# A joint evaluation of local and systemic disease activity in treated-to-target rheumatoid arthritis

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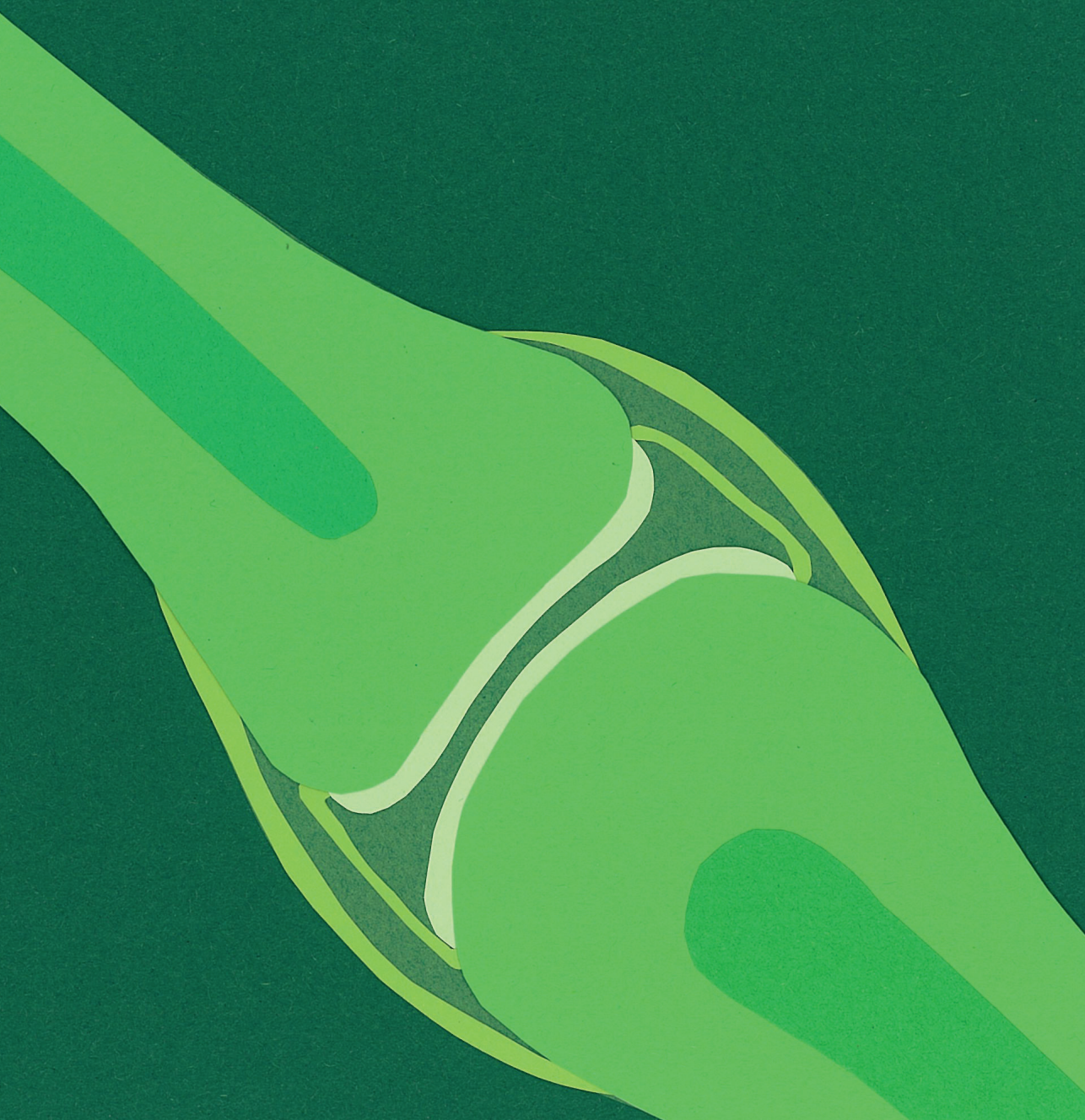
**Chapter 1**

# General introduction and thesis outline



## Rheumatoid arthritis

Rheumatoid arthritis (RA) is a systemic disease, characterized by joint pain and swelling in multiple joints, primarily caused by inflammation of the synovium. Hand and foot joints are most commonly affected, although other joints can also be involved. Globally, the prevalence of RA is 0.5 to 1%, with women being more often affected than men.[1-3] The age of disease onset differs worldwide, but is usually around the 5th decade.[4] Diagnostic criteria are unavailable, but classification criteria have been developed for research purposes. Currently, the ACR/EULAR 2010 criteria are used, which replaced the 1987 ACR criteria (table 1).[5, 6] In some studies, RA is defined as meeting either the 2010 ACR/EULAR or the 1987 ACR criteria.



