we found no association between recurrence of symptoms and type of corticosteroid used for the injections. However, incorrect placement of some injections, which in our study were almost all given blind, may have occurred. Previous studies have shown that 'blind' injections are misplaced in 18-63% of cases.[16, 17] However, some reports described that incorrect located injection still results in local symptom relief.[18] Furthermore, the treating rheumatologists may have injected joints that were most severely or persistently inflamed and were less likely to show a complete and lasting immediate response. Since our study relies on joint assessments from study nurses (unaware of treatment strategy) rather than those of treating rheumatologists, some discrepancies may be explained. On the other hand, some joints injected might not have been inflamed with rheumatoid arthritis. The fact that some were injected more than once and never responded might also indicate non-inflammatory osteoarthritis or cuff lesions.

The BeSt protocol required radiographs to be taken of all large joints after 8 years, but was found only available in 51% of the injected joints (and 53% of non-injected joints). We cannot verify if damage was already present at baseline, which might have triggered the injections, nor can we evaluate whether damage has developed or progressed over time in relation to the injections. The fact that damage was found in 17% of available injected joints and in 14% of available non-injected joints suggests that injected joints do not have more damage than non-injected joints, and that the injections at least were not detrimental to the integrity of the joints. A further limitation of the study was the incomplete data on intra articular injections in the years 2-8. We estimate that this occurred less often than in year 1, as during treat-to-target therapy, in the majority of patients disease activity was well suppressed,[19, 20] and few joints in year 1 were repeatedly injected, but we verify this for lack of details. The small number of injections the second and the third time and the available data of swollen and tender joints 1 year after injection may be a limitation in itself.

In conclusion, rheumatologists injected large joints with corticosteroids predominantly in recent onset RA patients with high disease activity, resulting in an adequate local response in about 50% of the injected joints. Joint swelling recurred within 1 year in only 14% which suggests that in early RA, joint injections with corticosteroid are associated with symptom relief and adequate suppression of local inflammation. Overall DAS and HAQ were reduced and over following years similar to DAS and HAQ in non-injected patients, and the numbers of three-monthly systemic treatment adjustments in this treat to target study were similar. Finally, radiographs of injected versus non-injected joints at 8 years suggests that there is similar damage in these joints. Thus, IA injections might provide both short and long term benefit.

REFERENCE LIST

1 Smolen, JS, Landewé R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann rheumc dis*, 2010. **69**(6): p. 964-975.

2 Bouysset, M., Hugueny, B Gintz, et al. Corticosteroid injections and synoviortheses of the foot and ankle in rheumatoid arthritis. *J Foot Ankle Surg*. 2006: p. 123-130.

3 Hollander JL. Intra-articular hydrocortisone in the treatment of artrhtis. *Ann Intern Med*. 1953. 39(4): p. 735.

4 Hollander, JL, Brown EM, Jessar RA, et al. Hydrocortisone and cortisone injected into arthritic joints. *J Am Med Assoc*. 1951. 147(17): p. 1629.

5 Ostergaard M, Halberg P. [Intra-articular glucocorticoid injections in joint diseases]. *Ugeskr Laeger*, 1999. 161(5): p. 582.

6 Daley EL, Bajaj S, Bisson LJ et al. Improving Injection Accuracy of the Elbow, Knee, and Shoulder. *Am J Sports Med*. 2011. 39(3): p. 656-662.

7 Jones A, Regan M, Ledingham J, et al. Importance of placement of intra-articular steroid injections. *BMJ*, 1993. 307(6915): p. 1329-1330.

8 Vermeulen HM, Breedveld FC, Le Cessie S, et al. Responsiveness of the shoulder function assessment scale in patients with rheumatoid arthritis. *Ann rheum dis*. 2006. 65(2): p. 239-241.

9 Hetland ML, Stengaard-Pedersen K, Junker P, et al. Aggressive combination therapy with intra-articular glucocorticoid injections and conventional disease-modifying anti-rheumatic drugs in early rheumatoid arthritis: second-year clinical and radiographic results from the CIMESTRA study. *Ann rheum dis*. 2008. 67(6): p. 815.

10 Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum*, 2005. 52(11): p. 3381-3390.

11 Siegert CE, Vleming LJ, Vandenbroucke JP, et al. Measurement of disability in Dutch rheumatoid arthritis patients. *Clin Rheumatol.* 1984. 3(3): p. 305-309.

12 D'Agostino RB. Tutorial in biostatistics: Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med.* 1998. 17(19): p. 2265-2281.

13 Felson DT, Anderson JJ, Boers M,et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum*. 2005. 38(6): p. 727-735.

14 Wolfe F, Michaud K, Strand V. Expanding the definition of clinical differences: from minimally clinically important differences to really important differences. Analyses in 8931 patients with rheumatoid arthritis. *J rheumatol.* 2005. 32(4): p. 583-589.

15 Blyth TJ, Hunter J, Stirling A. Pain relief in the rheumatoid knee after steroid injection a

single-blind comparison of hydrocortisone succinate, and triamcinolone acetonide or hexacetonide. *Rheumatology*, 1994. 33(5): p. 461-463.

16 Eustace JA ,Brophy DP, Gibney RP, et al. Comparison of the accuracy of steroid placement with clinical outcome in patients with shoulder symptoms. *Ann rheum dis*, 1997. 56(1): p. 59-63.

17 Eustace JA, Brophy DP, Gibney RP, et al. Accuracy of intra-articular injections in peripheral joints performed blindly in patients with rheumatoid arthritis. *Rheumatology*. 2008. 47(12): p. 1792-1794.

18 Hartung W. Comment on: Ultrasound-guided sacroiliac joint injection in patients with established sacroiliitis: precise IA injection verified by MRI scanning does not predict clinical outcome: response. *Rheumatology*. 2012. 51(6): p. 1138-1139.

19 Van den Broek, M, Dirven L, Kroon HM,et al. Early Local Swelling and Tenderness Are Associated with Large-joint Damage After 8 Years of Treatment to Target in Patients with Recent-onset Rheumatoid Arthritis. *J rheumatol.* 2013. 40(5): p. 624-629.

20 Van den Broek M, , Dirven L, Klarenbeek NB, et al. The association of treatment response and joint damage with ACPA-status in recent-onset RA: a subanalysis of the 8-year follow-up of the BeSt study. *Ann rheum dis.* 2012. 71(2): p. 245-248.

Chapter 4

Assessment of global disease activity in RA patients monitored in the METEOR database: The patient's versus the rheumatologist's opinion

E. Gvozdenović, R. Koevoets, R. Wolterbeek, D. van der Heijde, T.W.J. Huizinga, C.F. Allaart, R Landewé.

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ABSTRACT

Objective

To compare the patient's (PtGDA) and physician's (PhGDA) assessment of global disease activity and to identify factors that might influence these differences, as well as factors that may influence the patients and the physicians score separately.

Methods

Anonymous data were used from 2.117 Dutch patients included in the METEOR database. PtGDA and PhGDA were scored independently on a 100mm visual analogue scale (VAS) with 0 and 100 as extremes. The agreement, Intraclass correlation coefficients (ICC), was calculated and a Bland Altman plot was created to visualize the differences between PtGDA and PhGDA. Linear Mixed Model analysis was used to model PtGDA and PhGDA. Logistic repeated measurements were used to model the difference in PtGDA and PhGDA (PtGDA>PhGDA vs. PtGDA≤PhGDA). Gender patient, gender physician, age, swollen joint count, tender joint count, VAS pain, disease duration and ESR were considered as possible determinants in both models.

Results

Mean (SD) age was 57 (15) years and 67% of the patients were female. Agreement between PtGDA and PhGDA was moderate (ICC: 0.57). Patients scored on average 11 units higher (worse) than rheumatologists (95% limits of agreement: -25.2 to 47.6). Patient's perception of pain (VAS) was positively associated with a PtGDA being higher than PhGDA. Similarly, ESR and swollen joint counts were positively associated with a PtGDA being lower or equal to the PhGDA.

Conclusion

Patients rate global disease activity consistently higher than their rheumatologists. Patients base their judgment primarily on the level of pain; physicians on the level of SJC and ESR.

INTRODUCTION

The importance and use of patient reported outcomes (PROs) in health care increased during the past decades. PROs are considered valuable in measuring status and change in health care.[1] However, in addition to the PRO, similar information is also collected by the physician, e.g. assessment of level of disease activity. As patients and physicians may differ in their perception of health status, discordant observations may occur and may affect patient care. For example, patients are likely to report dissatisfaction with a treatment if their physician underestimates their perceived level of disease activity.[2-4] The 100mm visual analogue scale (VAS) is an instrument used to measure global disease activity (GDA) in rheumatoid arthritis (RA). It can be completed by the patient (PtGDA) (and is considered then a PRO) as well as by the physician (PhGDA). Discordances between patients and rheumatologists rating their impression of GDA on a VAS have been reported; patients tend to score their GDA higher than their physician. Determinants reported to be of influence on the discrepancies between patients' and physicians' perceptions are pain, swollen joint count, tender joint count and erythrocyte sedimentation rate.[5-7] However, the magnitude and direction of the influence of these factors is unclear. A determinant, to our knowledge not studied yet, which might be of influence on the difference between physicians' and patients' perception is the gender of the physician. This might be a plausible factor of difference in score since male and female physician perceptions differ in clinical practice regarding communication of information, compliance and satisfaction of the patient.[8]

The METEOR (Measurement of efficacy of Treatment in the Era of Rheumatology) database provides data on several patient- and physician-reported outcome measures in RA, including gender of the rheumatologist. Here we have compared PtGDA and PhGDA reported in individual patients, and identified which factors determined the discordance in PtGDA and PhGDA.

METHODS

Patients

Data collected in the ongoing prospective international METEOR database were used. METEOR is an acronym for Measurement of efficacy of Treatment in the Era of Rheumatology hat has been started in 2008. METEOR is used by rheumatologists to monitor patients with rheumatic diseases. Data are collected in a central database in a completely

anonymous way. Both newly diagnosed patients and patients with more advanced disease are included in de database. Measures of disease activity and Health Assessment Questionnaire data are registered every visit. Currently, the tool is used worldwide and data is available from 100 hospitals, which included more than 14.800 patients. More details on the METEOR database are described elsewhere.[9]

A sample of 2.117 Dutch patients was taken from the METEOR database covering the time span between 2008 and 2011. The number of visits (8.509 in total) varied with a range of 1 to 19 visits per patient as did time intervals between visits. PtGDA and PhGDA were measured on a 100mm visual analogue scale (VAS) with 0 (best possible) and 100 (worst possible) as extremes. PtGDA and PhGDA separately were operationalized as continuous variables. The 20mm difference between PtGDA and PhGDA was used as a binary outcome variable (patient scores higher versus rheumatologist scores equal or higher). A difference in rating of 20mm between PtGDA and PhGDA score was chosen as cut-off value, since it is considered to be a frequent chosen value for minimum clinically important improvement in PtGDA.[5]

Statistical analyses

Descriptive statistics were performed using the mean and standard deviation (SD) or median and interquartile ranges (IQR) as appropriate for continuous variables, and number and percentages for categorical variables. A Bland and Altman plot was performed to visualize the differences between PtGDA and PhGDA. This is based on the standard deviation of the differences in PtGDA and PhGDA calculated from variance components in a linear mixed model (LMM), and used to construct the 95% limits of agreement.[9] The agreement between patient and physician was expressed as intraclass correlation coefficient (ICC) using variance components in a LMM with a random intercept for patients. LMM was also used to model the PtGDA and PhGDA. Gender patient, gender rheumatologist, age, swollen joint count, tender joint count, pain (VAS), disease duration (diagnosis until first visit) and erythrocyte sedimentation rate (ESR) were considered as possible determinants for the model. Furthermore LMM was used to estimate means of DAS28, ESR, tender and swollen joint count between male and female. Non-linear mixed modelling (repeated measures logistic regression) was used to model the difference in PtGDA and PhGDA as binary outcome (patient's score higher than physician's score as "event"). Gender patient, gender rheumatologist, age, swollen joint count, tender joint count, pain (VAS), disease duration and ESR were considered as possible determinants for the model. Software programs SAS

version 9.2 and SPSS version 17.0 were used for the analyses and p-values smaller than 0.05 were considered statistically significant.

RESULTS

Of the 2.117 patients, 1.338 (67%) were female. The mean (SD) age at entry was 57 (15) years (table 1).

Table 1. Baseline characteristics (Visit 1)

Variables	Patient	n total (n=2.117)
Age (years), mean (SD)	57 (15)	1879
Patient female, n (%)	1339 (67)	2007
Physician female, n (%)	1072 (67)	1598
CRP, median (IQR)	5 (3 to 13)	167
ESR, median (IQR)	14 (6 to 29)	1491
DAS 28, mean (SD)	3.2 (1.4)	1408
HAQ, median (IQR)	0.7 (0.1 to 1.4)	573
Duration complaints until diagnosis (months), median (IQR)	4 (1 to 12)	855
Duration complaints until first visit in METEOR (years), median (IQR)	6 (1 to 14)	862
Duration diagnosis until first visit in METEOR (years), median (IQR)	3 (0 to 11)	996
CCP positive, n (%)	215 (64)	334
RF positive, n (%)	734 (77)	959
Erosions present, n (%)	605 (66)	923
Swollen joint count 28, median (IQR)	1 (0 to 3)	1799
Tender joint count 28, median (IQR)	2 (0 to 4)	1799
VAS (visual analogue scale), median (IQR)		
Global disease activity physician	21 (10 to 41)	903
Global disease activity patient	34 (14 to 55)	1615
Pain patient	39 (15 to 60)	1474

n=number, SD=standard deviation, IQR= interquartile range, CRP=C-reactive protein, ESR= erythrocyte sedimentation rate, DAS28=Disease Activity Score 28 joints, HAQ= Health Assessment Questionnaire, CCP=cyclic cictrullinated ceptide antibody, RF=rheumatoid factor.

978 of the observed patient scores were higher (20mm) compared to the physicians score, 2.747 of patients and physicians score where concordant (-20 mm until 20 mm) and 102 patients score were lower (20 mm) than the physician's score.

Agreement between PtGDA and PhGDA was moderate (ICC: 0.57; p<0.01; 95% limits of agreement: -25.2 to 47.6). Patients rated their GDA on average 11mm higher (worse) than rheumatologists at the first registered visit. A few scores (n=19) showed a discrepancy between the PtGDA and PhGDA of 70 or more (patient scored higher) (figure 1).

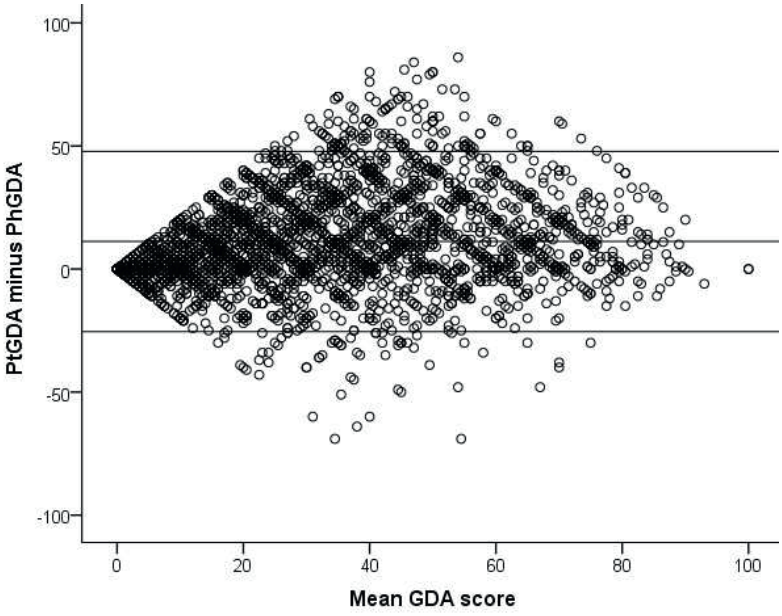

Figure 1. Bland and Altman's plot; global disease activity patient (PtGDA) versus global disease activity physician (PhGDA)

Both patients and physicians scored the GDA significantly higher when the number of tender joints, number of swollen joints, and VAS pain was higher (p<0.01). Furthermore, a higher ESR (p<0.01) and male gender (p=0.02) were independently associated with a higher GDA score by the physician. Physician's scores decreased by increasing disease duration (p=0.01). The gender of the physician was not associated with the GDA score by physician or patient (table 2). Pain (VAS), ESR and the number of swollen joints all independently were

Table 2. Linear mixed model predictors of global disease activity by patients (PtGDA) and physicians (PhGDA)

	PtGDA		PhGDA	
Variable	**Estimate β, (95% CI)**	**p-value**	**Estimate β, (95% CI)**	**p-value**
Patient male	0.82 (-0.47 to 2.11)	0.21	1.86 (0.32 to 3.39)	0.02
Physician male	0.58 (-0.55 to 1.71)	0.31	1.21 (-0.18 to 2.60)	0.09
Age (years)	0.01 (-0.04 to 0.05)	0.82	-0.05 (-1.00 to 0.01)	0.08
Disease duration (years)	-0.05 (-0.12 to 0.01)	0.12	-0.10 (-0.17 to -0.02)	0.01
ESR	0.02 (-0.01 to 0.05)	0.82	0.11 (0.07 to 0,14)	<0.01
Swollen joint count 28	0.87 (0.60 to 1.15)	<0.01	3.24 (2.91 to 3.57)	<0.01
Tender joint count 28	0.41 (0.22 to 0.61)	<0.01	0.75 (0.49 to 1.01)	<0.01
VAS pain patient	0.72 (0.69 to 0.74)	<0.01	0.29 (0.26 to 0.32)	<0.01

CI=Confidence interval, β = beta, VAS=visual analogue scale, ESR= erythrocyte sedimentation rate.

associated with the difference between patient's GDA and physician's GDA score. Patient scored GDA higher than their physician by increasing VAS pain (p<0.01); and physician scored GDA higher than the patient by increasing swollen joint count and ESR (p<0.01). Gender of the patient or gender of the physician did not have an effect on the difference between patient's GDA and physician's GDA score (table 3).

Table 3. Non-linear mixed model predictors of global disease activity (GDA) difference between patients and physicians.

	PtGDA (n=978) versus PhGDA (2747)*	
Variable	**Estimate β, (95% CI)**	**p-value**
Patient male	-0.06 (-0.49 to 0.38)	0.79
Physician male	0.17 (-0.23 to 0.59)	0.40
Age (years)	0.00 (-0.01 to 0.02)	0.42
Disease duration (years)	0.00 (-0.02 to 0.02)	0.65
ESR	-0.02 (-0.03 to -0.00)	<0.01
SJC28	-0.38 (-0.53 to -0.22)	<0.01
TJC28	-0.06 (-0.14 to 0.12)	0.14
VAS pain patient	0.08 (0.05 to 0.11)	<0.01

*1= patient scores higher, 0= physician scores equal or higher; Reference category=0, VAS=visual analogue scale, ESR= erythrocyte sedimentation rate, CI=Confidence interval, β=beta.

Mean ESR and TJC28was lower in male patients compared to female patients (p=0.02). Also DAS28 was lower in male patients (p<0.01) (table 4).

