Introduction

INFLAMMATORY RHEUMATIC DISEASES

Chronic inflammatory rheumatic diseases are of crucial interest because of their major impact on public health, as they combine a high prevalence in the general population and a potentially severe impact on functional abilities and global health [1]. Rheumatoid arthritis (RA) and spondyloarthritis (SpA) are the most frequent chronic inflammatory diseases, with an estimated worldwide prevalence of 0.5 to 1% respectively [2] and of around 0.5% in European and North-American populations [3].

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder that can affect tissues and organs, but most frequently involves peripheral joints of patients. A considerable part of the world's population is affected by the disease, women approximately three times more often than men. Age at onset is most frequently between 40 and 50, but people of any age can develop the disease. RA is a disabling and painful condition, as it usually starts with a period of swelling and pain in the peripheral joints, which can thereafter lead to substantial loss of function and mobility of affected joints, especially if no adequate therapy is started [4]. Treatment of RA has recently changed to a more intensive approach, with most recent recommendations aiming at an early introduction of disease-modifying anti rheumatic drug (DMARD), preferentially methotrexate, as soon as the diagnosis is made [5, 6]. Initial management of a patient suffering from RA should also comprise periodic and close clinical and laboratory evaluations. The predefined goal is disease remission or low disease activity state, as assessed by appropriate instruments like the DAS28 (disease activity score-28 joints) [6-8]. Regular tailoring of therapy based on the disease activity status of the patient is recommended, aiming at achieving remission in patients with recent RA, and at least a low disease activity state in patients with established disease and already irreversible functional impairment. In the last two decades, the insight into the physiopathology of the disease has led to the development of so called targeted therapies, also called biologics or biotherapies [9]. Thanks to these new treatments, ambitious short term and long term outcomes have become possible in most patients, because of the high potential of these treatments to improve symptoms and halt radiographic progression of involved joints [10]. This specific feature of damage to bone and cartilage structures of the joint still remains the most

disabling consequence of RA, as it causes functional loss. Structural damage affects both the bony parts and the cartilage surfaces of the target joint, causing erosive defects in the cortical bone and narrowing of the joint space, respectively, when measured on plain radiography. Different scoring systems have successively been designed to assess the level of damage in a patient, with the two types of abnormalities (erosions and joint space narrowing) either scored as global damage or as two independent features, measured according to two independent scales. The number and sites of joints to be scored are also different across the various systems, but usually radiographs of hands, wrists and feet are taken into account in the scoring methods. Because the scales used to assess the erosions and the joint space are of different range and precisions, the performances and difficulties to apply the respective methods are also variable, and the time required to apply one method is usually inversely proportional with its accuracy and performances to differentiate radiographic damage or change [11, 12]. A challenging task would therefore be the development of a scoring system which combines feasibility and optimal metrological performance, i.e. an acceptable time required to apply the score with a fair reliability and discriminatory ability. Indeed, the main aim of a radiographic scoring system is to capture change in radiographic damage over time and, especially in the context of a clinical trial, to compare observed levels of change in lesions across the treatment arms. Consequently, these radiographic lesions can be measured in a patient either as an evaluation at a certain point of time, or two time points can be used and compared to define a change in radiographic damage (radiographic change). This observed change in radiographs of RA patients was -until recently- regarded an irreversible consequence of the disease. With the advent of new treatments, especially the biologicals, so called "negative change scores" have been introduced in the radiographic assessment suggesting that radiographs can improve over time [13]. The fact that radiographs of a given patient are scored by a reader who is unaware of the real chronological order ("concealed time order") makes it possible to differentiate a negative change score as a surrogate for a repair of lesions from a negative change score caused by measurement error. Further insight into radiographic data is needed to make this differentiation and this will be presented in this thesis.

ANKYLOSING SPONDYLITIS AND OTHER SPONDYLOARTHRITIDES

Ankylosing spondylitis (AS), also known as Pierre Marie Strumpel's disease [14, 15] or Morbus Bechterew [16], is a chronic inflammatory rheumatic disor-