**Table 1.** ACR 1987 and ACR/EULAR 2010 criteria for RA

| ACR 1987 criteria | ACR/EULAR 2010 criteria |
|---|---|
| At least 4/7 criteria:<br>1. Morning stifness ≥1 hour<br>2. Clinical arthritis in ≥3 joint areas<br>3. Arthritis of min. 6 weeks in ≥1 of the following: wrist, metacarpophalangeal or proximal interphalangeal joint<br>4. Symmetric arthritis (min. 6 weeks)<br>5. Presence of rheumatoid nodules<br>6. Positive rheumatoid factor (RF) in serum<br>7. Radiographic joint changes typical for RA | At least 6/10 points based on:<br>Joint involvement<br>• 1 large joint (0)<br>• 2-10 large joints (1)<br>• 1-3 small joints (2)<br>• 4-10 small joints (3)<br>• >10 joints, of which min. 1 small (5)<br>Serology:<br>• Negative RF and anticitrullinated protein antibodies (ACPA) (0)<br>• Low-positive RF or ACPA (2)<br>• High-positive RF or ACPA (3)<br>Acute phase reactants:<br>• Normal CRP and ESR (0)<br>• Abnormal CRP or ESR (1)<br>Duration of symptoms<br>• <6 weeks (0)<br>• ≥6 weeks (1) |

RA, especially if insufficiently treated, can cause joint damage and functional disability and can have a negative impact on quality of life. In the past century, before the introduction of currently used disease modifying therapies and treatment strategies, joint damage often led to joint deformities and severe limitations in daily activities, and patients with RA had an increased risk for mortality, with a reported reduction of life expectancy of 6-7 years.[7]

## Pathophysiology of RA

Although the pathophysiology of RA is not fully elucidated, a genetic predisposition combined with environmental exposure, including smoking, plays a significant role in the development of the disease. These factors probably lead to a breach of immunological tolerance, that is, failure to discriminate between self and nonself antigens. If followed by an additional trigger, potentially an infection, this can lead to abnormal activation of the innate and adaptive immune system.[2] Consequently, leukocytes infiltrate the synovium. As part of the tissue response, synovial fibroblasts acquire a more aggressive and invasive phenotype.[8] These synovial fibroblasts can invade cartilage and cause cartilage destruction.[9] Furthermore, via other inflammatory processes, including cytokine production, osteoclastogenesis is promoted.[9] These two processes contribute to joint space narrowing and development of bone erosions, features that can be visualised by X-ray and that are referred to as radiographic joint damage.

RA disease activity typically fluctuates over time. Although inflammation can be suppressed by antirheumatic drugs, flares of disease activity may occur when the treatment is tapered or when it is insufficiently effective.

Auto-antibodies, most importantly rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPA), often arise during the development of RA. An increase in circulating ACPA-producing B-cells and rise of cytokine concentrations has been observed just before articular symptoms develop.[2] Patients with auto-antibodies tend to have a more severe RA phenotype with worse radiographic and functional outcomes. It has been proposed that auto-antibody, and specifically ACPA-, positive and negative RA are two different disease entities.[10] The exact pathophysiological role of these auto-antibodies is not yet determined.

## RA treatment

Several types of disease modifying drugs (DMARDs) are available for the treatment of RA. Generally, conventional synthetic DMARDs (csDMARDs), including methotrexate, sulfasalazine, leflunomide and hydroxychloroquine, are used as a first treatment step and can be combined with short-term glucocorticoids. In case of insufficient effect, other (cs)DMARDs can be added, or patients can switch to another (cs)DMARD. Since the last two decades, biological DMARDs (bDMARDs) are also available for RA treatment, for example tumour necrosis factor (TNF)-α inhibitors, such as adalimumab and infliximab. In current guidelines, it is advised to treat patients with a treatment target of remission or low disease activity (treat-to-target strategy), with treatment intensification in case of insufficient suppression of disease activity.[11, 12]

Treat-to-target strategies have, together with the effort to initiate DMARD treatment early in the disease, considerably improved treatment outcomes in patients with RA. While patients with RA previously developed considerable radiographic joint damage and invalidating joint deformities, radiographic joint damage was shown to be limited, and functional ability relatively preserved in patients treated with a treat-to-target approach.[13, 14] Before the introduction of treat-to-target therapies, mortality in patients with RA was higher than in the general population. In trials using a treat-to-target approach for early RA, mortality was reported to be normalized after 10-11 years of follow-up.[13, 14] However, it remains unclear what the effects of current treat-to-target strategies are on (very) long term, since results of treat-to-target strategies with more than 10 years follow-up are scarce.