Table 4. Linear mixed models for means of DAS and DAS components between man and women

	Male	**Female**	
	Mean (95% CI)	**Mean (95% CI)**	**p-value**
DAS28	2.8 (2.7 to 2.9)	3.1 (3.07 to 3.2)	<0.01
ESR	17.9 (16.5 to 19.3)	20.0 (19.3 to 21.0)	0.02
Swollen joint count 28	1.6 (1.5 to 1.8)	1.5 (1.42 to 1.63)	0.38
Tender joint count 28	2.3 (2.1 to 2.5)	2.6 (2.5 to 2.8)	0.02

DAS28=Disease Activity Score for 28 joints, ESR= erythrocyte sedimentation rate, CI=confidence interval.

DISCUSSION

On average, patients tend to score GDA systematically higher than rheumatologists. The agreement between patients and rheumatologists is only moderate. Physicians and patients both take into consideration tender joint count, swollen joint count and pain in their assessment of GDA. In addition, when rating GDA, the physician is influenced by the gender of the patient, disease duration and ESR. The difference in GDA score between patient and physician can best be explained by differences in pain, swollen joint count and ESR. Physicians put more weight on the value of ESR and SJC, whilst patients put more weight on pain.

Patients and physicians take partly the same determinants in consideration when they assess global disease activity. The physician takes both ‘objective’ (swollen joint count, acute phase reactants and disease duration) and ‘subjective’ (patients’ pain and tender joint count) variables into account when assessing the GDA. Furthermore, physicians tend to rate GDA in male patients higher than in female patients. The latter finding might be related to the difference in perception of disease activity between male and female patients, since male patients tend to underestimate their disease activity compared to female patients.[7] In our study male patients have indeed lower DAS and fewer tender joints when compared to female patients, while the number of swollen joints does not differ. This finding provides

input to the suggestion that the physician may implicitly compensate for this difference by rating disease activity in higher than in female.

The different factors patients and physician taken into consideration for their GDA assessment might be the explanation for the systematic difference in patients and physicians scores of almost 11 units (on a scale from zero to 100) and to the only moderate agreement between patients and physicians. Other studies also have reported discordances between patients and physicians in rating the GDA. Barton et al. showed that patients' GDA score was on average 15 points higher than the physicians' mean GDA score.[10]Also, the QUEST-RA study showed a higher mean GDA of patients (approximately 11 points) than GDA of physicians.[5] In concordance with the latter study, we also found a difference of approximately 11 points. However, it is questionable if 11 points is a clinical relevant discrepancy between patient' and physician' GDA score since we defined 20 points to be a difference. On the other hand, the moderate agreement between patients and physicians might support that patients and physicians rate RA disease activity differently. This confirms the statement of an earlier study that patient and physicians differ in perception of disease activity.[6] A previous study, carried out in several European countries, also showed only a moderate agreement between GDA patient and GDA physician.[5] Other studies, performed in the United States and in Europe showed low correlations and low agreement between physician and global health assessments.[11,12] The discrepancies between the results of previous studies might suggest differences between countries in GDA of patient and physician due to cultural factors.

Our study shows that the difference in scoring might be explained by differences in the perception of ESR, swollen joints and pain. Pain is more likely to be associated with an equal or higher score of the patient. This statement was confirmed by the large QUEST-RA study, which studied factors on discordance between GDA of the patient and that of the physician. Pain was one of the most important factors that caused discordances. Pain increased significantly when patient scored GDA higher compared to the physician. Furthermore, the QUEST-RA also used 20mm difference in GDA score as the cut off value of a true difference between patient and physician.[5]

In our study, patients with a high ESR and swollen joint count are more likely to be scored higher by the physician. A previous study confirms this result.[10] Another study showed that, besides swollen joints, physician put more weight on ESR than patients.[6]

As we can see from the results of our study, patients and physicians focus on different factors when assessing disease activity. Patients are more influenced by subjective feelings, such as

pain, while physicians base their score more on objective measures, such as number of swollen joints and 'blood levels'. This is supported by previous literature.[13] Patients base their assessments on needs, priorities, experiences, expectations and attitude, which are all subjective domains. Physicians, on the other hand, rely on the patient's physical health status, which is considered more objective in nature.[14,15]

This study has some limitations. The first is missing values, as these might not be randomly missing. Patients that perform worse in their opinion may stay at home and miss an appointment with the physician. This can result in selection of patients with unknown consequences. Another limitation is that the included patients were not always newly diagnosed RA patients. Some patients are already treated for years and patients expectations and perceptions can change as a result of improvement or worsening of their health.[16] Therefore, long treatment duration might influence patient's assessment of GDA.

In conclusion, patients and physicians both assess GDA using partly similar determinants. Differences in GDA scores may be explained by pain, ESR and swollen joint count. Patients put more weight on pain and physicians on ESR and swollen joint count. Also cultural differences may have contributed to the moderate level of agreement between patients and physicians. We already see a difference in agreement between patient's and physician's score by comparing studies performed in several countries. In clinical practice, it should be recommended to spend more time educating patients on how to rate the global disease activity. Patients need to be clearly informed on the difference between the disease activity and pain, as patients let pain influence their GDA score. A good understanding of the GDA score by the patient is important since a previous study showed that patients with a high PtGDA score, while having a normal ESR and low SJC and TJC, are not in remission.[17] Further research should be conducted to find out what the clinical impact is of these discrepancies between patients and physicians since previous research might suggest that treatment strategy is only based on the rheumatologist's opinion and not on the patient's opinion or the DAS28.[18] Also differences in PtGDA and PhGDA score per country should be studied and whether GDA assessment is influenced by cultural factors.

REFERENCE LIST

1 Otter SJ, Lucas D, Springett K, et al. Identifying Patient-Reported Outcomes in Rheumatoid Arthritis: The Impact of Foot Symptoms on Self-Perceived Quality of Life. *Musculoskelet. Care* 10 (2012); 65–75.

2 Hewlett SA. Patients and clinicians have different perspectives on outcomes in arthritis. *J Rheumatol.* 2003; 30 (4) :877-9.

3 Suarez-Almazor ME, Conner-Spady B, Kendall CJ, et al. Lack of congruence in the ratings of patients' health status by patients and their physicians. *Med Decis Making*. 2001; 21(2): 113-21.

4 Wartman SA, Morlock LL, Malitz FE et al. Impact of divergent evaluations by physicians and patients of patients' complaints. *Public Health Rep*. 1983; 98(2):141-5

5 Khan NA, Spencer HJ, Abda E, et al. Determinants of discordance in patients' and physicians' rating of rheumatoid arthritis disease activity. *Arthritis Care Res (Hoboken)*. 2012; 64(2): 206-14.

6. Nicolau G, Yogui MM, Vallochi TL, et al. Sources of discrepancy in patient and physician global assessments of rheumatoid arthritis disease activity. *J Rheumatol.* 2004; 31(7): 1293-6.

7. Sokka T, Toloza S, Cutolo M, et al. Women, men, and rheumatoid arthritis: analyses of disease activity, disease characteristics, and treatments in the QUEST-RA study. *Arthritis Res Ther.* 009; 11(1): R7

8 Weisman CS,Teitelbaum MA. Physician gender and the physician-patient relationship: recent evidence and relevant questions. *Soc Sci Med.* 1985; 20(11):1119-27.

9 Foti C, Cisari C, Carda S, et al. A prospective observational study of the clinical efficacy and safety of intra-articular sodium hyaluronate in synovial joints with osteoarthritis. *Eur J Phys Rehabil Med.* 2011; 47(3):407-15

10 Barton JL, Imboden J, Graf J, et al. Patient-physician discordance in assessments of global disease severity in rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2010; 62(6):857-64

11 Kwoh CK, O'Connor GT, Regan-Smith MG, et al. Concordance between clinician and patient assessment of physical and mental health status. *J Rheumatol.* 1992;19(7):1031-7

12 Ward M. Clinical measures in rheumatoid arthritis: which are most useful in assessing patients? J *Rheumatol.* 1994; 21(1):17-27

13 Neville C, Clarke AE, Joseph L, et al. Learning from discordance in patient and physician global assessments of systemic lupus erythematosus disease activity. *J Rheumatol.* 2000; 27(3) :675-9.

14 Liang M, Cullen K and Larson M. In search of a more perfect mousetrap (health status or quality of life instrument). *J Rheumatol*. 1982;9(5): 775-9.

15 Pincus T, Summey JA, Soraci SA Jr, et al. Assessment of patient satisfaction in

activities of daily living using a modified Stanford Health Assessment Questionnaire. *Arthritis Rheum.* 1983; 26(11): 1346-53

16 Ward MM. Rheumatology care, patient expectations, and the limits of time. *Arthritis Rheum.* 2004; 51(3):307-8

17 Vermeer M, Kuper HH, van der Bijl AE, et al. The provisional ACR/EULAR definition of remission in RA: a comment on the patient global assessment criterion. *Rheumatology (Oxford).* 2012; 51(6): 1076-80

18 Pyne L, Bykerk VP, Boire G, et al. Increasing Treatment in Early Rheumatoid Arthritis Is Not Determined by the Disease Activity Score But by Physician Global Assessment: Results from the CATCH Study. *J Rheumatol.* 2012; 39(11) :2081-7

Chapter 5

Assessment of global disease activity in RA by patients and physicians: differences across countries in the METEOR database

E. Gvozdenović, R. Wolterbeek, C.F. Allaart, G.C. Brenol, M. Dougados, P. Emery, G.F. Ferraccioli, D. van der Heijde, T.W.J. Huizinga, J. Kay, E. Martin Mola, R.J. Moots, J.A.P da Silva, J.S. Smolen, D. Veale, R. Landewé.

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ABSTRACT

Objective

To compare the differences between patient (Pt) and physician (Ph) global disease activity score (GDA) within and across 13 countries in the Measurement of efficacy of Treatment in the 'Era of outcome' in Rheumatology (METEOR) database.

Methods

Data from METEOR were used to compare PtGDA and PhGDA, scored independently on a 100 mm visual analogue scale (VAS) from 0 (best possible) until 100 (worst possible), in 23.117 visits in 5.709 anonymized patients during the period between 2008 and 2012. Linear Mixed Models (LMM) were used to model mean differences between PtGDA and PhGDA in 13 countries (Brazil, Czech, France, Ireland, Italy, Latvia, Mexico, the Netherlands, Pakistan, Portugal, Spain, United Kingdom and the United States), adjusted for differences in DAS28. Generalized Estimating Equation (GEE) were used to model differences (>20mm) between PtGDA and PhGDA score as the outcome and countries as determinants, adjusted for DAS28.

Results

Mean difference between PtGDA and PhGDA score varied by country, from -2mm (physician scores higher) in Mexico to +14mm (patient scores higher) in Brazil. 'Country' was a significant determinant of the difference between PtGDA and PhGDA score, independent of differences in DAS28. With Netherlands as reference, PtGDA and PhGDA scores for individual patients differ significantly in almost all (n=10) countries, with the exception of France and Spain.

Conclusion

Differences between patients' and physicians' assessment of global disease activity vary across the countries. Influence of country must be taken into account when interpreting discordances between the patient's and the physician's assessment of global disease activity in RA.

INTRODUCTION

The use of patient reported outcomes is valuable when measuring status and change in health care.[1] Both the patient's perception and the physician's assessment of the disease play an important role in making treatment decisions and achieving therapeutic goals. However, discordances in the patient's and physician's assessment of health status may adversely affect patients care.[2-5] In rheumatoid arthritis (RA), the visual analogue scale (VAS) is used to rate global disease activity (GDA) on a scale from 0 to 100 millimeter (0 representing best, 100 representing worst). The VAS can be used either as a patient reported outcome (patient GDA, PtGDA) or as a physician reported outcome (physician GDA, PhGDA).

Previous studies have shown that patients and rheumatologists may differ in rating their impression on a GDA scale. These studies have suggested that patients tend to score GDA higher than their physicians, which suggests that patients and physicians take into account different factors when rating global disease activity.[6-12]

However, it is not well known whether the country in which patient and physician live influences the discrepancy in GDA assessment. Differences between PtGDA and PhGDA may for example be dependent on the language used by patient and physician, but also on differences in the physician-patient relationship across different cultures.[13,14]

The Measurement of efficacy of Treatment in the 'Era of outcome' of Rheumatology (METEOR) initiative has developed an online database that provides an easy to use program to register clinical data of RA patients monitored in daily practice. Anonymized data uploaded by participating rheumatologists in 13 countries on three continents were used to compare the mean differences between PtGDA and PhGDA within and across the Netherlands and 12 other countries on three continents.

METHODS

A cross-sectional study was conducted to investigate the influence of country on the difference between PtGDA and PhGDA. We used data from the METEOR database, a worldwide online tool for disease monitoring in RA. Clinical data on anonymized patients with newly diagnosed and patients with established RA of 26 countries and 81 hospitals are collected in this central database until 6 July 2012. A more detailed description of the METEOR database was published previously.[11,15]

For the current analysis, we selected countries for which at least 100 patient visits had been recorded in METEOR between 1 January 2008 and 6 July 2012: Brazil, Czech Republic, France Ireland, Italy, Latvia, Mexico, the Netherlands, Pakistan, Portugal, Spain, United Kingdom and the United States. There were 23.117 visits of 5.709 patients, ranging from 108 to 6.718 visits per country and from 1 to 29 visits per patient containing both PtGDA and PhGDA scores. Patients rated the PtGDA and physicians rated the PhGDA on a 100mm VAS scale. The order in which the PtGDA and PhGDA were to be scored was not specified.
A difference of ≥20mm between PtGDA and PhGDA score was chosen as cut-off value for clinically relevant differences between patient and physician score and was dichotomously (yes versus no) evaluated.[11] Country was defined as a categorical variable with Netherlands as a reference category, because it has provided the highest number (n=6.272) of patient data. We adjusted for DAS28 (based on four variables) status at the time of the visit, since disease activity can be a determinant of a difference between PtGDA and PhGDA.[10,11] 'Short' or 'long' disease duration was categorized according to the median disease duration of 2 years in this study and definitions in previous studies.[16,17]

Statistical analysis

A Bland and Altman plot was performed to visualize the differences between PtGDA and PhGDA among countries. A multilevel approach was followed to allow for the correlation between multiple visits within a subject. Mean GDA (the average of PtGDA and PhGDA) and the mean differences between PtGDA and PhGDA for each country were estimated using linear mixed models (LMM). LMM were also used to estimate the mean difference between PtGDA and PhGDA for gender and for disease duration stratified per country. Generalized estimated equations (GEE) were used to model a difference of 20 mm between PtGDA and PhGDA, with 'country' as a determinant and the Netherlands as reference category, adjusted for DAS28. Software program SPSS version 17.0 was used for the analyses and p-values smaller than 0.05 were considered statistically significant.

RESULTS

The numbers of PtGDA and PhGDA assessments (respectively) per country were as follows: Brazil: 1.220 and 1.195; Czech: 487 and 460; Spain: 238 and 244; France: 522 and 412; United Kingdom: 1.730 and 148; Ireland: 656 and 534; Italy: 3.987 and 3.747; Latvia: 135

and 110; Mexico: 570 and 563; Netherlands: 17.923 and 6.804; Pakistan: 267 and 264, Portugal: 8.772 and 5.966; and United States: 2.025 and 1.939. Overall, patients scored GDA higher than physicians, resulting in an overall mean difference (mean (95% CI)) between PtGDA and PhGDA of +9 mm (95% CI: 8.9 to 9.4) (Patients score higher). Figure 1 shows the distribution of mean differences between PtGDA and PhGDA per country as a function of mean GDA in that country. The difference in scores between patient and physician was highest in Brazil (+14 (12.5 to 16.2) mm) while Mexico was the only country in which average PtGDA was lower than the average PhGDA (-1 9 (-4.8 to +2.6) mm).

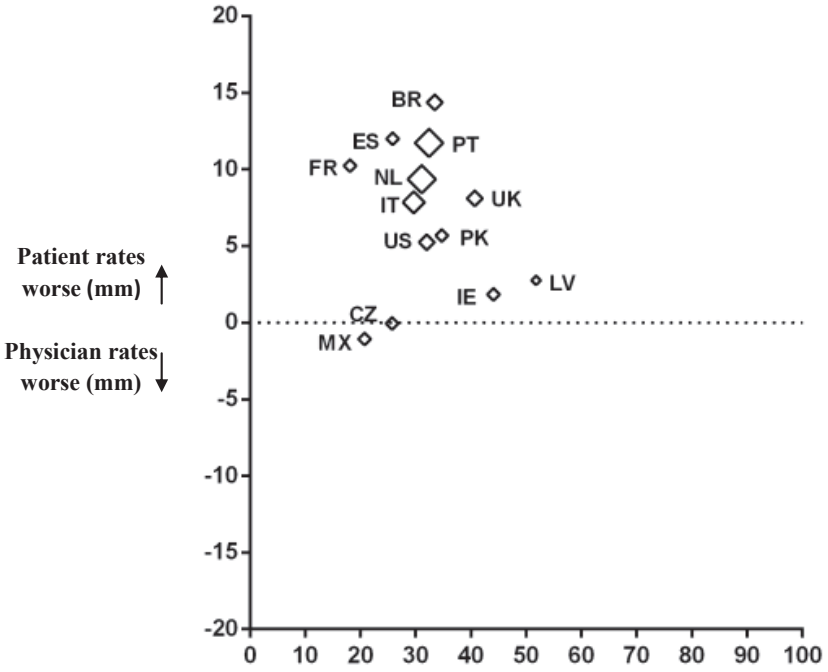

Figure 1. Crude Mean difference (mm) between patient (PtGDA) and physician (PhGDA) global disease activity score per country.

BR=Brazil, ES=Spain, PT=Portugal, NL=Netherlands, IT=Italy, US=United States, UK=United Kingdom, PK=Pakistan, CZ=Czech, MX=Mexico, FR=France, IE=Ireland, LT=Latvia. The size of the bubble is a reflection of the number of available visits.

Latvia was the country with the highest mean values of both patient and physician GDA scores (51.8 (45.6 to 58)). Absolute mean values of PtGDA and PhGDA were lowest in Mexico (20.7 (15.2 to 26.2)) and in France (18.1 (15.2 to 21.1)). The differences between PtGDA and PhGDA stratified for males and females are shown in table 1.

Table 1. Mean difference (mm) between patient (PtGDA) and physician (PhGDA) global disease activity score for men and women stratified by country

	PtGDA minus PhGDA		
Country	**Male**	**Female**	**p-value**
	Mean (95% CI)	**Mean (95% CI)**	
Brazil	14.1 (6.7 to 21.4)	14.4 (11.5 to 17.3)	0.93
Czech	-1.4 (-5.7 to 3.0)	0.65 (-2.5 to 3.8)	0.46
Spain	7.9 (1.0 to 14.7)	12.9 (9.3 to 16.5)	0.20
France	7.6 (3.3 to 11.8)	11.27 (8.9 to 13.7)	0.14
United Kingdom	5.4 (3.3 to 7.6)	8.9 (7.7 to 10.1)	<0.01
Ireland	1.8 (-1.5 to 5.1)	1.6 (-0.3 to 3.5)	0.93
Italy	5.8 (3.9 to 7.6)	8.0 (7.1 to 8.9)	0.04
Latvia	-1.6 (-9.6 to 6.6)	3.9 (1.1 to 6.7)	0.12
Mexico	-1.3 (-9.9 to 7.2)	0.2 (-1.3 to 1.7)	0.73
Netherlands	7.7 (6.8 to 8.7)	10.2 (9.5 to 10.8)	<0.01
Pakistan	6.5 (-2.1 to 15.0)	5.7 (2.17 to 9.2)	0.86
United States	4.7 (2.2 to 7.1)	5.4 (4.0 to 6.8)	0.63
Portugal	10.2 (8.1 to 12.2)	12.0 (11.2 to 12.9)	0.10
Overall	**6.9 (6.2 to 7.6)**	**9.3 (8.9 to 9.7)**	**<0.01**

CI=confidence interval.