der primarily affecting the axial skeleton and causing a painful and potentially disabling condition, with a significant proportion of affected patients having a major impairment of spinal mobility. The prevalence of AS varies between 0.2 and 2.1% of the population, with a probable underestimation due to frequently benign forms of the disease as well as potential misdiagnosis due to the high prevalence of a-specific low back pain in the population [17]. Disease onset usually occurs in late adolescence or in early adulthood, and is rare after 45 years of age [18]. Major symptoms of AS are chronic back pain and stiffness, often of insidious onset, tending to worsen after periods of physical inactivity especially during the night, while it usually improves by exercise, which is also called inflammatory back pain [19]. Pathophysiology of the disease relies on inflammatory processes involving entheses located on vertebrae and vertebral ligaments, facet joints as well as peripheral interfaces between tendons or ligaments with thoracic or limb bones, as well as in the pelvis. Moreover, approximately 25% of patients affected by AS will develop peripheral disease and suffer from painful and potentially destructive arthritis of limb joints, especially shoulders and hips. Besides these rheumatic manifestations, other extra-articular features including acute anterior uveitis, inflammatory bowel disease and psoriasis occur in about 40% of the patients [20]. AS is part of a group of diseases named spondyloarthritis (SpA) which also comprises psoriatic arthritis, arthritis/spondylitis with inflammatory bowel disease (IBD), and reactive arthritis. In addition, patients who do not fulfill classification criteria for one of the aforementioned disorders but nevertheless show characteristics of SpA are usually considered as having undifferentiated SpA. Because the clinical presentation is often predominantly characterized by either axial symptoms, such as inflammatory back pain, or peripheral manifestations (arthritis or enthesitis), the Ankylosing Spondylitis (ASAS) working group has recently developed classification criteria separately for axial and peripheral SpA [24, 25]. With regard to axial disease, radiographic sacroiliitis is an essential part of existing criteria sets for AS, especially the modified New York cirteria, the reference in clinical studies conducted in the disease [23]. A major limitation of the modified New York criteria was the fact that radiographic abnormalities usually develop several years after symptom onset, which often precludes an early diagnosis of the disease. Recognition of the inflammatory processes in the sacroiliac joints is however possible early in the disease course when magnetic resonance imaging (MRI) is applied, and this alternative has been included in the recent ASAS classification criteria for axial SpA as an important feature. Another major feature of SpA is the presence of the HLA-B27 gene, and in the new criteria set for axial SpA HLA-B27 positivity also serves as a starting

point for a classifying diagnosis. In summary, axial SpA is diagnosed when, in a patient suffering from chronic low back pain below the age of 45 years at symptom onset, sacroiliitis (recognized on plain X-Rays or MRI) is associated with at least 1 other SpA feature, or when HLA-B27 is present together with at least 2 other SpA features [25]. Peripheral SpA is diagnosed when arthritis, enthesitis or dactylitis as a starting feature is recognized in a patient with at least 1 or 2 other SpA features (depending on the weight of individual SpA features) [24].

Similarly as in RA, treatment of AS patients has recently changed into a more intensive anti-inflammatory approach by TNF blocking drugs [4, 10]. Patients with an insufficient clinical response or intolerance to non-steroidal anti-inflammatory drugs (NSAIDs), which remain the first-line treatment of AS, should be considered for a TNF-blocking drug. This treatment is very effective in mitigating the symptom of sacroiliitis associated with AS and SpA. In this context, because TNF-blockers can be discussed only once the diagnosis of AS is ascertained, a confirmation of SpA/AS at an early stage makes a timely treatment start in severe or refractory cases possible, even though specific radiographic abnormalities are (still) lacking.

CLINICAL RESEARCH AND OUTCOME MEASURES

Clinical research in the field of rheumatology has recently evolved from a pragmatic and global approach to a more systematic and scientific evaluation of patients, especially in the context of inflammatory rheumatic diseases like RA and AS.

These major changes were first summarized, then promoted and enhanced under the auspices of an informal international global network of clinicians and researchers in the field of rheumatology named OMERACT (for Outcome Measures in Rheumatology Clinical Trials) and which first took place in 1992 in Maastricht, the Netherlands [26]. The major goals of the recommended process aiming at developing efficient outcome measures were summarized under the global term of "OMERACT filter", which encompasses every characteristic an assessment tool should ideally fulfill to be regarded as effective and applicable. The OMERACT filter proposes an evaluation of performances of an outcome tool based on three concepts: truth, discrimination, and feasibility. Truth encompasses face, content, construct, and criterion validity, and addresses the question whether the measure assesses what it was meant to in an

unbiased and relevant way. Discrimination addresses the issue of reliability and sensitivity to change by answering the question whether the measure discriminates between situations of interest. Feasibility relates to whether a measure can be applied pragmatically, given financial and interpretation constraints in longitudinal observational studies and randomized controlled trials. It is expected that measures used to assess rheumatological conditions will "pass" the OMERACT filter [27].