### Local inflammation and treatment in RA

Joint swelling and tenderness are clinical signs of joint inflammation. On imaging, synovitis, tenosynovitis and osteitis are observed in joints that are involved during flares. Why certain joints are affected at the start of the disease and during the disease course, and others not, might be dependent on local factors. For example, it has been described that DNA methylation patterns of fibroblast-like synoviocytes in RA differ between joint locations.[15] It has also been proposed that differences in joint innervation and vascularisation might affect the susceptibility for local inflammation. Furthermore, mechanical stress on joints, which varies between different types and locations of joints, can aggravate local joint inflammation. Defining the role of systemic and local processes in the occurrence of disease flares might help in finding improved therapy strategies.

Local inflammation is sometimes treated locally with glucocorticoid injections in addition to systemic DMARD treatment, especially during mono- or oligoarticular flares. Intra-articular glucocorticoid injections can provide quick relieve of symptoms of local inflammation, with sometimes long-term reduction of symptoms.[16-18] For monoarthritis, intra-articular injection of methotrexate and TNF-inhibitors has also been studied, but the effect does not seem to be superior to that of glucocorticoids.[19]

### Extra-articular features and comorbidity

Several extra-articular manifestations may occur in patients with RA, including rheumatoid nodules, vasculitis and scleritis.[20, 21] In previous decades, involvement of kidneys and other internal organs were feared disease outcomes. Cardiovascular disease has also been reported to be more frequent in patients with RA.[22] Increased RA disease activity has been associated with the occurrence of cardiovascular disease, potentially mediated by systemic

inflammation.[22] In previous studies, cardiovascular diseases have been described as an important cause of death.[23-25]

Rheumatoid-arthritis associated interstitial lung disease (RA-ILD) contains a spectrum of inflammatory and fibrotic lung diseases that have also been considered to be an extra-articular manifestation of rheumatoid arthritis.[20, 21] The estimated prevalence of RA-ILD varies widely depending on the definition and method of detection.[26-29] ILD might either precede RA symptoms or may develop during the RA disease course. The clinical expression may vary from interstitial lung abnormalities on imaging without any symptoms to restricted lung function with severe dyspnoea. RA-ILD is also associated with increased mortality. Currently, there is no consensus on the treatment of patients with RA-ILD. Both a protective effect of DMARDs and a pulmonary toxic effect of some DMARDs have been assumed, but data to substantiate a protective effect is lacking and reports on toxic effects show conflicting results.[30-33] Specific medication for ILD has also been investigated, with positive results of antifibrotic drugs in fibrosing interstitial lung diseases.[34] International data collection can contribute to the understanding of RA-ILD and its potential treatment.

## Undifferentiated arthritis

Undifferentiated arthritis (UA) comprises arthritis for which specific types of arthritis have been considered and found unlikely. For research, an additional requirement is that RA classification criteria (2010 and/or 1987 criteria) are not met. In two Dutch early arthritis cohorts, 12-34% of the patients with arthritis was diagnosed with UA (not meeting 2010 RA criteria) at the first visit.[35] Because of this definition, patients with UA typically have a lower number of involved joints and are mostly antibody negative. Of the patients with UA, 13-54% later develops RA.[36] UA can also progress to other types of arthritis, or persists as UA in 21-87%.[36] UA might also resolve spontaneously. Treatment strategies for patients with UA are largely based on those used in RA. In this thesis, we only focus on UA that is clinically suspected to be an early form of RA.