Physicians rated disease activity on average 6.9 (6.2 to 7.6) mm lower than male patients and 9.3 (8.9 to 9.7) mm lower than female patients. We were not informed about the gender of the

rating rheumatologist. The overall difference between men and women was statistically significant ($p<0.01$). Within countries, the difference between physicians and female patients is numerically higher than the difference between physicians and male patients. This was true for all countries except Ireland and Pakistan. These discrepancies reach statistical significance for the UK, the Netherlands and Italy. The overall mean difference between PtGDA and PhGDA also differed significantly for patients with 'short' vs. those with 'long' disease duration (table 2).

Table 2. Mean difference (mm) between patient (PtGDA) and physician (PhGDA) global disease activity score for disease duration in years stratified by country

	PtGDA minus PhGDA		
Country	**Dis Dur ≤2 year, mean (95% CI)**	**Dis Dur >2 year, mean (95% CI)**	**p-value**
Brazil	11.4 (6.0 to 16.9)	15.9 (12.6 to 19.1)	0.12
Czech	-1.2 (-4.5 to 3.0)	-	-
Spain	8.9 (0.5 to 17.3)	12.2 (6.6 to 17.7)	0.52
France	4.7 (-4.5 to 13.8)	10.7 (8.4 to 12.9)	0.21
United Kingdom	3.7 (-0.1 to 7.5)	9.0 (6.8 to 11.1)	0.02
Ireland	1.0 (-2.3 to 4.2)	3.50 (0.8 to 6.2)	0.23
Italy	7.1 (5.6 to 8.6)	6.7 (5.8 to 7.6)	0.58
Latvia	-0.5 (-6.3 to 5.3)	2.8 (-5.2 to 10.7)	0.47
Mexico	-1.8 (-4.3 to 0.9)	-	-
Netherlands	9.8 (7.8 to 11.8)	8.8 (7.5 to 10.0)	0.37
Pakistan	9.1 (3.4 to 14.7)	4.3 (0.3 to 8.4)	0.18
United States	8.2 (5.5 to 10.9)	2.4 (0.4 to 4.4)	<0.01
Portugal	11.2 (8.8 to 13.5)	12.4 (11.5 to 13.3)	0.31
Overall	**6.9 (6.0 to 7.9)**	**9.1 (8.6 to 9.6)**	**<0.01**

CI=confidence interval. Dis Dur=disease duration

Patients with a short disease duration scored on average 6.9 (6.0 to 7.9) mm higher than their physician, while patients with a longer disease duration scored on average 9.3 (8.9 to 9.7) mm higher than their physician ($p<0.01$) for the difference between short and long disease duration). Within the countries, significant differences between short and long disease duration in PtGDA versus PhGDA score were present in the UK and in the United States. In the UK, differences between PtGDA and PhGDA were smaller when disease duration was short (3.7, (-0.1 to 7.5) mm) compared to long (9.0 (6.8 to 11.1) mm). In the United States the opposite was observed: differences between PtGDA and PhGDA were on average smaller when disease duration was long (2.4 (0.35 to 4.4) mm), as compared to short (8.2 (5.5 to 10.9) mm).

Table 3. Difference (20mm) between patient (PtGDA) and physician (PhGDA) global disease activity score (yes/no), comparison between countries*

	Difference present (n=6.190) versus difference absent (n=14.684)			
Country, visits (n)	PtGDA higher	PhGDA higher	OR (95% CI)	p-value
Brazil (958)	342 (36)	71 (7)	1.63 (1.33 to 2.00)	<0.01
Czech (457)	60 (13)	46 (10)	0.70 (0.53 to 0.93)	0.01
Spain (193)	47 (24)	2 (1)	0.92 (0.62 to 1.37)	0.69
France (396)	106 (27)	2 (0)	1.18 (0.91 to 1.54)	0.22
United Kingdom (1.076)	221 (21)	28 (3)	0.61 (0.51 to 0.73)	<0.01
Ireland (475)	59 (13)	39 (8)	0.59 (0.46 to 0.76)	<0.01
Italy (3.414)	742 (22)	99 (3)	0.75 (0.65 to 0.88)	<0.01
Latvia (105)	6 (6)	5 (5)	0.17 (0.07 to 0.40)	<0.01
Mexico (445)	31 (7)	30 (7)	0.37 (0.26 to 0.52)	<0.01
Pakistan (160)	44 (28)	23 (14)	1.70 (1.13 to 2.56)	0.01
Portugal (5.526)	1837 (33)	207 (4)	1.35 (1.22 to 1.50)	<0.01
United States (1.397)	280 (20)	77 (6)	0.85 (0.72 to 1.00)	0.05

* Reference category= Netherlands (n visits=6.272), corrected for DAS28 (Disease Activity Score for 28 joints), n=number, CI=confidence interval, OR=Odds Ratio.

In databases of the Czech Republic and Mexico, only patients with short disease duration were recorded in the METEOR database. In both of these countries, physicians scored global disease activity on average higher than the patients. Table 3 shows, by country, the likelihood (in odds ratios) that a difference in GDA between physician and patient of more than 20mm was found, relative to the Netherlands corrected for DAS28. Among RA patients from the Netherlands who enrolled in the METEOR database, 28% of the visits showed a discrepancy of at least that magnitude. In Brazil, Pakistan and Portugal the likelihood of a discrepancy of at least that magnitude was higher than in the Netherlands, whereas in the UK, Ireland, Italy, Latvia, Mexico, Czech Republic and the United States this likelihood was lower. Table 3 also shows the number of times that the patient scored higher (20mm) than the physician and vice versa per country. In all countries it was more frequent that PtGDA is higher (20mm) than PhGDA.

DISCUSSION

The analyses described in this study report the influence of country of residence on the comparison of patients' and physicians' assessments of global disease activity in RA. While we have investigated already such differences in the Netherlands only,[11] we now have described patterns in 13 different countries all over the world. In these countries, the patient usually rated his or her global disease activity to be worse than did the assessing physician.
With the Netherlands as reference, we found clinically relevant differences between physicians' and patients' ratings in almost all countries, except for France and Spain. The magnitude to which these patient-reported and physician-reported GDA deviates varies per country. Gender differences seem to contribute, reaching statistical significance in Italy, Netherlands and the United Kingdom. The relationship between disease duration and patient/physician discrepancy is more heterogeneous across countries but may also contribute to overall differences between countries.

Since DAS28 is likely to be associated with a difference between PtGDA and PhGDA, we adjusted for DAS28. Even after correction, country of residence appeared to be a determinant of discrepancy in assessment of global disease activity between patient and physician, making it more likely that there is a true country-specific influence. Our finding that the difference between PtGDA and PhGDA varies by country has important implications. Multi-national observational studies, in which patient-reported outcomes are analyzed, may be

interpreted in the context of cultural differences between countries, or alternatively in the context of ethnicity.[18] This is in line with findings in some previous studies. It has been shown that the disease burden by patients differs per country.[19-22] Several studies have demonstrated a large variation between countries in the prevalence of low back pain and chronic pain.[19] Gureje et al. showed that the prevalence of chronic pain is relatively high in South American countries, such as Brazil, compared to Asian countries.[19] Besides, RA-patients may have concomitant fibromyalgia syndrome that may explain excess of pain.[24,25] In our study, Brazil was the country with the largest differences between patient's and physician's GDA score. Patients scored on average 14 mm higher than their physician, which might share similar origins with the higher prevalence of chronic pain in Brazil.[26] Along similar lines, patients from the Mediterranean have been shown to report more pain than patients living in Northern and Western Europe.[27] The findings of our study show similar trends: a greater discrepancy between PtGDA and PhGDA, resulting from patients scoring higher disease activity than their physicians, was observed in Portugal and Spain than in Ireland and the United Kingdom. These differences in patient-reported vs physician-assessed disease burden is difficult to explain. Cross-cultural differences may play a role, just as ethnic differences. Alternatively, different expectations about the disease RA between physicians and patients may play a role.[28]

In three countries we have also found associations between gender and the differences in GDA scores between patients and their physicians. In the United Kingdom, the Netherlands and Italy the discrepancy between PtGDA and PhGDA was significantly higher for women than for men, while the direction of the difference was the same in males and females (patients scored higher than physicians). In each of the other 10 countries these gender differences were not statistically significant, but were in the same direction in all countries except Ireland and Pakistan. Pooling the data of all 13 countries resulted in statistically significant gender associations. These associations pertained to small effects (differences of +2mm) but at least suggest that the country where patient and physician reside should be taken into account when comparing gender differences in GDA assessment. We should further not rule out measurement error as potential explanations when looking at such small differences. Previous studies have also suggested gender differences with regard to patient reported outcomes in multiple countries. In general, female patients often report more pain and higher disease activity compared to men, both within- and across countries.[29]

We found longer disease duration to be associated with different patient's and physician's GDA assessment in two countries; The United States and the United Kingdom. Further

studies should elucidate if this association is true (and requires explanation) or based on statistical artifacts. As said, pooling the data of all 13 countries yielded a mean difference of only 2 mm, which appears not to be very important, especially since the differences within countries are heterogeneous.

A strength of this study was the availability of a large number of patients and visits, which increases the power of the study. A limitation is the cross-sectional nature of the study, which does not allow to assess cause and effect. In addition, PtGDA and PhGDA were not assessed independently, which may have influenced the differences in scores between countries. Also, the patients entered into the METEOR database do not represent a random sample of the population of RA patients in each country. The number of visits available for analysis varied by country from 105 to 6.200, which might result in less reliable conclusions drawn from data collected in countries in which there were only small numbers of visits. Furthermore, data of physical functioning and comorbidities, which may also influence the perception of GDA (by patient and physician), were often not reported in METEOR and could not be adjusted for. A last limitation to be mentioned is that PtGDA and PhGDA in this database with data obtained in regular clinical practice (without pre-specified protocol) may not have been obtained independently; the physician most often must have been aware of the patient's judgement when giving his own judgement. This is inherent to common clinical practice and, even though it may decrease rather than increase a difference between PtGDA and PhGDA, precludes a robust scientific explanation for the observed differences.

In conclusion, differences between patient's and physician's assessment of global disease activity are partly dependent on the country in which the patient and the physician reside. In some countries, these differences are related to gender and disease duration, while this is not so obvious in others. Our findings may have implications for generalizing international data. There may be restrictions as to what extent we can combine and interpret data obtained in different countries. The influence of country must be further investigated and taken into account when interpreting discordances between the patient's and the physician's assessment of global disease activity in RA and perhaps also when incorporating these scores into recommendations regarding decision algorithms on medication use, such as Treat-to-Target strategies.

REFERENCE LIST

1 Otter SJ, Lucas K, Springett K, et al. Identifying patient-reported outcomes in rheumatoidarthritis: the impact of foot symptoms on self-perceived quality of life. *Musculoskeletal Care*. 2012;10:65-75.

2 Agrawal H, Hay MC, Volkmann ER, et al. Satisfaction and access to clinical care in a rheumatology clinic at a large urban medical center. *J Clin Rheumatol*. 2012;18:209-211.

3 Hewlett SA. Patients and clinicians have different perspectives on outcomes in arthritis. *J Rheumatol*. 2003;30:877-879.

4 Suarez-Almazor ME, Conner-Spady B, Kendall CJ, et al. Lack of congruence in the ratings of patients' health status by patients and their physicians. *Med Decis Making*. 2001;21:113-121.

5 Wartman SA, Morlock LL, Malitz FE, et al. Impact of divergent evaluations by physicians and patients of patients' complaints. *Public Health Rep*. 1983;98:141-145.

6 Ward MM. Clinical measures in rheumatoid arthritis: which are most useful in assessing patients? *J Rheumatol*. 1994;21:17-27.

7 Sokka T, Toloza S, Cutolo M, et al. Women, men, and rheumatoid arthritis: analyses of disease activity, disease characteristics, and treatments in the QUEST-RA study. *Arthritis Res Ther*. 2009;11:R7.

8 Nicolau G, Yogui MM, Vallochi TL, et al. Sources of discrepancy in patient and physician global assessments of rheumatoid arthritis disease activity. *J Rheumatol*. 2004;31:1293-1296.

9 Kwoh CK, O'Connor GT, Regan-Smith MG, et al. Concordance between clinician and patient assessment of physical and mental health status. *J Rheumatol*. 1992;19:1031-1037.

10 Khan NA, Spencer HJ, Abda E, et al. Determinants of discordance in patients' and physicians' rating of rheumatoid arthritis disease activity. *Arthritis Care Res*. (Hoboken) 2012;64:206-214.

11 Gvozdenovic E, Koevoets R, Wolterbeek R, et al. Assessment of global disease activity in RA patients monitored in the METEOR database: the patient's versus the rheumatologist's opinion. *Clin Rheumatol*. 2014;33:461-466.

12 Markenson JA, Koenig AS, et al. Comparison of physician and patient global assessments over time in patients with rheumatoid arthritis: a retrospective analysis from the RADIUS cohort. *J Clin Rheumatol*. 2013;19:317-323.

13 Barton JL, Imboden J, Graf J, et al. Patient-physician discordance in assessments of global disease severity in rheumatoid arthritis. *Arthritis Care Res (Hoboke*n). 2010;62:857-864.

14 Ferguson WJ, Candib LM. Culture, language, and the doctor-patient relationship. *Fam Med*. 2002;34:353-361.

15 Koevoets R, Allaart CF, van der Heijde DM, et al. Disease activity monitoring in rheumatoid arthritis in daily practice: experiences with METEOR, a free online tool. *J Rheumatol*. 2010;37:2632-2633.

16 Banal F, Dougados M, Combescure C, et al.: Sensitivity and specificity of the American College of Rheumatology 1987 criteria for the diagnosis of rheumatoid arthritis according to disease duration: a systematic literature review and meta-analysis. *Ann Rheum Dis*. 2009;68:1184-1191.

17 Hawley DJ, Wolfe F. Sensitivity to change of the health assessment questionnaire (HAQ) and other clinical and health status measures in rheumatoid arthritis: results of short-term clinical trials and observational studies versus long-term observational studies. *Arthritis Care Res*. 1992;5:130-136.

18 Yazici Y, Kautiainen H, Sokka T: Differences in clinical status measures in different ethnic/racial groups with early rheumatoid arthritis: implications for interpretation of clinical trial data. *J Rheumatol*. 2007;34:311-315.

19 Gureje O, Von Korff M, Simon GE, et al. Persistent pain and well-being. *JAMA: the journal of the American Medical Association*. 1998;280:147-151.

20 Sanders SH, Brena SF, Spier CJ, et al. Chronic low back pain patients around the world: cross-cultural similarities and differences. *Clin J Pain*. 1992;8:317-323.

21 Bates MS, Edwards WT, Anderson KO. Ethnocultural influences on variation in chronic pain perception. *Pain*. 1993;52:101-112.

22 Edwards RR, Doleys DM, Fillingim RB, et al. Ethnic differences in pain tolerance: clinical implications in a chronic pain population. *Psychosom Med*. 2001;63:316-323.

23 Coggon D, Ntani G, Palmer KT, et al. Disabling musculoskeletal pain in working populations: is it the job, the person, or the culture? *Pain* 2013;154:856-863.

24 Wolfe F, Michaud K. Severe rheumatoid arthritis (RA), worse outcomes, comorbid illness, and sociodemographic disadvantage characterize ra patients with fibromyalgia. *J Rheumatol*. 2004; 31:695-700.

25 Ranzolin A, Brenol JC, Bredemeier M, et al. Association of concomitant fibromyalgia with worse disease activity score in 28 joints, health assessment questionnaire, and short form 36 scores in patients with rheumatoid arthritis. *Arthritis Rheum*. 2009;61:794-800.

26 Sa KN, Baptista AF, Matos MA, et al. Chronic pain and gender in Salvador population, Brazil. *Pain*. 2008; 139:498-506.

27 Vlaar AP, ten Klooster PM, Taal E, et al. A cross-cultural study of pain intensity in Egyptian and Dutch women with rheumatoid arthritis. *J Pain*. 2007;8:730-736.

28 Wen H, Ralph SH, Li X, et al. Comparison of expectations of physicians and patients with rheumatoid arthritis for rheumatology clinic visits: a pilot, multicenter, international study. *Int J Rheum Dis*. 2012;15:380-389.

29 Tsang A, Von KM, Lee S, et al. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. *J Pain*. 2008;9:883-891.

30 Lipton RB, Scher AI, Steiner TJ, et al. Patterns of health care utilization for migraine in England and in the United States. *Neurology*. 2003;60:441-448.

Chapter 6

DAS steered therapy in clinical practice; cross-sectional results from the METEOR database

E.Gvozdenović , R. Wolterbeek, D. van der Heijde, T.W.J. Huizinga, C.F. Allaart, R. Landewé.

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ABSTRACT

Objective

Little is known on how well targeted treatment, for instance targeting towards low DAS, is implemented in clinical practice. Our aim was to evaluate treatment adjustments in response to DAS in RA patients in clinical practice.

Methods

We used data from one referral centre, multiple rheumatologists, from the METEOR database. Generalized Estimating Equations (GEE) were used to assess whether in case of non-low disease activity (DAS>2.4) treatment intensifications in DMARD therapy occurred (change or increase in dose or number of DMARDs, including synthetic (s)DMARDs, biologic (b)DMARDs and corticosteroids compared to the visit before). Determinants of not intensifying the treatment when DAS>2.4 were investigated using GEE.

Results

5.157 registered visits of 1.202 patients were available for the analyses. A DAS>2.4 was weakly (OR: 1.19; 95%CI 1.07 to 1.33) associated with a treatment intensification. In 69% (n=3.577) of the visits patients were in low disease activity. In 66% (n=1.028) of the visits with DAS>2.4 treatment was not intensified. These patients had a higher tender joint count and received more often methotrexate plus a bDMARD, or csDMARD monotherapy, as compared to patients that received treatment intensification.

Conclusion

In the majority of visits in the METEOR database patients were already in a state of low disease activity, reflecting appropriate treatment intensity. When DAS was greater than 2.4, treatment was often not intensified due to high tender joint count or specific treatment combinations. This data suggest that while aiming for low DAS, physicians per patient weigh whether all DAS elements indicate disease activity or will respond to DMARD adjustment or not, and make treatment decisions accordingly.

INTRODUCTION

The aim of treatment in rheumatoid arthritis (RA) is to achieve low disease activity or remission using a 'treat to target' (tight control) approach in which the disease activity of patients is monitored intensively and measured frequently with composite measures.[1-3] Treatment intensity can be adjusted by changing DMARDs or by increasing the dose and/or number of anti-rheumatic drugs, including synthetic (s)DMARDs and biologic (b)DMARDs and corticosteroid.[4] Since treatment to target and tight control have been proven to result in better clinical and radiological outcomes than routine care,[5-11] these concepts are at the basis of the current recommendations for the management of rheumatoid arthritis in daily practice. When sustained remission or low disease activity is achieved and medication is tapered or discontinued and following patients and tight control is important as half of the patient may flare with decreasing medication.[12,13] Despite the fact that rheumatologists have reported to use treat-to-target in daily practice,[14-16] some studies have suggested that targeted treatment may not be widely practiced yet[17,18]. Besides, it is well known that limited adherence to guidelines is prevalent in many chronic conditions, such as atrial fibrillation, hypertension and osteoporosis.[19-21]

We used the Measurement of Efficacy of Treatment in the 'Era of Outcome' in Rheumatology (METEOR) database,[22] to investigate the association between level of the DAS and whether or not physicians adjusted treatment with sDMARDs and bDMARDs and corticosteroids in patients with RA in daily clinical practice.