In the specific field of AS, an international working group on ASsessment in Ankylosing Spondylitis (ASAS, later named as Assessment of SpondyloArthritis international Society) was formed in 1995. In 1997, the domains for the core sets aiming at assessing all aspects of the disease in an individual patient and their change over time were defined [28, 29]. The minimum core set for each setting comprised physical function, pain, spinal mobility, spinal stiffness and patient global assessments. The core set was updated to include fatigue in the core domain. The following domains were added for clinical record keeping: acute phase reactants, peripheral joints, entheses, and finally to asses the disease modifying effect of drugs on spine and hip radiographs [30]. Further choice of most relevant instruments to assess disease outcomes for both clinical practice and study purposes was performed to create uniformity and comparability in AS management [31]. Physical function, which is both related to disease activity and damage in AS, is usually measured by self-administered questionnaires, with the BASFI (Bath Ankylosing Spondylitis Functional Index) being the most frequently used by rheumatologists, both in daily care and clinical trials. The BASFI consists of 10 questions on a visual analogue scale, all questions dealing with activities of daily living. The score is the average of the ratings of the 10 questions, ranging from 0 to 10. In order to assess disease activity of AS, several instruments have been developed, but the BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) remains a recognized standard to date both for clinical management of AS patients and clinical studies. It consists of a self-administered questionnaire with 6 questions rated from 0 to 10 on a visual analogue scale. The questions pertain to fatigue, spinal pain, joint pain/swelling, areas of localized tenderness and morning stiffness. Although the metrological performances of the instrument have been demonstrated, several weaknesses are acknowledged by the rheumatologic community, especially the fact that only patient-reported outcomes are taken into account, whereas objective measurements of disease activity like the acute phase reactants are not included in the calculation of the index.

AIMS OF THE THESIS

The main aims of this thesis were to further develop outcome measurement in RA and AS. With regard to RA, the focus is on optimizing, re-designing and testing the assessment of change in radiographic damage.

With regard to AS, the focus is on designing and validating instruments for measuring disease activity, using clinical tools and magnetic resonance imaging.

Chapters 1, **2**, **3** and **4** focus on radiographic evaluation of RA. Firstly, the performance of a new scoring method of radiographic damage, the SENS (for *Simple Erosion and Narrowing Score*) is evaluated [32]. This scoring method was derived from the Sharp method, with a simplification of the scoring process aiming at a wider use by any rheumatologist, while the original Sharp method and derived scores require specific training and certification of the reader [12, 33]. Confirmation of the metrological values of the new score according to the predefined "OMERACT filter" was required before its dissemination could be approved. **Chapter 2** compares different computer-based methods that were developed to assess joint space narrowing progression as is usually observed in hands and feet joints of patients with RA. The feasibility, discriminatory ability and reproducibility of five methods are assessed and compared with the current gold standard, the "manual" scoring of joint space according to Sharp van der Heijde score [34] .

Chapter 3 and 4 further investigate the value of radiographic results observed in recent clinical trials of RA, where negative change scores have been reported in patients treated with biologics, which at first sight might be regarded as a potential improvement of radiographic lesions due to RA, a surrogate for a potential "repair" of erosions in most actively treated patients [13]. Data from a clinical trial (TEMPO) that has compared clinical and radiographic efficacy of etanercept (a recombinant soluble receptor of TNF) alone or in combination with methotrexate were used, and analyzed at the single-joint level [13]. In **chapter 3**, reproducibility of negative change scores is assessed, thanks to four repeated readings of baseline- and 1 year radiographs of included patients. **Chapter 4** evaluates the plausibility of this potential "repair" phenomenon in comparing its chance to occur as a function of the treatment that was used, the radiographic status of the joint at study inclusion and the clinical response that was observed in that individual joint.

Chapters 5 and 6 evaluate the current therapeutic strategies in early inflammatory arthritis. The ESPOIR cohort study, a French multicenter collabora-

tive observational initiative was used as a working support [35, 36]. **Chapter 5** investigates which of the baseline characteristics of the patient and physician are predictive of a treatment start with a DMARD over the first year of follow-up, similarly as what was done more recently to develop the ACR/EULAR 2010 criteria for RA, where the initiation of methotrexate was regarded as the external standard to define the diagnosis of RA in a patient [37, 38]. **Chapter 6** aims at confirming that a very early DMARD initiation can be beneficial on short-term radiographic outcome in a study in daily clinical practice,. In this work, a propensity analysis of ESPOIR therapeutic behavior and 1-year radiographic data compares the efficacy of starting a DMARD of known structural efficacy within the first 3 months of disease versus later.