## Juvenile idiopathic arthritis

JIA describes a heterogeneous cluster of different forms of chronic arthritis of unknown origin with age at onset before 16 years of age. Currently, these are subdivided into 7 categories, of which 3 categories are studied in this thesis

(oligoarticular, RF-negative polyarticular and psoriatic JIA). In oligoarticular JIA, maximum 4 joints are affected. Oligoarthritis mostly affects the lower extremity joints.[37] In polyarticular JIA, 5 or more joints are affected, typically the metacarpophalangeal joints and wrists. Psoriatic JIA is characterized by presence of psoriasis or psoriasis-associated features (dactylitis, nail pitting/ onycholysis, psoriasis in a first-degree relative). Psoriatic arthritis most commonly involves the small joints.[37, 38]

As in RA, development of JIA is thought to be dependent on a combination of genetic and environmental factors and eventually abnormal activation of the innate and adaptive immune system.[37] In oligoarticular and polyarticular JIA, an important role is attributed to disruption of the balance between regulatory and effector T cells. Erosions, cartilage loss and bone deformity can occur in patients with juvenile idiopathic arthritis, especially if disease activity is insufficiently suppressed.[39, 40]



Both systemic and local inflammatory features can be observed in JIA and extra-articular manifestations vary between the different types of JIA, with for example higher risk of uveitis in patients with oligoarthritis and psoriatic arthritis.[37] What specific role local and systemic inflammation play during the disease course of the different types of JIA is not fully elucidated.

Both local and systemic therapies are used in the treatment of JIA. The recommended treatment target is inactive disease.[41] Local treatment is more frequently given for oligoarthritis, where current guidelines advise intra-articular glucocorticoid administration as a first treatment step, followed by conventional synthetic disease modifying drugs (csDMARDs) and thereafter biological DMARDs (bDMARDS) in case of insufficient effect.[42] For patients with polyarthritis systemic (csDMARD) therapy is currently recommended as the first treatment step, with addition of bDMARDs, intra-articular glucocorticoid injection, csDMARD dose increase or csDMARD change as a second step in case of insufficient effect, depending on the level of disease activity.[43] For psoriatic JIA, treatment recommendations are dependent on the number and type of joints involved and mainly based on treatment strategies used in oligoarthritic and polyarthritic JIA.[43]

## Research databases

The chapters in this thesis are based on analysis of various databases. Data from the BeSt study, IMPROVED study, BeSt for Kids study, Early arthritis clinic (EAC) and METEOR have been used. The characteristics of these studies are

described in the following sections. Results of the RECALL study, a follow-up study of the BeSt and IMPROVED studies, are also reported in this thesis.

### BeSt

The BeSt (*BehandelStrategieën*, Dutch acronym for 'treatment strategies') study is a randomized clinical trial, performed between 2000 and 2012, in which 508 patients with early RA (1987 criteria) were treated with a target of DAS ≤2.4.[14, 44] At baseline, patients were randomized into four different treatment strategy arms. Patients from arm 1 received methotrexate, and in case of insufficient response (DAS>2.4) switched to other csDMARD therapy (sequential monotherapy). In arm 2, patients also started with initial methotrexate monotherapy, but another csDMARD was added in case of insufficient response (step-up combination therapy). In arm 3, patients started treatment with a combination of multiple csDMARDs (methotrexate, sulfasalazine and hydroxychloroquine) and prednisone. In arm 4, patients started treatment with a combination of methotrexate and infliximab. For 10 years, disease activity was monitored every 3 months with treatment adjustments in case of DAS >2.4 and tapering of medication in case of sustained DAS-remission (DAS<1.6 for ≥6 months).

### IMPROVED

The IMPROVED (Induction therapy with Methotrexate and Prednisone in Rheumatoid or Very Early arthritic disease) study is a randomized clinical trial, performed between 2007 and 2015, in which 610 patients with early RA or UA clinically suspected for RA were treated with a target of drug-free DAS-remission.[45] All patients started with induction therapy with methotrexate and prednisone tapered to low dose. After four months, patients who were not in early remission were randomized between arm 1: addition of sulfasalazine and arm 2: switching to methotrexate and adalimumab. For 5 years, disease activity was monitored every 4 months with treatment adjustments in case of DAS≥1.6 and tapering medication to stop in case of DAS<1.6. Patients who achieved early remission, but subsequently flared (DAS≥1.6), without sufficient effect of reintroduction of prednisone, were also randomized between csDMARD combination therapy and adalimumab/MTX combination therapy. In this thesis, these patients were analysed in the 'early remission' group.