METHODS

Patients

For the current cross-sectional analyses we have used data from METEOR, which is an international prospective database aiming to improve tight monitoring and treatment to target in patients with rheumatic diseases. METEOR started in 2008 and is used as an online daily practice tool for rheumatologists to collect clinical data and calculate disease activity, registering the effectiveness of their treatment practice over time in patients with RA.

Data of both patients with advanced disease and with newly diagnosed RA were collected in a central database. Data is uploaded anonymously and therefore an ethics statement is not required for this study. A more detailed description of the METEOR database was published previously.[22,23] We have used data from the Leiden University Medical Center (LUMC) since

at the time of evaluation the data of this site were most complete with information on both DAS outcomes and anti-rheumatic treatment. Patients were included in METEOR between January 2008 and May 2013. We have selected 1.202 patients (5.157 visits ranging from 1 to 31 visits per patient) where DAS (5.157 visits) as well as information on treatment were available.

Outcome variables and determinants

Treatment adjustment was divided into three categories; 1) dose decrease (either a lower dose or fewer sDMARDs or bDMARDs or corticosteroids, including intra articular injections, compared to the previous visit), 2) stable dose (the same sDMARDs or bDMARDs or corticosteroids, including intra articular injections, and the same dose compared to the previous visit) and 3) treatment change or intensification (higher dose or more or other sDMARDs or bDMARDS or corticosteroids, including intra articular injections, compared to the previous visit).

DAS was classified in four categories, according to the EULAR classification criteria (DAS<1.6 representing clinical remission, DAS>1.6 and ≤2.4 representing low disease activity, DAS>2.4 and ≤3.7 representing moderate disease activity, and DAS>3.7 representing high disease activity). For secondary analyses DAS was divided in two categories; DAS ≤2.4 and DAS>2.4.

We used hypothetical conditions, based on a previous study, in which there was a discrepancy between components of the DAS representing inflammation (joint swelling, laboratory results) or pain (potentially regardless of inflammation) as secondary outcomes.[24] These conditions included 1) cases in which a patient had ≤1 swollen joints but 2 or more tender joints 2) cases in which a patient had ≤1 swollen joints but reported a high disease activity (≥20 on a visual analogue scale, VASpt) 3) cases in which a patients had ≤ 1 swollen joints but an erythrocyte sedimentation rate (ESR) ≥ 28 mm/hr 4) cases in which VASpt was ≥20mm higher than the physician's score of the patients global disease activity (VASphys) and 5) cases in which the VASphys was ≥20mm higher than the VASpt.[23-25]

Statistical analyses

Descriptive statistics were performed using median and interquartile ranges (IQR) for continuous variables, and number and percentages for categorical variables.

The association between DAS and treatment adjustments was assessed using generalized estimating equations (GEE) in order to adjust for the spurious effects of repeated measurements and treatment adjustments within the same subject. The probability of a treatment outcome (decreased, stable or change/intensified) was modelled using the GEE ordinal (cumulative) regression analysis approach.[26] In the regression model, treatment adjustment was the dependent variable, with increase of treatment being the last ordinal category (reference). DAS>2.4 (yes or no) was used as the determinant. We tested the proportional odds for treatment adjustment with crude calculations in cross tables and the goodness-of-fit test. These did not indicate a violation of the proportional odds assumption.[27]
In a set of subanalyses, a first GEE binary logistic regression was performed to compare decreased dose versus stable dose. A second binary GEE was performed to compare decreased dose versus increased dose; and a third binary GEE analysis was performed to compare increased dose versus stable dose. In all three analyses DAS>2.4 was the determinant. A fourth GEE was performed to model patients with DAS>2.4 (no intensification versus intensification of treatment) as dependent variable, with erythrocyte sedimentation rate (ESR), SJC, VASpt (patient assessment of global disease activity), TJC and actual treatment as determinants. This model was corrected for gender and age.
SPSS version 17.0 was used for the analyses and a two-sided p-value less than 0.05 was considered statistically significant.

RESULTS

In total 5.157 registered visits in 1.202 patients who were treated with sDMARDs and/or bDMARDs and/or corticosteroids, were available for the analyses. Mean age was 56 (SD: 14) and disease duration was on average 17 months (IQR: 3 to 84). 71% (n=854) of the population were women (table 1). In 1.580 of these 5157 visits (31%) DAS was >2.4 (and in 4% of these, DAS was >3.7), in 3577 visits (69%), DAS was ≤2.4 (in 39% of these DAS was <1.6). In 1.692/5.157 visits (33%) medication was intensified, in 2.881 visits (56%), medication was kept stable, and in 584 visits (11%) medication was tapered or discontinued (table 2). GEE showed that on patient level a higher DAS was only weakly but yet statistically significantly correlated with a change/increase in medication (OR: 1.19, 95%CI: 1.07 to 1.33, table 3). The binary logistic GEE regression showed that in patients with a DAS>2.4 treatment was more often changed/intensified (OR: 1.30, 95%CI: 1.05 to 1.60) than tapered, but not significantly more often changed/intensified than kept stable (table 3).

Table 1. Baseline characteristics (visit 1) for patients in the METEOR database.

	Total patients, n=1.202
Female, n (%)	854 (71)
Age (years), mean (SD)	56 (14)
Disease duration (months), median (IQR)	17 (3 to 84)
CCP positive, n (%)	407 (71)
RF present, n (%)	722 (75)
DAS, mean (SD)	2.5 (1.1)
HAQ, mean (SD)	1.0 (0.7)
ESR, median (IQR)	19 (9 to 34)
RAI, median (IQR)	4 (1 to 7)
SJC, median (IQR)	3 (0 to 7)
VAS, median (IQR)	
Patient global	39 (19 to 59)
Doctor global	21 (10 to 40)
Patient pain	43 (23 to 64)

n=number, SD=standard deviation, IQR= interquartile range, VAS=visual analogue scale, CRP= C-reactive protein, ESR= erythrocyte sedimentation rate, DAS=Disease Activity Score, RAI=Ritchie Articular Index, HAQ= Health Assessment Questionnaire, CCP=cyclic cictrullinated peptide antibody, RF=rheumatoid factor

In only 552/1.580 (35%) of the visits in which the patient had a DAS>2.4 medication was indeed changed/intensified, and this percentage was not higher in patients with a DAS>3.7 (table 2).

Table 2. Number of visits with decreased, stable or increased dose per level of disease activity based on DAS (Disease Activity Score).

		Decreased dose	**Stable dose**	**Increased dose**	**Total**
DAS	Remission: < 1.6, n (%)	257 (13)	1149 (56)	629 (31)	2035 (100)
	LDA: 1.6 - 2.4, n (%)	179 (12)	852 (55)	511 (33)	1542 (100)
	MDA: 2.4 - 3.7, n (%)	125 (9)	770 (56)	479 (35)	1374 (100)
	HDA: > 3.7, n (%)	23 (11)	110 (53)	73 (35)	206 (100)

n=number, LDA=low disease activity, MDA=moderate disease Activity, HDA=high disease activity.

In 23 visits (11%) in which patients had high disease activity (DAS>3.7) the dose was even decreased. In comparison, in 629 of the 2.035 visits (31%) where patients were in remission (DAS<1.6) medication was still changed/intensified (table 2).

Table 3. Association between DAS (Disease Activity Score) and treatment adjustment in METEOR

		DAS>2.4*
	ß	OR (95% CI)
Overall ordinal correlation**	0.175	1.19 (1.07-1.33)
Stable versus decreased dose***	0.259	1.30 (1.05-1.60)
Increased versus stable dose***	0.096	1.10 (0.97-1.26)
Increased versus decreased dose***	0.36	1.43 (1.17-1.74)

*Reference category is a DAS ≤ than 2.4. ** Ordinal and *** binary generalized estimating equation regression analysis. DAS > 2.4: higher odds to increase treatment. ß=beta, CI=confidence interval.

In the 1.028/1.580 (65%) visits in which patients had a DAS>2.4 treatment was nevertheless not changed/intensified. On the visit level we investigated whether there were discrepancies in DAS components in these 1.028 visits by comparing the median (interquartile range, IQR) tender joint count, swollen joint count, ESR and patient VAS: the median for tender joint count (6, IQR 2 to 8) was slightly higher than the median for swollen joint count (median 4, IQR 2 to 8) (table 4).

Table 4. Median of DAS components in visits where medication is not increased when patients have moderate/high disease activity.

	DAS>2.4 and medication not increased
	n=1.028 visits, median (IQR)
VASpt	60.0 (46.0-72.8)
Swollen joint count	4.0 (2.0-8.0)
Tender joint count	6.0 (4.0-8.0)
ESR	25.0 (11.0-38.0)*

* n=1 missing visit for ESR. n= number, IQR= interquartile range, ESR= erythrocyte sedimentation rate, VASpt=Patient assessment of Global Disease Activity.

In 20% of the visits in which DAS was >2.4 and medication was not changed/intensified, SJC was low (≤1) while TJC and patient's VAS for global disease activity were high (≥2 or ≥20, respectively). A higher patient-reported- than physician-assessed global disease activity (difference in VAS ≥20mm) was found in 33% of these visits (table 5).

Table 5. Number of visits in which there are discrepancies in DAS components in patients with moderate/high disease activity that did not receive treatment intensification.

	DAS>2.4 and medication not increased	
	n (%)	**Total**
SJC ≤1 and TJC ≥2	201 (19.6)	1028
SJC ≤1 and VASpt ≥20	198 (19.3)	1028
SJC ≤1 and ESR ≥28	98 (9.5)	1027
VASpt ≥20 mm higher than VASphys	148 (32.9)	450
VASphys ≥ 20 mm higher than VASpt	25 (5.6)	450

ESR= erythrocyte sedimentation rate, VASpt= patient assessment of global disease activity, TJC=tender joint count, SJC=swollen joint count, VASphys= physician assessment of global disease activity.

In a GEE binary logistic regression we checked in patients with a DAS>2.4 which factors were associated with NO intensification of treatment (intensification of treatment=reference), corrected for age and gender.

These factors were (high) tender joint count (OR: 1.05, 95%CI: 1.01 to 1.10), current treatment with conventional synthetic (cs) DMARD monotherapy (OR: 3.28, 95%CI: 2.40 to 4.48) and combination therapy with methotrexate (MTX) and a bDMARD (OR: 1.93, 95%CI: 1.25 to 2.98) (table 6). Finally, we checked on a visit level whether an improvement in DAS was found compared to the previous visit, but also at the following visits. However, we did not have drug data on all the previous and following visits. In 82 of the available 874 visits (9%) there had been an improvement in DAS (EULAR (European League Against Rheumatism) response moderate or good)) compared to the previous visit (table 7).

After a high DAS was followed with no change or increase in medication, at the following visit a good or moderate improvement in DAS was observed in 47 (17%) of the recorded 283 visits.

Table 6. Determinants for not increasing medication when patients have moderate/high disease activity, measured by a generalized estimating equation binary logistic regression.*

	DAS>2.4: medication is not increased vs medication is increased (n=1.574 visits)		
	ß	OR (95%CI)	P-value
ESR	0.00	1.00 (0.99 to 1.01)	0.86
SJC	-0.02	0.99 (0.96 to1.01)	0.20
VASpt	0.00	1.00 (0.99 to1.01)	0.98
TJC	0.05	1.05 (1.01-1.10)	<0.01
Actual drug**			
DMARD monotherapy	1.19	3.28 (2.40 to 4.48)	<0.01
MTX + bDMARD	0.66	1.93 (1.25 to 2.98)	<0.01
DMARD combination therapy	0.12	1.12 (0.83 to 1.53)	0.46
DMARD + prednisone	0.03	1.03 (0.67 to 1.57)	0.90

*Analysis is corrected for gender and age. ** Reference category = other drugs. ESR= erythrocyte sedimentation rate, SJC= swollen joint count, TJC=tender joint count, VasPtGlobal=Patient Assessment of global disease activity.

Table 7. Number of visits in which patients show improvement in DAS according to the EULAR criteria.

	DAS>2.4, medication not increased	Total
DAS improvement compared to the previous visit		
None: ≤0.6, N (%)	792 (91)	874
Moderate: 0.6-1.2, N (%)	60 (7)	874
Good: >1.2, N (%)	22 (2)	874
DAS improved in the following visit		
None: ≤0.6, N (%)	236 (83)	283
Moderate: 0.6-1.2, N (%)	33 (12)	283
Good: >1.2, N (%)	14 (5)	283

DAS=Disease Activity Score, EULAR= European League Against Rheumatism.

DISCUSSION

In this analysis from daily practice observations collected in the METEOR database, we obtained information about how the treat to target recommendation in RA is followed in a single large academic referral centre (LUMC). Most patients had low disease activity or remission (69% of visits DAS=<2.4, 39% even <1.6) during the majority of visits. These percentages approach figures that have been reported in treat-to-target studies such as CAMERA,[28] DREAM[29] and BeSt[30] in which 50-82% achieved low disease activity or remission.

This observation, together with the apperception that DAS-results were indeed measured and recorded, support a conclusion that rheumatologists in the LUMC follow the treat to target approach in daily practice quite well. Since rheumatologists working in the LUMC conducted the Best study, which aims at low disease activity using DAS-steered therapy, this could be expected. Many previous studies, such as TICORA, GUEPARD and ESPOIR showed that a treat to target strategy leads to better clinical outcomes compared to routine care.[5,8]

Since questionnaire-based studies suggest that rheumatologists are aware of the advantages of treatment to target and are willing to apply the treatment recommendations,[14-16] the METEOR tool was developed to help and stimulate rheumatologists to apply a treat to target approach in daily practice.

In spite of a high percentage of patients with DAS<2.4, we also found on a patient level, that DAS>2.4 itself was only weakly associated with a change or intensification of antirheumatic medication (OR: 1.19). In comparison to tapering the dose if DAS was ≤2.4, the likelihood of increasing the dose was only marginally higher in patients with a DAS >2.4. Furthermore, per visit where treatment was not intensified although DAS was higher than 2.4 we found discrepancies in subjective patient outcomes (high tender joint count and/or high patient reported global disease activity on a visual analogue scale) versus physician assessment of disease activity (low swollen joint count). This is reflected by an OR for tender joint count of 1.05 (CI95Q% 1.01-1.1) for not intensifying medication in case of DAS>2.4.

This observation may suggest that although rheumatologist may steer treatment decisions by the measured DAS, they consider other explanations of high DAS components, for instance secondary fibromyalgia or irreversible joint damage as explanation for a high tender joint count, which may not respond to a further increase of anti-inflammatory drugs. A discrepancy between subjective patient outcomes and objective physician assessments has been shown in earlier METEOR studies focused on patient's global disease activity (GDA).

Here we found that when patients rate their GDA, they base their opinion more on subjective signs (patient's perception of pain), while physicians put more weight on objective signs (swollen joint count, ESR) when rating GDA of the patient. Also is shown that discrepancies between patients and physicians in GDA assessment are different among countries, suggesting that reporting and acknowledging pain differs per country.[23,31] The METEOR database does not contain information on damage or secondary pain syndromes, or indeed other comorbidities, which may also have held rheumatologists back in increasing treatment where the DAS was high. Nor do we have information on reasons why patients may not have wanted to increase medication.

We also found that the likelihood of treatment intensification in case of DAS>2.4 was less if the patient was currently using csDMARD monotherapy, which may indicate a reluctance among patients to change or expand medication,[32] or methotrexate in combination with a biological agent. The latter may indicate that rheumatologists may be reluctant to change the biologic, as it is currently unclear which is the optimal treatment choice if the first biologic is ineffective.[33-35] Previous studies suggest that an important reason for the rheumatologist to not (yet) intensify the treatment was that they anticipated further improvement on the current medication. We tested this hypothesis but we found only in 9% of the available visits clinical relevant improvement in DAS.

An important limitation to this study is that we do not have data on comorbidities, which might influence the decision of the rheumatologist to change or not change the treatment. Furthermore, we used a rather broad categorization of treatment adjustment without any hierarchy in for instance type or number of drugs that were adjusted, which may have influenced the results. Another limitation is that we have no imaging data, although presence or absence of radiologic damage progression, in clinical practice can influence the decision on treatment intensification. A final restriction is that we used only data form the LUMC since data of other centers/countries were not (sufficiently) available yet. These results may therefore not be generalizable to all patients treated in clinical practice, since perception of pain seems to be country dependent.

In conclusion, we have found a high percentage of patients with remission or a low level of disease activity in the majority of regular registered visits of RA patients to the outpatient clinic of a large academic hospital in the Netherlands. We have also found that a moderate- to high disease activity does not automatically lead to treatment intensification, which may still suggest that Treat-to-Target and EULAR recommendations for the management of patients

with RA are well followed, but also that the doctor is looking critically at possible reasons for elevation of elements of the DAS before deciding on treatment intensification. Future research is needed to study the relationship between disease activity and treatment adjustment using different categorizations, such as type of medication. Also, it will be useful to understand how comorbidities influence the relationship between treatment adjustment and disease activity.

REFERENCE LIST

1 Allaart CF, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. Aiming at low disease activity in rheumatoid arthritis with initial combination therapy or initial monotherapy strategies: the BeSt study. *Clin exp rheum.* 2006;24:S.

2 Katchamart W, Bombardier C. Systematic monitoring of disease activity using an outcome measure improves outcomes in rheumatoid arthritis. *J rheumatol.* 2010;37:1411-1415.

3 Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis.* 2014;73:492-509.

4 Smolen JS, van der Heijde D, Machold KP, et al. Proposal for a new nomenclature of disease-modifying antirheumatic drugs. *Ann Rheum Dis.* 2014;73:3-5.

5 Grigor C, Capell H, Stirling A, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *The lancet.* 2004;364:263-269.

6 Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Kerstens PJ, et al. DAS-driven therapy versus routine care in patients with recent-onset active rheumatoid arthritis. *Ann Rheum Dis.* 2010;69:65-69.

7 Soubrier M, Lukas C, Sibilia J, Fautrel B, Roux F, et al. Disease activity score-driven therapy versus routine care in patients with recent-onset active rheumatoid arthritis: data from the GUEPARD trial and ESPOIR cohort. *Ann Rheum Dis*. 2011;70:611-615.

8 Fransen J, Moens HB, Speyer I, et al. Effectiveness of systematic monitoring of rheumatoid arthritis disease activity in daily practice: a multicentre, cluster randomised controlled trial. *Ann Rheum Dis.* 2005;64:1294-1298.

9 Schipper LG, Vermeer M, Kuper HH, et al. A tight control treatment strategy aiming for remission in early rheumatoid arthritis is more effective than usual care treatment in daily clinical practice: a study of two cohorts in the Dutch Rheumatoid Arthritis Monitoring registry. *Ann Rheum Dis.* 2012;71:845-850.

10 Castrejon I, Pincus T, Soubrier M, et al. GUEPARD treat- to-target strategy is significantly more efficacious than ESPOIR routine care in early rheumatoid arthritis according to patient-reported outcomes and physician global estimate. *Rheumatology (Oxford).* 2013;52:1890-1897.

11 Pope JE, Haraoui B, Rampakakis E, et al. Treating to a target in established active rheumatoid arthritis patients receiving a tumor necrosis factor inhibitor: results from a real-world cluster-randomized adalimumab trial. *Arthritis Care Res (Hoboken)* 2013;65:1401-1409.