In **chapters 7 and 8**, the development of outcome measures in AS is extended. Firstly, disease activity as evaluated by magnetic resonance imaging (MRI) of the spine is evaluated by comparing three different scoring methods from the previously described "OMERACT filter" point of view. The Ankylosing Spondylitis spine Magnetic Resonance Imaging-activity (ASspiMRI-a); the Berlin modification of the ASspiMRI-a; and the Spondyloarthritis Research Consortium of Canada (SPARCC) scoring systems are compared [39-41]. Finally, in **chapter 8**, the development of a score aiming at assessing disease activity in a patient with AS including the most relevant aspects is presented. Indeed, measuring disease activity in AS is quite challenging, because the varying clinical presentation of the disease, its spontaneous course and the inconsistent presence of biological abnormalities, especially for the acute phase reactants. The process that was previously applied to derive the disease activity score (DAS) in RA is described and used in **chapter 8** to obtain a similar disease activity score in AS, named ASDAS for Ankylosing Spondylitis-Disease Activity Score [42]. Data were collected in ISSAS (*International Study on Starting tumour necrosis factor-blocking agents in Ankylosing Spondylitis)*, a large cohort of consecutively included patients from 10 countries referred to a rheumatologist who decided, based on all available clinical, biological and reported assessments whether the patient was in a state of active disease, i.e. required a treatment with TNF blocking drug [43].

Finally, this thesis ends with a global summary and general discussion of reported results.

REFERENCES

1. Majithia V, Geraci SA. Rheumatoid arthritis: diagnosis and management. The American journal of medicine. 2007;120(11):936-9.
2. Guillemin F, Saraux A, Guggenbuhl P et al. Prevalence of rheumatoid arthritis in France: 2001. Ann Rheum Dis. 2005;64(10):1427-30.
3. Saraux A, Guillemin F, Guggenbuhl P et al. Prevalence of spondyloarthropathies in France: 2001. Ann Rheum Dis. 2005;64(10):1431-5.
4. Pincus T, Callahan LF. The 'side effects' of rheumatoid arthritis: joint destruction, disability and early mortality. British journal of rheumatology. 1993;32 Suppl 1:28-37.
5. Smolen JS, Aletaha D, Bijlsma JW et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Annals of the rheumatic diseases. 69(4):631-7.
6. 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). Annals of the rheumatic diseases. 2007;66(1):34-45.
7. Saag KG, Teng GG, Patkar NM et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis and rheumatism. 2008;59(6):762-84.
8. 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. 69(6):964-75.
9. Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. The New England journal of medicine. 2001;344(12):907-16.
10. Braun J, Kalden JR. Biologics in the treatment of rheumatoid arthritis and ankylosing spondylitis. Clinical and experimental rheumatology. 2009;27(4 Suppl 55):S164-7.
11. Guillemin F, Billot L, Boini S et al. Reproducibility and sensitivity to change of 5 methods for scoring hand radiographic damage in patients with rheumatoid arthritis. The Journal of rheumatology. 2005;32(5):778-86.
12. van der Heijde DM. Plain X-rays in rheumatoid arthritis: overview of scoring methods, their reliability and applicability. Bailliere's clinical rheumatology. 1996;10(3):435-53.
13. Klareskog L, van der Heijde D, de Jager JP et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet. 2004;363(9410):675-81.
14. Strümpel A. Lehrbuch der speziellen Pathologie und Theralpe der innerenKrankheiten. Leipzig, Vogel. Band 2, Teil 2:152-3. 1884.
15. Marie P. Sur la spondylose rhizomélique. Revue Médicale. 1893;18:285.
16. Bechterew vW. Steifheit der Wirbelsäule und ihre Verktümmung als besondere Erkrankungs-form. Neurologisches Zentralbl. 1893;12:426.
17. Sieper J, Rudwaleit M, Khan MA et al. Concepts and epidemiology of spondyloarthritis. Best practice & research. 2006;20(3):401-17.
18. Gran JT, Husby G. Clinical, epidemiologic, and therapeutic aspects of ankylosing spondylitis. Current opinion in rheumatology. 1998;10(4):292-8.
19. Braun J, Sieper J. Ankylosing spondylitis. Lancet. 2007;369(9570):1379-90.
20. Khan MA, van der Linden SM. Ankylosing spondylitis and other spondyloarthropathies. Rheumatic diseases clinics of North America. 1990;16(3):551-79.

21. Amor B, Dougados M, Mijiyawa M. [Criteria of the classification of spondylarthropathies]. Revue du rhumatisme et des maladies osteo-articulaires. 1990;57(2):85-9.
22. Dougados M, van der Linden S, Juhlin R et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. Arthritis and rheumatism. 1991;34(10):1218-27.
23. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis and rheumatism. 1984;27(4):361-8.
24. Rudwaleit M, van der Heijde D, Landewe R et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis. 70(1):25-31.
25. Rudwaleit M, van der Heijde D, Landewe R et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009;68(6):777-83.
26. Boers M, Brooks P, Strand CV et al. The OMERACT filter for Outcome Measures in Rheumatology. The Journal of rheumatology. 1998;25(2):198-9.
27. Gladman DD, Strand V, Mease PJ et al. Developing assessment methodology in psoriatic arthritis OMERACT 7 psoriatic arthritis workshop: synopsis. Ann Rheum Dis. 2005;64:ii115-ii116 doi:10.1136/ard.2004.032615.
28. van der Heijde D, Bellamy N, Calin A et al. Preliminary core sets for endpoints in ankylosing spondylitis. Assessments in Ankylosing Spondylitis Working Group. The Journal of rheumatology. 1997;24(11):2225-9.
29. van der Heijde D, Calin A, Dougados M et al. Selection of instruments in the core set for DC-ART, SMARD, physical therapy, and clinical record keeping in ankylosing spondylitis. Progress report of the ASAS Working Group. Assessments in Ankylosing Spondylitis. The Journal of rheumatology. 1999;26(4):951-4.
30. van der Heijde D, van der Linden S, Bellamy N et al. Which domains should be included in a core set for endpoints in ankylosing spondylitis? Introduction to the ankylosing spondylitis module of OMERACT IV. The Journal of rheumatology. 1999;26(4):945-7.
31. Zochling J, Braun J, van der Heijde D. Assessments in ankylosing spondylitis. Best practice & research. 2006;20(3):521-37.
32. van der Heijde D, Dankert T, Nieman F et al. Reliability and sensitivity to change of a simplification of the Sharp/van der Heijde radiological assessment in rheumatoid arthritis. Rheumatology (Oxford, England). 1999;38(10):941-7.
33. Sharp JT, Young DY, Bluhm GB et al. How many joints in the hands and wrists should be included in a score of radiologic abnormalities used to assess rheumatoid arthritis? Arthritis and rheumatism. 1985;28(12):1326-35.
34. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. The Journal of rheumatology. 2000;27(1):261-3.
35. Combe B, Benessiano J, Berenbaum F et al. The ESPOIR cohort: a ten-year follow-up of early arthritis in France: methodology and baseline characteristics of the 813 included patients. Joint Bone Spine. 2007;74(5):440-5.
36. Combe B. The French early arthritis registry. Clinical and experimental rheumatology. 2003;21(5 Suppl 31):S123-8.

37. Aletaha D, Neogi T, Silman AJ et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis and rheumatism. 62(9):2569-81.
38. Aletaha D, Neogi T, Silman AJ et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Annals of the rheumatic diseases. 69(9):1580-8.
39. Maksymowych WP, Inman RD, Salonen D et al. Spondyloarthritis Research Consortium of Canada magnetic resonance imaging index for assessment of spinal inflammation in ankylosing spondylitis. Arthritis and rheumatism. 2005;53(4):502-9.
40. Braun J, Baraliakos X, Golder W et al. Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis, before and after successful therapy with infliximab: evaluation of a new scoring system. Arthritis and rheumatism. 2003;48(4):1126-36.
41. Braun J, van der Heijde D. Imaging and scoring in ankylosing spondylitis. Best practice & research. 2002;16(4):573-604.
42. van der Heijde DM, van 't Hof M, van Riel PL et al. Development of a disease activity score based on judgment in clinical practice by rheumatologists. The Journal of rheumatology. 1993;20(3):579-81.
43. Pham T, Landewe R, van der Linden S et al. An international study on starting tumour necrosis factor-blocking agents in ankylosing spondylitis. Annals of the rheumatic diseases. 2006;65(12):1620-5.