12 Van den Broek M, Klarenbeek NB, Dirven L, et al. Discontinuation of infliximab and potential predictors of persistent low disease activity in patients with early rheumatoid arthritis and disease activity score-steered therapy: subanalysis of the BeSt study. *Ann Rheum Dis.* 2011;70:1389-1394.

13 Smolen JS, Aletaha D, Bijlsma JW, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010;69:631-637.

14 Schoels M, Aletaha D, Smolen JS, et al. Follow-up standards and treatment targets in rheumatoid arthritis: results of a questionnaire at the EULAR 2008. *Ann Rheum Dis.* 2010;69:575-578.

15 Park YB, Koh EM, Kim HY, et al. Treating rheumatoid arthritis to target: recommendations assessment questionnaire in Korea. *Clin Rheumatol.* 2013;32:1791-1797.

16 Haraoui B, Bensen W, Bessette L, Le CS, et al. Treating rheumatoid arthritis to target: a Canadian physician survey. *J Rheumatol.* 2012;39:949-953.

17 Littlejohn G, Roberts L, Arnold M, et al. A multi-center, observational study shows high proportion of Australian rheumatoid arthritis patients have inadequate disease control. *Int J Rheum Dis*. 2013;16:532-538.

18 Kruger K, Karberg K. [Treat-to-target from the perspective of office-based rheumatology]. *Z Rheumatol*. 2011;70:664-669.

19 Hyman DJ, Pavlik VN. Self-reported hypertension treatment practices among primary care physicians: blood pressure thresholds, drug choices, and the role of guidelines and evidence-based medicine. *Arch Intern Med.* 2000;160:2281-2286.

20 Huntjens KM, van Geel TA, Blonk MCet al. Implementation of osteoporosis guidelines: a survey of five large fracture liaison services in the Netherlands. *Osteoporos Int.* 2011;22:2129-2135.

21 Allen LaPointe NM, Lokhnygina Y, Sanders GD et al. Adherence to guideline recommendations for antiarrhythmic drugs in atrial fibrillation. *Am Heart J* 2013;166:871-878.

22 Koevoets R, Allaart CF, van der Heijde DM, et al. Disease activity monitoring in rheumatoid arthritis in daily practice: experiences with METEOR, a free online tool. *J Rheumatol.* 2010;37:2632-2633.

23 Gvozdenovic E, Koevoets R, Wolterbeek R, et al. Assessment of global disease activity in RA patients monitored in the METEOR database: the patient's versus the rheumatologist's opinion. *Clin Rheumatol.* 2013.

24 Markusse IM, Dirven L, Han KH, et al. Evaluating adherence to a treat-to-target protocol in recent-onset rheumatoid arthritis: Reasons for compliance and hesitation. *Arthritis Care Res (Hoboken)*. 2015.

25 Khan NA, Spencer HJ, Abda E, et al. Determinants of discordance in patients' and physicians' rating of rheumatoid arthritis disease activity. *Arthritis Care Res (Hoboken).* 2012;64:206-214.

26 Fullerton JN, Roberts KJ, Wyse M. Should non-anaesthetists perform pre-hospital rapid sequence induction? an observational study. *Emerg Med J.* 2011;28:428-431.

27 Stiger TR, Barnhart HX, Williamson JM. Testing proportionality in the proportional odds model fitted with GEE. *Stat Med.* 1999;18:1419-1433.

28 Verstappen SM, Jacobs JW, van der Veen MJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). *Ann Rheum Dis.* 2007;66:1443-1449.

29 Vermeer M, Kuper HH, Hoekstra M, et al. Implementation of a treat-to-target strategy in very early rheumatoid arthritis: results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study. *Arthritis Rheum*. 2011;63:2865-2872.

30 Klarenbeek NB, Guler-Yuksel M, van der Kooij SM, et al. The impact of four dynamic, goal-steered treatment strategies on the 5-year outcomes of rheumatoid arthritis patients in the BeSt study. *Ann Rheum Dis*. 2011;70:1039-1046.

31 Gvozdenovic E, Wolterbeek R, Allaart CF, et al. Assessment of Global Disease Activity in Rheumatoid Arthritis by Patients and Physicians: Differences Across Countries in the METEOR Database. *J Clin Rheumatol.* 2015;21:349-354.

32 Wolfe F, Michaud K. Resistance of rheumatoid arthritis patients to changing therapy: discordance between disease activity and patients' treatment choices. *Arthritis Rheum*. 2007;56:2135-2142.

33 Bombardieri S, Ruiz AA, Fardellone P, et al. Effectiveness of adalimumab for rheumatoid arthritis in patients with a history of TNF-antagonist therapy in clinical practice. *Rheumatology (Oxford)*. 2007;46:1191-1199.

34 Kristensen LE, Saxne T, Geborek P. The LUNDEX, a new index of drug efficacy in clinical practice: results of a five-year observational study of treatment with infliximab and etanercept among rheumatoid arthritis patients in southern Sweden. *Arthritis Rheum*. 2006;54:600-606.

35 Yazici Y, Erkan D. Do etanercept-naive patients with rheumatoid arthritis respond better to infliximab than patients for whom etanercept has failed? *Ann Rheum Dis*. 2004;63:607-608.

Chapter 7

Does reporting to follow a guideline imply that this guideline is really applied in clinical practice? The International Recommendation Implementation Study (IRIS)

E. Gvozdenović, C.F. Allaart, D. van der Heijde, G. Ferraccioli, J. S. Smolen, T.W.J. Huizinga, R. Landewé.

Submitted

ABSTRACT

Objective

To investigate if rheumatologists that report to follow up guidelines really do this by monitoring practice performance in clinical practice.

Methods

Data of the International Recommendation Implementation Study (IRIS) is used, which included 132 participating rheumatologists from 14 countries. Participants received a questionnaire measuring their awareness/commitment with the EULAR/T2T recommendations, followed by an educational program. They were asked to include and monitor 5-10 new-onset RA patients in the IRIS database for a period of 1-2 years.

Results

In total, 72 of the 132 participants have added 378 patients in the database. Of these participants 70 (98%) agreed that DMARD-therapy should be started as soon as possible after diagnosis in every patient and 69 (96%) agreed that methotrexate should be part of the first treatment strategy. Treatment changes according to these recommendations were reported in 253 (67%) and 225 (60%) of the recorded patients, respectively. Of the participants 60 (83%) agreed that composite measures should be recorded regularly, while in 134 (54%) of the patients composite scores were recorded in ≥50% of patient visits.

Conclusion

Reporting to follow EULAR recommendations and T2T principles after an educational programme does not mean actual compliance with this guidance in clinical practice.

INTRODUCTION

During the last decades, many guidelines and recommendations have been formulated with the aim to improve the quality of care.[1-5] In rheumatology, international recommendations for the management of patients with rheumatoid arthritis (RA) focus on treatment decisions including the choice of initial therapy and subsequent alternatives, on monitoring disease activity as a measure of treatment success and on reasons for treatment adjustments. Besides, they emphasise shared decision making, patient education, how to deal with comorbidities and the role of specialized nurses in the treatment care of RA.

These recommendations include concepts of 'treating-to-target' (further referred to as T2T) and 'tight control'. The treat-to-target approach requires that patients will receive medication, and if necessary intensification or adjustment of therapy, until a predefined treatment goal (a certain level of disease activity, often clinical remission or low disease activity) is achieved. The 'tight control' concept requires frequent assessments of disease activity in order to check if the treatment goal has been achieved and to avoid delays in optimal treatment. It is recommended that monitoring disease activity should be done by composite measures (DAS, DAS28, SDAI and CDAI).[6-8]

In many surveys rheumatologists report that they follow the recommendations for RA in clinical practice.[9-11]Although, some studies suggest that recommendations are not practiced yet outside of clinical trials.[12,13] These studies indicate that there is a discrepancy between reporting agreement with recommendations and actual performance in clinical practice (implementation). Only a few studies have shown a successful implementation of recommendations, such as treat to target, and suggestions to improve DAS steered therapy in clinical practice.[14,15] Many obstacles may postpone a successful implementation, such as a lack of awareness and lack of agreement,[16-18] or lack of treatment-protocols.[15] A previous study has shown that educational programs may effectively help to implement clinical guidelines in practice.[19]

In order to test the efficacy of such an implementation initiative, the International Recommendation Implementation Study (IRIS) was initiated. As part of this study we have investigated whether rheumatologists that report to follow the European League Against Rheumatism (EULAR) recommendations on the management of RA and the T2T recommendations really do this in clinical practice. In order to increase the chance of successful implementation, we have provided them a web-delivered educational program.

METHODS

Study participants

IRIS is a 2-year follow-up implementation study in which rheumatologists received a questionnaire on their awareness of-, agreement with- and adherence to the EULAR/T2T recommendations formulated in 2010 (see attachment I and II).[6,8]
The questionnaire started with general questions about whether participating rheumatologists were aware of the recommendations and whether they follow them in clinical practice. Then, we asked per recommendation whether they follow it in clinical practice. Participants were able to choose three options for answering the questions: 'yes', 'for some patients/sometimes' or 'no'. The answers on whether the participants were applying the following four EULAR and Treat to target recommendations in clinical practice were used in this study:

- *'Treatment with synthetic DMARDs should be started as soon as the diagnosis of RA is made'*
- *'MTX is part of the first treatment strategy'*
- *'When MTX contraindications (or intolerance) are present, the following DMARDs should be used: Leflunomide, sulfasalazine or injectable gold'*
- *'Measures of disease activity must be obtained and documented regularly as frequently as monthly for patients with high/moderate disease activity or less frequently (such as every 3–6 months) for patients in sustained low disease activity or remission'*

After completing the questionnaire, participating rheumatologists took part in a short education programme on these recommendations, consisting of reading two articles on the EULAR recommendations for the management of RA and the T2T recommendations and watching an online video in which the principles of the recommendations and the aims of IRIS were explained by expert rheumatologists and researchers. It was also optional to follow an online training to get familiar with the Measurement of efficacy of Treatment in the Era of Outcome of Rheumatology (METEOR) registration tool. After this, they were required to record data on disease monitoring and adjustment of treatment in 5-10 patients with newly diagnosed RA per rheumatologist. Registration took place in METEOR,[20,21] which is a large online database developed for rheumatologists providing an online tool to register data from RA patients and monitor them in daily practice. The patients were followed for 1-2 years. During this follow-up period participating rheumatologists received every month one of the EULAR/T2T

recommendation per email to remind them on the study and to encourage them to follow all the recommendations in clinical practice.

We compared the proportion of rheumatologists that agreed with the EULAR and T2T recommendations with the proportion of their patients who were actually treated according to these recommendations in clinical practice.

From December 2011 rheumatologists worldwide were approached via their national RA societies to participate in IRIS. 132 rheumatologists from the following 14 countries agreed to participate in this study: Bosnia, Brazil, Croatia, Cyprus, Greece, Italy, Malta, the Netherlands, Nigeria, Poland, Portugal, Russia, Spain, and Turkey. The first rheumatologist started with the educational program in March 2012 and the final participant started in February 2014.The database is still ongoing and will close 2 years after the last participant added the last patient (February 2016).

The participants have received a payment of 250 euro per included patient to compensate for the work in this study.

Outcome variables

We compared how often rheumatologists agreed with the following four recommendations with how the proportion of their patients actually treated according to these recommendations:

- EULAR recommendation 1: *'Treatment with synthetic DMARDs should be started as soon as the diagnosis of RA is made'*. We determined the proportion of patients in whom the time interval between the date of diagnosis and the date of start of a DMARD (disease-modifying anti rheumatic drug) was <= 4 weeks.
- EULAR recommendation 2: *'MTX is part of the first treatment strategy in patients with active RA'*. We determined the proportion of RA patients in whom MTX was (part of) the first treatment strategy.
- EULAR recommendation 3: *'When MTX contraindications (or intolerance) are present, the following DMARDs should be used: Leflunomide, sulfasalazine or injectable gold'*. We determined the proportion of patients that did not start with MTX in whom leflunomide, sulfasalazine or injectable gold was prescribed.
- Treat to Target recommendation 5: *'Measures of disease activity must be obtained and documented regularly as frequently as monthly for patients with high/moderate disease activity or less frequently (such as every 3–6 months) for patients in sustained low disease activity or remission'*. We created three categories: 'T2T always' represents the

number of patients for whom a composite score (DAS, DAS28, CDAI or SDAI) was reported at least every 2 months during moderate or high disease activity (DAS>2.4, DAS28>3.6 CDAI>10, SDAI>11) and at least every 7 months for low disease activity in 100% of the visits. A patient was categorized as 'T2T sometimes/never' when this was found in some or none of the visits, with an estimation of the percentage of visits in which the recommendation was followed. A category 'not reported' reflects patients in whom composite scores were missing in all of the visits.

RESULTS

Of the 132 participating rheumatologist who agreed participation in the IRIS, 122 (92%) completed the questionnaire, finished the web-based educational program and were followed for 1-2 years. During the follow-up period 72 (55%) of the participating rheumatologists have recorded 1155 visits from 378 newly diagnosed patients in the database prospectively. The remaining participants dropped out (n=44) or were lost to follow-up (n=6) before including patients in the METEOR database (Figure 1).

Reasons for dropping out of the study where lack of time to participate or withdrawn consent with regard to participation in the study. The remaining 72 rheumatologists were from the following countries: Bosnia, Cyprus, Greece, Italy, the Netherlands, Nigeria, Russia and Spain. We compared the results of the questionnaire from 72 rheumatologists who entered patients in the database with the 50 rheumatologists who did not, and found that agreement was similar between the two groups (Attachment I and II).

Of the 72 participating rheumatologists 70 (98%) had reported to be compliant with the recommendation '*Treatment with synthetic DMARDs should be started as soon as the diagnosis of RA is made'* (table 1). In 253 of the 378 (67%) patients that were recorded in the database, they had indeed prescribed a DMARD within four weeks after the diagnosis.

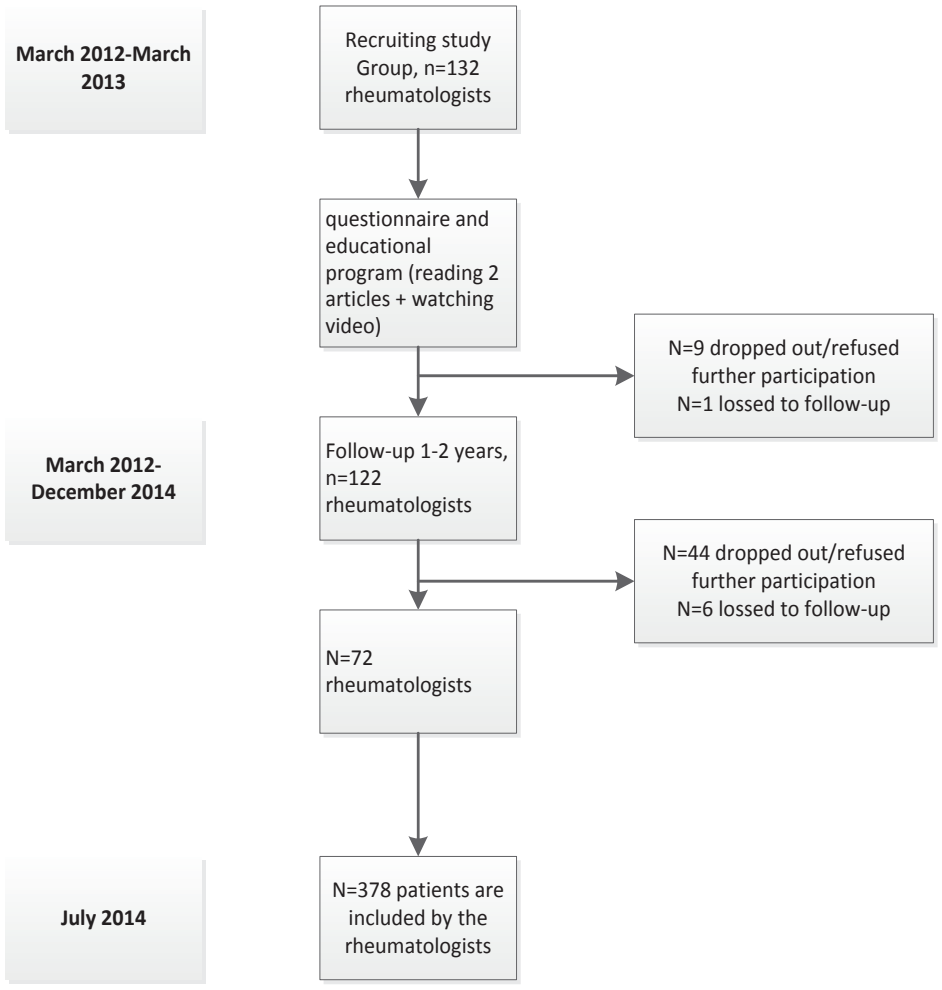

Figure 1. Flow-chart International Recommendation Implementation Study (IRIS).

Table 1. Comparison between agreement with the EULAR and Treat to Target recommendations and managing patients in clinical practice

	Rheumatologists opinion about adherence (measured in 72 Rheumatologists)*			**Rheumatologists performance in daily practice (Measured in 378 patients)****		
	Always, n (%)	(Some)times/ Never, n (%)	Missing, n (%)	Always, n (%)	(Some)times/ Never, n (%)	Not reported, n (%)
EU 1. 'Treatment with synthetic DMARDs should be started as soon as the diagnosis of RA is made'.	70 (98)	1 (1)	1 (1)	253 (67)	65 (17)	60 (16)
EU 3. 'MTX is part of the first treatment strategy'.	69 (96)	2 (3)	1 (1)	225(60)	93 (24)	60 (16)
EU 4. 'When MTX contraindications (or intolerance) are present, the following DMARDs should be used: Leflunomide, sulfasalazine of injectable gold'.	59 (82)	12 (17)	1 (1)	15 (19)	78 (81)	
T2T 'Measures of disease activity must be obtained and documented regularly'***	60 (83)	10 (14)	2 (3)	68 (27)	125 (51) 23 in ≥75% 45 in ≥50% 27 in <50 % 30 in 0 of the visits	54 (22)

* Always = rheumatologists report to follow this recommendation, sometimes/never= rheumatologist report to follow this recommendation sometimes or not, missing = no answer was filled in **Always = rheumatologists follow this recommendation, sometimes/never = rheumatologist follow this recommendation sometimes or not. Not reported= no information present on whether the recommendation is followed by the rheumatologist. *** As frequently as monthly for patients with high/moderate disease activity or less frequently (such as every 3–6 months) for patients in sustained low disease activity or remission. EU=EULAR recommendation. T2T=treat-to-target recommendation, MTX=methotrexate, DMARD=disease-modifying anti rheumatic drug.

In 50 of the 378 patients (13%) a DMARD was not started within 4 weeks, but after a median (interquartile range) period of 13 (7 to 57) weeks (table 2). For 60 of the 378 patients (1%) essential information was missing (date of diagnosis/ or date of start first DMARD).

Table 2. Average time from diagnosis (weeks) until a patient received a first DMARD in those patients in whom a DMARD was NOT started within 4 weeks after diagnosis

	Patients (n=65) (n, %)	Average time to start per therapy (median, IQR)
Methotrexate	41 (82)	13 (7 to 57)
Hydroxychloroquine	6 (12)	12 (1 to 606)
Sulfasalazine	1 (2)	10
Leflunomide	2 (4)	189 resp 245 weeks
No DMARD started	15 (23)	-

IQR= interquartile range

Of the 72 participating rheumatologists, 69 (96%) had reported that they are compliant with the recommendation *'MTX is part of the first treatment strategy'*. In 225 of the 378 patients (60%) MTX has indeed been prescribed as (part of) the first treatment. Of the 93 patients (26%) who did not start with MTX 15 (19%) have received leflunomide, sulfasalazine or injectable gold as first treatment, but 78 patients (81%) have started with other medications (table 3). Of the participating 72 rheumatologists, 60 (83%) had reported that they are compliant with the recommendation: '*Measures of disease activity must be obtained and documented regularly as frequently as monthly for patients with high/moderate disease activity or less frequently (such as every 3–6 months) for patients in sustained low disease activity or remission*'. Of the 378 patients 131 had less than 2 visits. For those patients with more than one visit recorded (247) we could check whether patients were monitored according to this recommendation. Of these 247 patients 68 (27%) had been monitored in full accordance with this recommendation, and were in the 'T2T always' group.

Another 23 (9%) patients had been monitored in partial accordance with this recommendation (75-100% of the visits) and were in the 'T2T sometimes' group. 45 (18%) patients had been monitored but insufficiently (in 50-75% of the visits) and also assigned to the 'sometimes' group (table 1).

Table 3. Medication prescribed as initial treatment and average time in weeks from diagnosis until start, in patients in whom MTX, leflunomide, Sulfasalazine or injectable gold was NOT started as first DMARD

	Patients (n total=78) (N, %)	Average time in weeks to start per therapy (median, IQR)
Hydroxychloroquine (+/- NSAID)	12 (15)	0 (0 to 0)
Parental corticosteroid (+/- HCQ)	28 (36)	0 (0 to 0)
Oral corticosteroid (+/- HCQ)	28 (36)	0 (0 to 3)
NSAID/analgetics	3 (4)	0 (0 to 0)
Ciclosporin	1 (1)	0 (0 to 0)
Biologic DMARD	6 (8)	64 (4 to 245)

IQR = interquartile range, NSAID=nonsteroidal anti-inflammatory drug, HCQ= Hydroxychloroquine, DMARD=disease-modifying anti rheumatic drug

27 (11%) patients were poorly monitored (<50% of the visits) and also in the 'sometimes' group (table 1). Finally 30 (13%) of the patients were in the 'T2T never' group where monitoring in none of the visits was done according to the recommendation.

DISCUSSION

The main conclusion of this study conducted in rheumatologists practicing in different parts of the world is that reporting to follow four EULAR/T2T recommendations does not mean that these recommendations are actually applied in daily clinical practice. We have found discrepancies between what rheumatologists report to do versus how they actually treat patients in clinical practice.

In our study less than 60% of the recruited rheumatologists that agreed to participate, expectedly the more dedicated rheumatologists, finished both the educational program and included patients in the METEOR database, which is rather disappointing. Yet even after participating in a dedicated educational program, in which those rheumatologists were actively stimulated to follow recommendations, which proved in many previous studies to have a positive effect on actually implementing recommendations,[19,22-24] rheumatologists still seem to be reluctant to follow up that recommendation. In fact, they report that they follow up recommendations, but act differently in clinical practice. What could potentially explain this

discrepancy? First, trivial logistic explanations may account. For instance, a patient may not show up for a visit, which in turn could lead to missing disease activity data within the recommended time period. Furthermore, there might be a time gap in obtaining knowledge on recommendations and actually implementing them. Rheumatologists might agree with recommendations and feel stimulated by an educational program to follow them, but time is too short to actually change practice (1-2 years follow- up). In the study by Forsetlund et al. physicians that were actively stimulated to treat patients according to evidence-based practice were compared with physicians that only received access to evidence based libraries, but no significant differences between the groups in behaviour of decision making was found. Their follow-up was 1.5 year, which was argued not to be long enough to change decision-making among physicians.[25] A Dutch study also showed discrepancies between compliance with- and actual application of recommendations about mental health in practice. However, in this study no educational program was used to encourage physicians to follow the recommendations.[26] An important strength of this study is that we have used study participants stemming from all over the world which increases generalizability. There are also limitations of this study. First of all, we investigated the agreement and adherence to the EULAR recommendations of 2010, which were new at the time of study initiation but have been updated since then (online publication in October 2013, while inclusion and instruction in the current study was finished in March 2013). However, the updated recommendations did not differ much with respect to the 4 recommendations studied. The only difference that is relevant for the interpretation of this study is that injectable gold is not recommended anymore when MTX is contraindicated. Another limitation is that we miss information about characteristics of the participating rheumatologists, due to privacy reasons. While rheumatologists from all over the world have participated in the study, we are still uncertain whether the study is fully generalizable to all rheumatologists. A more technical explanation for not following the recommendations in clinical practice is that we based our verdict about whether the recommendations were followed on the registration of rheumatologists' actions in the METEOR database. It is possible that recommendations were followed more often than was recorded. However, all rheumatologists were informed of this procedure when they agreed to participate in this study, were instructed to register their performance in the METEOR database and have been offered a training program to optimally use that database. We are not sure whether the participating rheumatologists have actually completed the educational program, so it is difficult to conclude that the program has influenced the behaviour of the rheumatologists. We did sent out monthly emails with a recommendation in order to remind the rheumatologist on the project, which has

been shown to be an effective tool in previous implementation studies.[27] Furthermore, we have offered the educational program via the internet, while a more effective approach could have been telephone interviews or educational visits to the physician. Some reviews have suggested that multifaceted strategies, such as educational meetings, educational resources and support from colleagues, are more successful strategies to assist in implementation of recommendations,[28-31] although another review suggested that it is not clear yet which implementation strategies are best.[32] A reluctance to record daily practice in the METEOR database, which is user-friendly[20] may explain why only 72 (55%) of the rheumatologists finished the educational program and included patients. When we compared the agreement with the recommendations between the rheumatologists that dropped out after the educational program (n=50) with the 72 participants that effectively included patients, the responses were similar. Technical or other problems with data entry in the METEOR database may also have led to incompleteness of data. In 16-22% of patient data information was not reported on the 4 studied recommendations. We do not know if these patients are randomly missing, and if entered data are inconsistent. In addition, we can only speculate about the reasons for not complying with recommendations, as additional data on treatment steps, contraindications for medication, side effects and comorbidities are not recorded.

In conclusion, the results of this study show that there is a discrepancy between agreeing with well-known and broadly accepted recommendations on treating-to-target, timing and choice of initial treatment as well as tight control in the management of patients with rheumatoid arthritis on one hand, and the actual performance in clinical practice when measured. A dedicated internet-based educational program might be insufficient to change the attitude of the rheumatologists. This observation has implications for the broadly advocated recommendation to implement quality-control initiatives in order to make practice performance more transparent: It looks as if the development and publication of evidence and consensus-based treatment recommendations do not suffice to change practice performance in rheumatology. Since these recommendations are usually a trade-off between best evidence and cost-effectiveness, it can be argued if nowadays patients with RA are indeed optimally treated in clinical practice. Further studies should focus on factors that explain the reluctance of rheumatologists to follow evidence based treatment recommendations, in particular reluctance of MTX prescription in patients with co-morbidities, and on strategies to overcome this reluctance. In addition, future studies should focus on investigating what type of education is most effective for implementing guidelines in clinical practice.

REFERENCE LIST

1 Grimshaw JM, Russell IT. Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. *Lancet.* 1993;342:1317-1322.

2 Woolf SH, Grol R, Hutchinson A, et al. Clinical guidelines: potential benefits, limitations, and harms of clinical guidelines. *BMJ.* 1999;318:527-530.

3 Amiel SA, Pursey N, Higgins B, et al. Diagnosis and management of type 1 diabetes in adults: summary of updated NICE guidance. *BMJ*. 2015;351:h4188.

4 Gruffydd-Jones K, Jones MM. NICE guidelines for chronic obstructive pulmonary disease: implications for primary care. *Br J Gen Pract*. 2011;61:91-92.

5 Cressy DS, DeBoisblanc BP. Diagnosis and management of asthma: a summary of the National Asthma Education and Prevention Program guidelines. National Institutes of Health. *J La State Med Soc*. 1998;150:611-617.

6 Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis*. 2010;69:964-975.

7 Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis.* 2014;73:492-509.

8 Smolen JS, Aletaha D, Bijlsma JW, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis.* 2010;69:631-637.

9 Haraoui B, Bensen W, Bessette L, et al. Treating rheumatoid arthritis to target: a Canadian physician survey. *J Rheumatol*. 2012;39:949-953.

10 Park YB, Koh EM, Kim HY, et al. Treating rheumatoid arthritis to target: recommendations assessment questionnaire in Korea. *Clin Rheumatol*. 2013;32:1791-1797.

11 Schoels M, Aletaha D, Smolen JS, et al. Follow-up standards and treatment targets in rheumatoid arthritis: results of a questionnaire at the EULAR 2008. *Ann Rheum Dis*. 2010;69:575-578.

12 Kruger K, Karberg K. [Treat-to-target from the perspective of office-based rheumatology]. *Z Rheumatol.* 2011;70:664-669.

13 Littlejohn G, Roberts L, Arnold M, et al. A multi-center, observational study shows high proportion of Australian rheumatoid arthritis patients have inadequate disease control. *Int J Rheum Dis.* 2013;16:532-538.

14 Vermeer M, Kuper HH, Hoekstra M, et al. Implementation of a treat-to-target strategy in very early rheumatoid arthritis: results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study. *Arthritis Rheum*. 2011;63:2865-2872.

15 van Hulst LT, Creemers MC, Fransen J, et al. How to improve DAS28 use in daily clinical practice?--a pilot study of a nurse-led

intervention. *Rheumatology (Oxford)*. 2010;49:741-748.

16 Michie S. Changing behavior: theoretical development needs protocol adherence. *Health Psychol.* 2005;24:439.

17 Rashidian A, Eccles MP, Russell I. Falling on stony ground? A qualitative study of implementation of clinical guidelines' prescribing recommendations in primary care. *Health Policy*. 2008;85:148-161.

18 Cabana MD, Rand CS, Powe NR, et al.Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999;282:1458-1465.

19 Zwerver F, Schellart AJ, Knol DL, et al. An implementation strategy to improve the guideline adherence of insurance physicians: an experiment in a controlled setting. *Implement Sci*. 2011;6:131.

20 Koevoets R, Allaart CF, van der Heijde DM, et al. Disease activity monitoring in rheumatoid arthritis in daily practice: experiences with METEOR, a free online tool. *J Rheumatol.* 2010;37:2632-2633.

21 Gvozdenovic E, Koevoets R, Wolterbeek R, et al. Assessment of global disease activity in RA patients monitored in the METEOR database: the patient's versus the rheumatologist's opinion. *Clin Rheumatol.* 2014;33:461-466.

22 Sanci LA, Coffey CM, Veit FC, et al. Effects of an educational intervention for general practitioners in adolescent health care principles: a randomized controlled study. *West J Med*. 2000;172:157-163.

23 Davis D, O'Brien MA, Freemantle N, et al. Impact of formal continuing medical education: do conferences, workshops, rounds, and other traditional continuing education activities change physician behavior or health care outcomes? *JAMA* 1999;282:867-874.

24 Smits PB, Verbeek JH, van Dijk FJ, et al. Evaluation of a postgraduate educational programme for occupational physicians on work rehabilitation guidelines for patients with low back pain. *Occup Environ Med.* 2000;57:645-646.

25 Forsetlund L, Bradley P, Forsen L, et al. Randomised controlled trial of a theoretically grounded tailored intervention to diffuse evidence-based public health practice [ISRCTN23257060]. *BMC Med Educ*. 2003;3:2.

26 Rebergen D, Hoenen J, Heinemans A, et al. Adherence to mental health guidelines by Dutch occupational physicians. *Occup Med (Lond)*. 2006;56:461-468.

27 Prior M, Guerin M, Grimmer-Somers K. The effectiveness of clinical guideline implementation strategies--a synthesis of systematic review findings. *J Eval Clin Pract*. 2008;14:888-897.

28 Grimshaw JM, Thomas RE, MacLennan G, et al. Effectiveness and efficiency of guideline dissemination and implementation strategies. *Health Technol Assess*. 2004;8:iii-72.

29 Hadely KA, Power E, O'Halloran R. Speech pathologists' experiences with stroke clinical practice guidelines and the barriers and facilitators influencing their use: a national descriptive study. *BMC Health Serv Res.* 2014;14:110.

30 Medves J, Godfrey C, Turner C, Paterson M, Harrison M, MacKenzie L, Durando P: Systematic review of practice guideline dissemination and implementation strategies

for healthcare teams and team-based practice. *Int J Evid Based Healthc* 2010;8:79-89.

31 Prior M, Guerin M, Grimmer-Somers K. The effectiveness of clinical guideline implementation strategies--a synthesis of systematic review findings. *J Eval Clin Pract*. 2008;14:888-897.

32 Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. *Lancet* 2003;362:1225-1230.

Attachment I. EULAR recommendations for the management of RA, differences between participating rheumatologists and rheumatologists that stopped or were lost to follow-up during the study.

	Participants (n=72)		Drop outs/LF (n=50)	
	Yes	(Some)times /No	Yes	(Some)times /No
Are you aware of the recommendations? N, %	72 (100)	-	50 (100)	-
Are you following the recommendations?	58 (81)	14 (19)	38 (76)	12 (24)
1. Treatment with synthetic DMARDs should be started as soon as the diagnosis of RA is made	70 (99)	1 (1)	48 (96)	2 (4)
2. Treatment should be aimed at reaching a target of remission or low disease activity as soon as possible in every patient; as long as the target has not been reached, treatment should be adjusted by frequent (every 1–3 months) and strict monitoring.	64 (90)	7 (10)	47 (94)	3 (6)
3. MTX should be part of the first treatment strategy in patients with active RA	69 (97)	2 (3)	47 (94)	3 (6)
4. When MTX contraindications (or intolerance) are present, the following DMARDs should be considered as part of the (first) treatment strategy: leflunomide, SSZ or injectable gold.	59 (83)	12 (17)	42 (84)	8 (16)
5. In DMARD naïve patients, irrespective of the addition of GCs, synthetic DMARD monotherapy rather than combination therapy of synthetic DMARDs may be applied.	56 (79)	15 (21)	41 (82)	9 (18)
6. GCs added at low to moderately high doses to synthetic DMARD monotherapy (or combinations of synthetic DMARDs) provide benefit as initial short-term treatment, but should be tapered as rapidly as clinically feasible.	64 (90)	7 (10)	43 (86)	6 (14)
7. If the treatment target is not achieved with the first DMARD strategy, addition of a biological DMARD should be considered when poor prognostic factors are present; in the absence of poor prognostic factors, switching to another synthetic DMARD strategy should be considered	60 (85)	11 (15)	39 (78)	11 (22)
8. In patients responding insufficiently to MTX and/or other synthetic DMARDs with or without GCs, biological DMARDs should be started; current practice would be to start a TNF inhibitor (adalimumab, certolizumab, etanercept, golimumab, infliximab) which should be combined with MTX	61 (86)	10 (14)	41 (82)	9 (18)
9. Patients with RA for whom a first TNF inhibitor has failed, should receive another TNF inhibitor, abatacept, rituximab or tocilizumab	67 (94)	4 (65)	45 (90)	5 (10)
10. In cases of refractory severe RA or contraindications to biological agents or the previously mentioned synthetic DMARDs, the following synthetic DMARDs might be also considered, as monotherapy or in combination with some of the above: azathioprine, ciclosporin A (or exceptionally, cyclophosphamide)	49 (69)	22 (31)	32 (64)	18 (36)
11. Intensive medication strategies should be considered in every patient, although patients with poor prognostic factors have more to gain.	67 (94)	4 (6)	42 (86)	7 (14)
12. If a patient is in persistent remission, after having tapered GCs, one can consider tapering biological DMARDs, especially if this treatment is combined with a synthetic DMARD	54 (76)	17 (24)	37 (76)	12 (24)
13. In cases of sustained long-term remission, cautious titration of synthetic DMARD dose could be considered, as a shared decision between patient and doctor	61 (86)	10 (14)	43 (88)	6 (12)
14. DMARD naïve patients with poor prognostic markers might be considered for combination therapy of MTX plus a biological agent	47 (86)	10 (14)	31 (63)	18 (37)
15. When adjusting treatment, factors apart from disease activity, such as progression of structural damage, comorbidities and safety concerns should be taken into account	69 (97)	2 (3)	47 (96)	2 (4)

Attachment II. Treat to target, differences between participating rheumatologists and rheumatologists that stopped during the study.

	participants		Drop outs/LF	
	Yes	(Some)times /No	Yes	(Some)times /No
Are you aware of the recommendations? N, %	70 (97)	2 (3)	47 (96)	2 (4)
Are you following the recommendations?	55 (79)	15 (21)	31 (66)	16 (34)
1. **The primary target for treatment of rheumatoid arthritis should be a state of clinical remission.**	65 (93)	5 (7)	41 (93)	3 (7)
2. **Clinical remission is defined as the absence of signs and symptoms of significant inflammatory disease activity.**	68 (97)	2 (3)	39 (89)	5 (11)
3. **While remission should be a clear target, based on available evidence low disease activity may be an acceptable alternative**	67 (96)	3 (4)	42 (95)	2 (5)
4. **Until the desired treatment target is reached, drug therapy should be adjusted at least every 3 months.**	65 (93)	5 (7)	37 (84)	7 (16)
5. **Measures of disease activity must be obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity or less frequently (such as every 3–6 months) for patients in sustained low disease activity or remission**	60 (86)	10 (14)	31 (70)	13 (30)
6. **The use of validated composite measures of disease activity, which include joint assessments, is needed in routine clinical practice to guide treatment decisions.**	65 (93)	5 (7)	39 (89)	5 (11)
7. **Structural changes and functional impairment should be considered when making clinical decisions, in addition to assessing**	64 (91)	6 (9)	41 (93)	3 (7)
8. **The desired treatment target should be maintained throughout the remaining course of the disease.**	65 (93)	5 (7)	37 (84)	7 (16)
9. **The choice of the (composite) measure of disease activity and the level of the target value may be influenced by consideration of co-morbidities, patient factors and drug-related risks.**	67 (96)	3 (4)	38 (86)	6 (14)
10. **The patient has to be appropriately informed about the treatment target and the strategy planned to reach this target under the supervision of the rheumatologist.**	65 (93)	5 (7)	41 (93)	3(7)

Chapter 8

Summary and general discussion

In this thesis we focussed on so-called 'treat to target' therapy in rheumatoid arthritis (RA). Treat to target relies on repetitive measurements of disease activity using a composite score that incorporates signs of disease activity such as laboratory results, findings of physical joint assessments, and the opinion of the patient. It is recommended that rheumatologists intensify treatment when a predefined level of disease activity, the target, has not yet been achieved. The implementation of treatment to target in daily practice depends on the faith of the rheumatologist and the patient to rely on a disease activity composite index (for instance the DAS) rather than on some judgemental estimate of disease activity ('the patient is doing well'). It also relies on a consensual opinion that a pre-set treatment target (for instance a DAS=<2.4, meaning low disease activity, or a DAS<1.6, meaning clinical remission) is a desirable as well as an achievable target, and especially on the willingness to intensify medication every time the treatment target has not been achieved. Several aspects of treat to target, in particular a plea for the improvement of the rheumatologists' awareness about and the implementation of treat to target recommendations in daily clinical practice, are discussed in the thesis. In this chapter the content of this thesis will be summarized and the main findings will be discussed.

Chapter 1 is a general introduction, which describes the characteristics of RA and the importance of treat to target therapy with the use of synthetic (s) DMARDs, biologic (b) DMARDs and corticosteroids.

Chapter 2 offers a systematic review of national and international databases in the field of rheumatoid arthritis. We have found four international databases, which have started between 2004 and 2008. They are quite similar, collecting data on patients with various degrees of disease severity and treated with a wide range of sDMARDs and bDMARDs.[1-3] It remains unclear to what extent these databases are a representation of normal daily practice. The owners of the databases do not collaborate in the EULAR repository of databases. The national databases (n=32) are more heterogeneous in size, year of inception (between 1986 and 2010), inclusion criteria, aims and frequency of data collection. Many databases share similarities in collecting patient-reported outcomes, physician's clinical evaluation and medication use. Only half of these databases, the older and larger ones with most publications, are included in the EULAR repository of databases. We conclude that this review provides a useful overview of RA databases, which can be consulted by researchers to find out which databases are available for collaboration and comparisons between cohorts.

For the future it would be valuable to be connected to the EULAR repository of databases to increase collaboration between researchers. Moreover, to decrease differences in set up, collection of data and other technical details to improve the quality of the databases.

Chapter 3 investigates the efficacy of intra-articular injections in a treat to target strategy study. Patients, in whom the treatment target of low disease activity or remission has not been reached because of residual inflammation in one or two single joints, may sometimes be treated with local intra-articular (IA) glucocorticoid injections. In particular, inflamed large joints may have a significant effect on physical function and general wellbeing, and can often easily be injected with glucocorticoids. This approach has reported to be as effective as adding oral glucocorticoids.[4] In the BeSt study, a 4-arm treat to target strategy trial in recent onset RA patients, intra-articular injections were optional additions to otherwise strictly protocolized treatment adjustments aiming at low disease activity (DAS<2.4). We found that intra-articular glucocorticoid injections most often resulted in short-term satisfactory symptom reduction but had only little impact on long-term clinical outcomes. Although not fully conclusive, IA injections appeared to be safe and not associated with an increase of local joint damage. Some previous studies have suggested that long term glucocorticoid treatment may prevent local radiologic joint damage.[5,6] We do not know if this pertains to intra articular injections with glucocorticoids. Therefore, future studies are needed to confirm our results and to evaluate the long-term benefits and harms of IA glucocorticoid injections.

In **chapter 4 and 5** we have compared patients'- and physicians'-reported outcomes as well as factors that were of influence in scoring differences between patients and physicians in this regard. For these studies we used the METEOR database. METEOR is an online tool, which serves as a software program for daily practice use and can be used by rheumatologists worldwide to register and monitor patients in the METEOR database. The tool has been developed for research and practical purposes, such as to implement guidelines for RA in clinical practice.

Based on data collected in the rheumatology outpatient clinic of the Leiden University Medical Center we have found that patients systematically rate their global disease activity score (GDA) higher (mean difference 11 mm on a 100 mm visual analogue scale (VAS)) than their physicians do; the agreement was only moderate. We found that patients base their decision more on subjective measures (VAS pain) while physicians value objective measures (SJC and ESR) as more important. We compared our results with other studies, in which we

found similar factors explaining PtGDA and PhGDA differences. Other studies performed in the United States and in Europe also described discrepancies in the agreement between physicians and global health assessments.[7,8] These discrepancies may reflect cultural differences between countries with respect to disease activity assessment rated by patient and physician. Therefore, we have investigated the differences in rating between patient and physician in 13 countries (Brazil, Czech, France, Ireland, Italy, Latvia, Mexico, the Netherlands, Pakistan, Portugal, Spain, United Kingdom and the United States), based on the availability of data using the METEOR database. We found differences between PtGDA and PhGDA score related to country of residence of patient and physician, ranging from +13 in Brazil to -2 in Mexico. In some countries, these differences were related to gender (Netherlands and United Kingdom) and disease duration (United Kingdom and United States); while in other countries such a relationship was not evident. These findings raise the question of how important it is that patients and physicians rate disease activity similarly. Pain is a dominant factor in the evaluation of disease activity by the patient, but does not necessarily overlap with 'objective' signs of disease activity that dominate the physician's decision. While the patient may falsely attribute the level of pain to RA-activity, the physician may underestimate the patient's suffering by qualifying the RA as not very active. Shared decision making between patient and physician aims to fill in this gap between patient and physician by increasing mutual understanding. Education is pivotal in this regard. The main question is: should we educate physicians how to understand the patients 'perception', or should we spend more time on teaching patients how physicians interpret their objective assessments? [9-11]And maybe more importantly: Do these discrepancies between patients' and physicians' GDA-ratings truly affect RA care? Future research may focus on a better understanding of the influence of education on the behaviour of physicians and their patients and also on whether education improves the care for RA.

In **chapter 6** we have used the METEOR database to investigate how well DAS-steered therapy is applied in clinical practice**,** based again on data of the Leiden rheumatology outpatient clinic. In 69% of all visits patients were in low disease activity or remission, which suggests that the treat to target approach is properly followed in clinical practice. However, in patients with a DAS>2.4, intensification of treatment (by protocol) was applied in only 35%. We found that medication was less likely to be increased in patients with DAS>2.4 when they were treated with MTX plus a biologic DMARD, or with conventional synthetic DMARD monotherapy. We hypothesized that rheumatologists would not intensify treatment

despite a DAS>2.4 when there had been a substantial improvement since the previous DAS measurement. But this scenario was only found in 9% of the available visits. From this study we conclude that, although in most of the registered visits the patients are in a state of remission or low disease activity, still the detection of moderate and high disease activity does not always lead to treatment intensification. This finding is remarkable since it is in violation with treat-to-target ACR/EULAR recommendations for the management of patients with rheumatoid arthritis, which the rheumatologists claimed to follow meticulously. It seems that individual patients' circumstances rather than protocols determine if treatment guidelines are followed properly. In future research patients' outcomes could be further improved, for instance by implementing treatment protocols with detailed instructions about how to act in case of a high-, a moderate- or a low DAS. Another approach to implement recommendations would be to increase awareness amongst rheumatologists on treat to target by means of educational programs, which will be discussed in the following chapter.

In **chapter 7** we described an international implementation study (IRIS), also conducted within METEOR, which aimed at investigating the awareness of -and improving the implementation of- the European League Against Rheumatism (EULAR) and treat to target recommendations in clinical practice. Participating rheumatologists were asked to complete a questionnaire on their awareness of the recommendations and they were invited to take part in an educational program, which included the reading of two articles and watching an educational video. The participants were asked to include 5-10 newly diagnosed RA patients in METEOR during a follow-up period of 1-2 years. During this period the participants received one recommendation, sent monthly by email, which intended to remind them about treating the patients according to the recommendations. We used the IRIS study to test whether the level of agreement with the recommendations is associated with their true application in clinical practice. For the purpose of this study we have investigated four recommendations and we have found that rheumatologists often report to agree with- and to follow these recommendations. The number of rheumatologists in the study that reported to comply with these recommendations varied from 82 up to 98%. On the other hand we found that only a moderate proportion of their patients were treated according to those same four recommendations: The recommendations were followed in 26-67% of the patients in the METEOR database.

From this study we can conclude that agreement with a recommendation will not necessarily be followed by the actual application of the recommendation. The question is whether the

duration of our 'intervention' was long and profound enough to change the behaviour of the rheumatologists from 'only' agreeing with its content to actually performing it in clinical practice. Future research may focus on the change of behaviour of the rheumatologist over a longer period of time after an educational program. Also, it should be explored which other factors may determine the reluctance to follow recommendations.

In addition, while setting up and conducting the study followed by collecting the data, it has become clear to us (Chapter 2) that there is increasing enthusiasm among rheumatologists to initiate databases and invest time and effort to promote therapies and/or treatment recommendations that may improve patient's lives as well as advance clinical science. However as also suggested by the data in chapter 2, extraction of relevant data from databases in a format that allows analysis often is far more difficult than envisioned at the phase of data collection. Despite best intentions, agreements and recommendable attempts, technical challenges often endanger the scientific success of these initiatives. Future initiatives should look at advanced professional support to ensure that databases are developed in such a manner that they are able to provide the appropriate answers to the relevant questions.

Conclusion and future perspectives

We will now discuss the main goals at the beginning of this thesis and to which outcomes they have led, but more importantly we will discuss what we can learn from this thesis.

The main focus was to improve care in patients with rheumatoid arthritis by investigating the awareness and the implementation of existing treatment-recommendations in clinical practice. Here we aimed at comparing rheumatologists' agreement with - and their actual performance of - treat-to-target recommendations in daily clinical practice and on investigating (cultural) differences in perceptions of both the RA-patient and the treating physician in rating the global disease activity of the patient. How well are these recommendations implemented in daily practice and how can we further improve implementation of recommendations?

Based on **chapter 7**, our main conclusion is that there is a discrepancy between the rheumatologists' agreement and will to follow recommendations and the actual application of recommendations in clinical practice. It seems that rheumatologists are willing to apply guidelines, but that there are still certain factors that inhibit them to follow recommendations

in individual patients. What can we do to reduce the gap between agreement with recommendations and behaviour in clinical practice?

We may want to investigate the effects of implementation initiatives, such as educational programs, meetings or reminders by email and/or telephone. In follow up studies of IRIS we will evaluate the benefits of stimulated training by an educational program on the application of guidelines in RA. However, to actually change the rheumatologist's behaviour we may also want to focus on reasons that hinder rheumatologists to follow recommendations in clinical practice. This may well be related to differences between patients' and rheumatologists' perspectives on the disease as we have observed in **chapter 4**. Here we have found that patients and physicians think about different determinants when assessing global disease activity. Patients put more weight on pain and physicians more on ESR and swollen joint count, which may easily jeopardise so called 'shared decision making' between patients and rheumatologists. In order to promote better agreement between patients and rheumatologists we should focus future research on investigating to what extent treatment goals for rheumatologists and patients differ and why. Interestingly, agreement between rheumatologist and patient about the severity of RA may be dependent on the country in which patient and physician both reside as has been suggested in **chapter 5.** Here we have found that the agreement between the patient and the physician regarding the assessment of global disease activity differs per country; Shared decision making, a common term, may have different cultural implications!

We hypothesize that improving the agreement between patient and physician on the activity of the disease will lead to better performance in clinical practice. Shared decision making may be enhanced if the rheumatologist communicates well with the patient on desirable and realistic target achievements. For instance, the rheumatologist and the patient can agree on a treatment target of DAS low disease activity when remission is not realistic.

In **chapter 6** we have observed that patients with high levels of disease activity are not always receiving the recommended treatment in daily practice. Reasons for this can be related to the physician: For instance, the rheumatologist may value the patient's will not to change treatment, as suggested in **chapter 6**. But also the complexity of RA and the increasing number of treatment options may make it difficult to decide for a rheumatologist which approach is the best to choose. Furthermore, the rheumatologist may believe that a slightly elevated level of disease activity does not justify rigorous treatment change.

On the other hand, the patient may be reluctant to intensify the medication thus following recommendations that she is not familiar with. Patients may, for instance, better accept

additional treatments with local corticosteroids in inflamed joints (**chapter 3**) that may provide short-term relief, and as such in agreement with principles of treat-to-target, but still with uncertain long term consequences.

Implementation research, studies on how recommendations will be adopted and applied in clinical practice, is of pivotal importance to further improve clinical practice. Consulting platforms such as the EULAR repository of databases discussed in **chapter 2**, containing a lot of information about various databases in Europe, with its aim to improve collaboration between researchers, but also initiatives such as METEOR (described in Chapter 4 - 7), with aggregated information available about thousands of patients from all over the world, could be of help with this.

Since only half of the identified European databases are connected to EULAR repository awareness among researchers should be promoted and a worldwide initiative for a repository of databases would be worthwhile to stimulate in the future.

In conclusion, to improve care in patients with rheumatoid arthritis we should seek for effective strategies to better implement recommendations in clinical practice. In addition, we should try to optimize shared decision making between rheumatologists and physicians by improving communication between them with regard to achievable treatment targets. Future studies, such as IRIS, will be carried out to prove whether implementation strategies, such as educational programs, will help to implement recommendations and improve RA care in clinical practice.

REFERENCE LIST

1 Chatzidionysiou K, Lie E, Nasonov E, et al. Highest clinical effectiveness of rituximab in autoantibody-positive patients with rheumatoid arthritis and in those for whom no more than one previous TNF antagonist has failed: pooled data from 10 European registries. *Ann Rheum Dis* 2011;70:1575-1580.

2 Koevoets R, Allaart CF, van der Heijde DM, Huizinga TW. Disease activity monitoring in rheumatoid arthritis in daily practice: experiences with METEOR, a free online tool. *J Rheumatol* 2010;37:2632-2633.

3 Sokka T, Kautiainen H, Toloza S, et al. QUEST-RA: quantitative clinical assessment of patients with rheumatoid arthritis seen in standard rheumatology care in 15 countries. *Ann Rheum Dis* 2007;66:1491-1496.

4 Keystone E, Haraoui B: Adalimumab therapy in rheumatoid arthritis. *Rheum Dis Clin North Am* 2004;30:349-64, vii.

5 Da Silva JA, Jacobs JW, Kirwan JR, et al. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. *Ann Rheum Dis* 2006;65:285-293.

6 de Jong PH, Hazes JM, Han HK, et al. Randomised comparison of initial triple DMARD therapy with methotrexate monotherapy in combination with low-dose glucocorticoid bridging therapy; 1-year data of the tREACH trial. *Ann Rheum Dis* 2014;73:1331-1339.

7 Ward MM. Clinical measures in rheumatoid arthritis: which are most useful in assessing patients? *J Rheumatol* 1994;21:17-27.

8 Kwoh CK, O'Connor GT, Regan-Smith MG, et al. Concordance between clinician and patient assessment of physical and mental health status. J Rheumatol 1992;19:1031-1037.

9 Riemsma RP, Kirwan JR, et al. Patient education for adults with rheumatoid arthritis. *Cochrane Database Syst Rev* 2003;CD003688.

10 Combe B, Landewe R, Lukas C, et al. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2007;66:34-45.

11 van den Bemt BJ, Den Broeder AA, van den Hoogen FH, et a.. Making the rheumatologist aware of patients' non-adherence does not improve medication adherence in patients with rheumatoid arthritis. *Scand J Rheumatol* 2011;40:192-196.

NEDERLANDSE SAMENVATTING

In dit proefschrift staat ‘treat to target’ therapie voor patiënten met reumatoïde artritis (RA) centraal. Het ‘treat to target’ concept berust op het maken van frequente en betrouwbare schattingen van de ziekteactiviteit aan de hand van scores van labwaarden, mate van gewrichtsklachten en de mening van de patiënt. Het is van belang dat reumatologen de patiënten frequent monitoren en de therapie aanpassen wanneer van tevoren gedefinieerde behandeldoelen met betrekking tot de ziekteactiviteit nog niet zijn behaald. De implementatie van ‘treat to target’ in de dagelijks praktijk is sterk afhankelijk van het vertrouwen van de reumatoloog en patiënt in de huidige maten voor de ziekteactiviteit, zoals bijvoorbeeld de DAS (“Disease Activity Score”), en de meerwaarde van zo’n score boven het (subjectieve) oordeel van de arts (“het gaat goed met de patiënt”). Daarnaast is implementatie afhankelijk van het behandeldoel. Men kan zich bijvoorbeeld richten op het bereiken van een DAS=<2.4 (lage ziekte activiteit) of een DAS=<1.6 (remissie, dat wil zeggen geen ziekteactiviteit meetbaar). De echte vraag is: Welk behandeldoel is wenselijk en haalbaar, en in hoeverre zijn reumatologen en patiënten bereid om zo nodig vergaande intensivering van behandeling te accepteren wanneer het doel niet behaald is. In dit proefschrift zullen verschillende aspecten van ‘treat to target’ toegelicht worden. Hierbij staan het vergroten van het bewustzijn- en de implementatie van de ‘treat to target’ richtlijnen onder reumatologen in de dagelijkse praktijk centraal. In dit hoofdstuk zal de inhoud van dit proefschrift worden samengevat met de belangrijkste resultaten en de conclusie.

Hoofdstuk 1 is een algemene introductie waarin karakteristieken van RA worden beschreven. Daarnaast wordt het belang van ‘treat tot target’ therapie en het gebruik van conventionele synthetische ‘disease-modifying antirheumatic drugs’ (cs) DMARDs, biologische (b) DMARDs en corticosteroïden toegelicht.

In h**oofdstuk 2** worden de resultaten beschreven van een systematisch literatuuronderzoek naar bestaande inter(nationale) databases in reumatoïde artritis. Het literatuuronderzoek leverde vier internationale databases op die recent (tussen 2004 en 2008) zijn opgericht en de volgende gemeenschappelijke eigenschappen bezitten: ze verzamelen data van patiënten in alle stadia van RA die worden behandeld met een grote verscheidenheid aan csDMARDs en bDMARDs. Het is nog niet duidelijk in hoeverre deze databases de dagelijkse praktijk reflecteren. De beheerders van de databases zijn niet aangesloten bij de ‘EULAR (European Leage Against Rheumatism) repository of databases’, een initiatief gestart door de EULAR

met als doel om de samenwerking tussen Europese onderzoekers te verbeteren. In de nationale databases (n=32) zijn meer verschillen gevonden dan in de internationale databases. De nationale databases verschillen in grootte, jaar van oprichting (tussen 1986 en 2010), inclusiecriteria, doelen en de frequentie van dataverzameling. De meeste nationale databases hebben ook gemeenschappelijke eigenschappen, zoals het rapporteren van patiënt-gerapporteerde uitkomsten, medicatiegebruik en de klinische evaluatie van de arts. Slechts de helft van deze 32 databases, de oudere en grotere, zijn aangesloten bij de 'EULAR repository of databases'. Dit literatuuronderzoek geeft een bruikbaar overzicht van RA databases dat kan worden geraadpleegd door onderzoekers om te weten welke databases er bestaan en welk soort onderzoek er gedaan wordt. Onderzoekers kunnen op deze manier samenwerken en bijvoorbeeld cohorten met elkaar vergelijken. Het zou waardevol zijn als er in de toekomst meer databases zijn verbonden met de 'EULAR repository of databases'. Door meer en betere samenwerking zal de kwaliteit van de databases verbeteren en de verschillen tussen de databases in o.a. onderzoeksopzet, het verzamelen van data en andere technische details, kleiner worden.

In **hoofdstuk 3** wordt de relatie tussen intraarticulaire (IA) injecties en klinische uitkomstmaten in een 'treat to target' setting beschreven. Het komt soms voor dat patiënten geen lage ziekte activiteit of remissie kunnen bereiken omdat er nog één of twee gewrichten ontstoken zijn. Met name een ontsteking van de grote gewrichten kan invloed hebben op het dagelijks functioneren en het algemeen welbevinden. Deze gewrichten kunnen gemakkelijk lokaal geïnjecteerd worden met corticosteroïden, hetgeen net zo effectief is als het oraal toedienen van corticosteroïden. BeSt is een gerandomiseerde studie waarin patiënten werden toegewezen aan vier verschillende behandelarmen. In deze studie was het toegestaan om IA-injecties toe te dienen wanneer nodig. In BeSt zijn patiënten behandeld volgens een strict protocol waarin behandeling werd gestuurd op het bereiken van een lage ziekteactiviteit (DAS<2.4). Uit deze studie is gebleken dat IA-injecties met corticosteroïden op korte termijn meestal tot verlichting van ontstekingsklachten leidt, maar op lange termijn is er maar weinig invloed op klinische uitkomstmaten. We vonden geen relatie tussen IA injecties en gewrichtsschade. Daaruit kunnen we niet concluderen dat IA injecties schade kunnen voorkomen.Toekomstig onderzoek moet zich richten op het bevestigen van onze resultaten en op het evalueren van de voor- en nadelen van IA-injecties met corticosteroïden op lange termijn.

In **hoofdstuk 4** en **5** zijn patient- en arts gerapporteerde uitkomstmaten met elkaar vergeleken en is onderzocht welke factoren invloed hebben op het verschil tussen deze uitkomstmaten. Deze studie is uitgevoerd in de METEOR database, een online programma dat gebruikt kan worden door reumatologen in de dagelijkse praktijk om patiënten te registreren en te monitoren. METEOR is ontwikkeld voor zowel onderzoeksdoeleinden als om praktische redenen, zoals bijvoorbeeld het implementeren van richtlijnen voor RA in de klinische praktijk. Uit data van het Leids Universitair Medisch centrum (LUMC) in de METEOR database is gebleken dat de patiënt zijn eigen globale ziekteactiviteit (GDA) hoger scoort dan zijn arts dat doet. Het verschil tussen beide scores is gemiddeld 11mm op een visuele analoge schaal (VAS): de overeenkomst tussen patiënt en reumatoloog is matig. Uit deze studie is ook gebleken dat patiënten hun GDA score vooral baseren op subjectieve (pijn) maten en dat reumatologen objectieve (gezwollen gewrichten en bloedbezinking) maten belangrijker vinden. Vroegere studies hebben ook laten zien dat bovengenoemde factoren de verschillen in GDA score tussen patiënt en arts lijken te verklaren. Daarnaast zijn er in Europa en de Verenigde Staten studies uitgevoerd met andere globale gezondheidsscores die ook hebben aangetoond dat er verschillen zijn tussen patiënt en arts wat betreft de beoordeling van die score. Deze discrepanties tussen patiënt en arts zullen wellicht te wijten zijn aan culturele verschillen tussen landen. Om die reden hebben we de verschillen in GDA score tussen patiënt en arts onderzocht in 13 verschillende landen (Brazilië, Tsjechië, Frankrijk, Ierland, Italië, Letland, Mexico, Nederland, Pakistan, Portugal, Spanje, Verenigd Koninkrijk en de Verenigde Staten) gebaseerd op beschikbare data in de METEOR database. De discrepantie in GDA score tussen patiënt en arts varieërde per land: van +13mm tussen patiënten en artsen wonend in Brazilië tot -2mm tussen patiënten en artsen wonend in Mexico. In sommige landen waren deze verschillen gerelateerd aan geslacht (Nederland en Verenigd Koninkrijk) en ziekteduur (Verenigd Koninkrijk en Verenigde Staten), terwijl in andere landen dergelijke relaties niet werden gevonden. Het is natuurlijk de vraag hoe belangrijk het is dat patiënten en artsen dezelfde score geven aan de ziekteactiviteit. Voor de patiënt heeft pijn een belangrijke bijdrage in de evaluatie van ziekteactiviteit, maar de mate van pijn hoeft niet persé overeen te komen met de objectieve kernmerken van de ziekteactiviteit die beoordeeld worden door de arts. Terwijl de patiënt de RA activiteit wellicht zal overschatten (omdat hij/zij veel pijn heeft), zal de arts deze eerder onderschatten als objectieve verschijnselen ontbreken. Het gezamenlijk maken van beslissingen tussen patiënt en arts heeft als doel de verschillen in interpretatie tussen patiënt en arts te verkleinen zodat ze elkaar beter leren begrijpen. Dit kan bevorderd worden door educatie. De vragen die hieruit volgen zijn:

Moeten we artsen onderwijzen in het beter leren begrijpen van de interpretatie van de patiënt, of moeten we meer tijd spenderen aan het onderwijzen van patiënten in het leren begrijpen hoe artsen objectieve maten interpreteren? En in welke mate hebben de verschillen in de beoordeling van ziekteactiviteit tussen patiënt en arts een invloed op de zorg voor patiënten met RA? Toekomstig onderzoek zou zich kunnen richten op het beter leren begrijpen van de invloed van educatie op het gedrag van artsen en hun patiënten. Daarnaast zou onderzocht kunnen worden of dergelijke educatie de zorg van RA verbetert.

In **hoofdstuk 6** wordt geëvalueerd hoe goed DAS gestuurd behandelen in de dagelijkse praktijk wordt toegepast. Voor deze studie werd gebruik gemaakt van METEOR data en wederom is een subselectie gemaakt van patiënten die behandeld zijn in het LUMC. Uit deze studie bleek dat in 69% van de gerapporteerde visites in METEOR, patiënten een lage ziekteactiviteit hadden. Dit resultaat wekt de suggestie dat behandelen volgens het 'treat to target' concept wel wordt toegepast in de klinische praktijk. Echter, tijdens visites waar patiënten een matige- of hoge ziekteactiviteit (DAS>2.4) hadden, werd de therapie in slechts 35% aangepast, terwijl dit volgens de richtlijnen wel wordt aanbevolen. Patiënten bij wie de therapie niet werd aangepast ondanks een DAS>2.4, ontvingen vaker therapie met MTX en een bDMARD, of csDMARD monotherapie. Een reden hiervoor zou kunnen zijn dat de reumatoloog besluit de medicatie niet op te hogen in deze patiëntengroep, omdat hij/zij een substantiële verbetering ziet ten opzichte van de vorige DAS meting. Echter, dit scenario was bij slechts 9% van de patiëntvisites waargenomen. Uit dit onderzoek kunnen we concluderen dat patiënten tijdens de meeste visites een lage ziekte activiteit hebben of in remissie zijn. De medicatie wordt echter lang niet altijd opgehoogd in patiënten met matige- of hoge ziekte activiteit. Dit resultaat is opmerkelijk omdat het niet in overeenstemming is met de EULAR richtlijnen voor de management van RA, die er natuurlijk voor bedoeld zijn om te worden nageleefd door de reumatoloog. Het is mogelijk dat individuele omstandigheden van de patiënt een grotere invloed hebben op het naleven van richtlijnen dan specifieke behandelprotocols. In toekomstig onderzoek zouden de klinische uitkomstmaten van de patiënt verbeterd kunnen worden door gedetailleerde behandelprotocollen te implementeren waar instructies in staan beschreven over hoe te handelen bij een patiënt met hoge, matige en lage zieteactiviteit. Een andere manier om richtlijnen te implementeren is door reumatologen te stimuleren zich bewust te worden van 'treat to target'. Dit zou kunnen door middel van educatie waar we in het volgende hoofdstuk dieper op in zullen gaan.

In **hoofdstuk 7** staan de resultaten van een studie naar internationale implementatie van richtlijnen (IRIS) beschreven, welke ook is uitgevoerd in de METEOR database. Deze studie had als doel om de bewustwording en de implementatie van de EULAR richtlijnen voor de behandeling van RA en de 'treat to target' richtlijnen te onderzoeken en te verbeteren. Deelnemende reumatologen werd gevraagd om een vragenlijst in te vullen over of ze de richtlijnen kennen en of ze deze in de dagelijkse praktijk toepassen. Vervolgens werden ze uitgenodigd om deel te nemen aan een educatief programma, waarbij ze ze twee artikelen moesten lezen en een educatie-video moesten bekijken. Daarna werd de deelnemers gevraagd om 5-10 'nieuw gediagnosticeerde' RA patiënten toe te voegen aan de METEOR database gedurende een follow-up periode van 1-2 jaar. Tijdens deze periode ontvingen deelnemende reumatologen maandelijks een email waarin één van de aanbevelingen uit de richtlijnen werd toegelicht. Deze email was bedoeld om reumatologen te stimuleren patiënten volgens de richtlijnen te behandelen. In de IRIS studie hebben we onderzocht of reumatologen die rapporteren dat zij patiënten behandelen volgens de richtlijnen dit ook daadwerkelijk doen in de dagelijkse praktijk. Hierbij zijn vier aanbevelingen uit de richtlijnen nader onderzocht. Uit de resultaten van dit onderzoek blijkt dat reumatologen in 82-98% van de gevallen rapporteren dat ze deze vier aanbevelingen inderdaad opvolgen. We vonden echter in de METEOR database dat er slechts een berperkt percentage van hun patiënten (26-67%) daadwerkelijk volgens deze vier aanbevelingen werden behandeld. Uit deze studie concludeerden we dan ook dat wanneer men rapporteert een richtlijn op te volgen dit niet betekent dat men deze richtlijn ook daadwerkelijk opvolgt in de dagelijkse praktijk. De vraag is dan ook of ons 'educatie-programma' voldoende impact heeft gehad om het gedrag van de reumatoloog te veranderen van 'het eens zijn met een aanbeveling' tot 'het daadwerkelijk toepassen van de aanbeveling' in de klinische praktijk. In de toekomst zou onderzocht moeten worden welke factoren van invloed zijn op het niet opvolgen van richtlijnen. Uit **hoofdstuk 2** is duidelijk geworden dat er enthousiasme onder reumatologen is om databases op te richten en therapieën/richtlijnen te promoten, hetgeen kan leiden tot verbetering van klinisch onderzoek en patiëntenzorg. In **hoofdstuk 2** is echter ook gebleken dat het moeilijk is om relevante informatie voor analyses uit deze databases te halen, aangezien hier onvoldoende op wordt geanticipeerd in de fase van dataverzameling. Ondanks de beste bedoelingen blijven er technische uitdagingen om deze databases tot een wetenschappelijk succes te maken. Toekomstige initiatieven zouden zich kunnen richten op het verbeteren van de ontwikkeling van databases, zodat we op een efficiëntere manier relevante onderzoeksvragen kunnen beantwoorden.

Conclusie en toekomstperspectieven

Dit proefschrift richtte zich op het verbeteren van zorg bij patiënten met reumatoïde artritis, met name door het bewustzijn en de implementatie van bestaande richtlijnen in de dagelijkse praktijk te onderzoeken en waar mogelijk te verbeteren. Hierbij hebben we onderzocht of reumatologen die het eens zijn met de richtlijnen ze ook daadwerkelijk toepassen in klinische praktijk. Daarnaast hebben we (culturele) verschillen bestudeerd in de perceptie van ziekteactiviteit van patiënt versus arts. Hoe goed zijn huidige richtlijnen al geïmplementeerd in de klinische praktijk en hoe kunnen we de implementatie verder verbeteren? Kortom, wat kunnen we leren van dit proefschrift?

Onze belangrijkste conclusie is dat er een discrepantie is tussen het eens zijn met- en het opvolgen van- richtlijnen door reumatologen in de dagelijkse praktijk. Het lijkt erop dat reumatologen de richtlijnen graag willen opvolgen maar dat er factoren zijn die hen belemmeren om ze ook daadwerkelijk toe te passen. Wat kunnen we doen om de kloof tussen het eens zijn met richtlijnen en gedrag in klinische praktijk te verkleinen? We zouden kunnen onderzoeken wat de effecten zijn van implementatie initiatieven zoals educatieve programma's, meetings of reminders per e-mail en/of telefoon. In vervolg studies van de IRIS zullen we evalueren welke de voordelen zijn van het volgen van een educatief programma met betrekking tot het opvolgen van richtlijnen. Echter, om het gedrag van reumatologen daadwerkelijk te beïnvloeden zullen we ons moeten richten op factoren die de reumatoloog belemmeren om richtlijnen op te volgen in dagelijkse praktijk. Die kunnen bijvoorbeeld gerelateerd zijn aan verschillen in perceptie van ziekteactiviteit tussen patiënt en reumatoloog, zoals is gebleken uit de resultaten in **hoodstuk 4**. Hier hebben we gevonden dat bij het beoordelen van de ziekteactiviteit patiënt en reumatoloog niet met dezelfde factoren rekening houden. De patiënt laat zich meer leiden door pijn en de reumatoloog meer door bloedbezinking en gezwollen gewrichten. Dit verschil kan een negatieve invloed hebben op het maken van gezamenlijke beslissingen door patiënt en reumatoloog. Om de overeenstemming tussen de patiënt en arts te vergroten zou toekomstig onderzoek zich moeten richten op verschillen in behandeldoel van zowel patiënt als arts en op waarom dergelijke verschillen bestaan. Zo zou het kunnen zijn dat de mate van overeenstemming in ziekteactiviteit afhankelijk is van het land van herkomst. Uit **hoofdstuk 5** is gebleken dat overeenstemming verschilt per land. Het gezamenlijk beslissingen nemen (zoals wordt gepropageerd) zou dus culturele connotaties kunnen hebben. De impliciete verwachting is dat

een verbetering in overeenstemming tussen de patiënt en arts in het beoordelen van de ziekteactiviteit zal leiden tot een betere patiëntenzorg in de dagelijkse praktijk. Het proces van gezamenlijk beslissingen nemen zou kunnen worden verbeterd door een goede communicatie tussen patiënt en arts over gewenste en realistische behandeldoelen. Wanneer remissie niet haalbaar is kunnen de patiënt en reumatoloog gezamenlijk beslissen om bijvoorbeeld het bereiken van lage ziekteactiviteit tot doel te stellen. Uit **hoofdstuk 6** is gebleken dat patiënten met matige tot hoge ziekteactiviteit niet altijd werden behandeld volgens de richtlijnen. Zowel arts- als patiënt-gerelateerde factoren kunnen hierbij een invloed hebben gehad. De reumatoloog kan moeite hebben met het kiezen van de juiste aanpak, aangezien er veel verschillende behandelopties zijn en RA een complexe ziekte is. Ook kan de reumatoloog het niet eens zijn met de DAS en er dan voor kiezen om bij een licht verhoogde ziekteactiviteit niet meteen de behandeling aan te passen. Aan de andere kant kan het de wens zijn van de patiënt om de therapie niet op te hogen. Sommige patiënten hebben vervolgens meer baat bij injectie van lokale ontstoken gewrichten met corticosteroïden. Deze injecties verminderen klachten op korte termijn, maar op lange termijn weten we nog niet goed wat de consequenties kunnen zijn (**hoofdstuk 3**). Om de behandeling van RA in de dagelijkse praktijk te verbeteren is het van belang om te onderzoeken hoe goed richtlijnen reeds worden toegepast in dagelijkse praktijk en hoe we dit verder kunnen verbeteren. Platforms, zoals de EULAR repository of databases (**hoofdstuk 2**), kunnen hierbij van dienst zijn omdat ze veel informatie bevatten over verscheidene databases in Europa en als doel hebben de samenwerking tussen reumatologen te verbeteren. Daarnaast kunnen initiatieven zoals METEOR, dat gegevens bevat over duizenden patiënten wereldwijd, helpen om richtlijnen beter te implementeren. Uit ons literatuuronderzoek is gebleken dat slechts de helft van de Europese databases is aangesloten bij de EULAR repository of databases. Daarom is het van belang onderzoekers te stimuleren hieraan deel te nemen. Ook zou het waardevol zijn om in de toekomst een ‘repository of databases’ op te richten waaraan onderzoekers van overal in de wereld kunnen deelnemen.

Tot slot, om de zorg voor patiënten met reumatoïde artritis te verbeteren, moeten we op zoek gaan naar effectieve strategieën om richtlijnen beter te implementeren in de klinische praktijk. Daarnaast moeten we stimuleren dat klinische beslissingen gezamenlijk door patiënt en reumatoloog worden gemaakt door onderlinge communicatie met betrekking tot haalbare behandeldoelen te bevorderen. Toekomstig onderzoek, zoals de IRIS, zal zich richten op strategieën die tot doel hebben de implementatie van richtlijnen te verbeteren en zodoende de zorg voor patiënten met reumatoïde artritis in de klinische praktijk te optimaliseren.

LIST OF PUBLICATIONS

E. Gvozdenović, R. Koevoets, J. Langenhoff, C.F. Allaart, R. Landewé. Comparison of characteristics of international and national databases in Rheumatoid Arthritis: a systematic literature review. *Scand J Rheumatol. 2014 Jun 5:1-7.*

E. Gvozdenović, R. Koevoets, R. Wolterbeek, D. van der Heijde, T.W.J. Huizinga, C.F. Allaart, R. Landewé. Assessment of global disease activity in RA patients monitored in the METEOR database: the patient's versus the rheumatologist's opinion. *Clin Rheumatol. 2014 Apr;33(4):461-6.*

E. Gvozdenović, L.Dirven, M. van den Broek, K.H. Han, E.T.H. Molenaar, R. Landewé, W.F. Lems, C.F. Allaart. Intra articular injection with corticosteroids in patients with recent onset rheumatoid arthritis: subanalyses from the BeSt study. *Clin Rheumatol. 2014 Feb;33(2):263-7.*

E. Gvozdenović, R. Wolterbeek, C.F. Allaart, G.C. Brenol, M. Dougados, P. Emery, G. Ferraccioli, D. van der Heijde, T.W.J. Huizinga, J. Kay, E. Martin Mola, R.J. Moots, J.A.P. da Silva, J. S. Smolen, D. Veale, R. Landewé. Assessment of global disease activity in RA by patients and physicians: cultural differences across countries in the METEOR Database. *J Clin Rheumatol. 2015 Oct;21(7):349-54.*

E. Gvozdenović , R. Wolterbeek, D. van der Heijde, T.W.J. Huizinga, C.F. Allaart, R. Landewé. DAS steered therapy in clinical practice; cross-sectional results from the METEOR database. *Accepted in BMC Musculoskeletal Disorders*

E. Gvozdenović, R. Wolterbeek, C.F. Allaart, G.C. Brenol, M. Dougados, P. Emery, G. Ferraccioli, D. van der Heijde, T.W.J. Huizinga, J. Kay, E. Martin Mola, R.J. Moots, J.A.P. da Silva, J. S. Smolen, D. Veale, R. Landewé. Does agreement with a guideline imply that this guideline is followed in clinical practice? The International Recommendation Implementation Study (IRIS) *Submitted.*

CURRICULUM VITAE

Emilia Gvozdenović werd geboren op 6 mei 1987 in Drammen, te Noorwegen. In 2004 behaalde zij haar havo diploma aan het Oranje Nassau College in Zoetermeer, waarna zij startte aan de sportacademie in Den Haag.

In 2005 besloot zij een andere weg in te slaan; zij begon de studie huidtherapie aan de Hogeschool in Utrecht. Begin 2008 vertrok zij voor een stage naar Zuid-Afrika om onderzoek te doen naar de bewustwording van afvalscheiding in het gebied Breede Rivier. Vanwege haar groeiende interesse in wetenschappelijk onderzoek besloot zij in 2008 een schakeljaar te gaan volgen in de studie gezondheidswetenschappen aan de Universiteit Maastricht. In 2009 sloot zij haar schakeljaar en bachelor huidtherapie af, waarna zij startte aan haar onderzoeksmaster in Maastricht. In 2010 behaalde zij een MSc in Epidemiology.

Vanaf januari 2011 was zij werkzaam als promovendus in het Leids Universitair Medisch Centrum. Onder leiding van mw. dr. C.F. Allaart, Prof. dr. T.W.J. Huizinga, Prof. dr. D.M.F.M. van der Heijde en Prof. dr. R.B.M. Landewé deed zij onderzoek naar het monitoren van de ziekte RA, met als focus de bewustwording en implementatie van richtlijnen onder reumatologen via een internationale studie. Daarnaast volgde zij cursussen in epidemiologie en gaf hierin ook onderwijs. Momenteel volgt zijn een Post-Master in Statistische Data-analyse in Gent. Zij verwacht deze studie af te ronden in September 2016.

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