### BeSt for Kids

In the BeSt for Kids study, a randomized clinical trial, 92 patients with oligoarticular, RF-negative polyarticular and psoriatic JIA were treated with a treatment target of an ACRPedi50 response (50% improvement in 3 of 6 core outcome variables) at three months and inactive disease (modified

Wallace 2004 criteria) at six months and further.[46] At baseline, patients were randomized between three different treatment strategy arms: arm 1, initial csDMARD monotherapy (methotrexate or sulfasalazine) with, in case of insufficient response, csDMARD dose increase, followed by switch to etanercept if necessary; arm 2, initial methotrexate combined with prednisolone bridging, if necessary followed by DMARD dose increase and subsequentially etanercept; arm 3, initial combination of etanercept and methotrexate, if necessary followed by subsequent treatment steps according to the choice of the treating physician. Clinical assessments were done at baseline, six weeks and every three months until end of follow-up (two years). Treatment was tapered once inactive disease was achieved for at least 3 months in oligoarticular and 6 months in polyarticular JIA.



### EAC

The EAC (Early Arthritis Clinic) is an observational cohort of patients with early arthritis who visited the outpatient clinic of the Leiden University Medical Centre.[47] Patients are clinically assessed at inclusion, after 3 months and thereafter yearly. Treatment choices are based on shared decision making between rheumatologist and patient.

### METEOR

METEOR is an international database with daily practice data from patients with RA (diagnosis according to treating physician). Currently, data of more than 25 countries is available. The database contains data of both newly diagnosed patients and patients with a longer disease duration at inclusion. Patient and disease characteristics, disease activity and physical functioning data as well as medication data are collected in this database.

## Outline of thesis

In this thesis, we investigate the local effects of non-suppressed inflammation under treat-to-target therapy and the long-term clinical and radiographic outcomes in patients with RA who were treated according to these treatment strategies. To improve the understanding of the underlying processes of disease activity flares during the disease course, in **chapter 2**, we investigate RA joint inflammation patterns over time and assess whether joint inflammation recurs locally in the same joints. Following from this, in **chapter 3**, we investigate whether persistence and recurrence of joint inflammation in a joint is associated with increased joint damage progression. To evaluate whether the results found in chapter 2 and 3 also apply to JIA, we studied local recurrence of joint inflammation and the association between joint

inflammation and radiographic damage in the same joint in children with JIA in **chapter 4**.

Long-term mortality of patients from BeSt and IMPROVED was studied in **chapter 5**. We also evaluated causes of death and the influence of RA disease activity on mortality. In **chapter 6**, we report the radiographic and clinical outcomes of a long-term follow-up study in patients who had been treated during BeSt and IMPROVED, 20 and 12 years since treatment initiation. In **chapter 7**, we assess the incidence of RA-ILD in different countries worldwide in clinical practice data of patients with RA. We also studied the relationship of RA-ILD with RA disease activity.

The results of the studies described in this thesis are summarized and discussed in **chapter 8**.

## References


1. Almutairi K, Nossent J, Preen D, Keen H, Inderjeeth C. The global prevalence of rheumatoid arthritis: a meta-analysis based on a systematic review. Rheumatol Int. 2021;41(5):863-77.
2. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. The Lancet. 2016;388(10055):2023-38.
3. Alamanos Y, Drosos AA. Epidemiology of adult rheumatoid arthritis. Autoimmun Rev. 2005;4(3):130-6.
4. Ramos-Remus C, Sierra-Jimenez G, Skeith K, Aceves-Avila FJ, Russell AS, Offer R, et al. Latitude gradient influences the age of onset in rheumatoid arthritis patients. Clin Rheumatol. 2007;26(10):1725-8.
5. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/ European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569-81.
6. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31(3):315-24.
7. Lassere MN, Rappo J, Portek IJ, Sturgess A, Edmonds JP. How many life years are lost in patients with rheumatoid arthritis? Secular cause-specific and all-cause mortality in rheumatoid arthritis, and their predictors in a long-term Australian cohort study. Intern Med J. 2013;43(1):66-72.
8. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011;365(23):2205-19.
9. Ospelt C. Synovial fibroblasts in 2017. RMD Open. 2017;3(2):e000471.
10. Daha NA, Toes RE. Rheumatoid arthritis: Are ACPA-positive and ACPA-negative RA the same disease? Nat Rev Rheumatol. 2011;7(4):202-3.
11. Fraenkel L, Bathon JM, England BR, St Clair EW, Arayssi T, Carandang K, et al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2021;73(7):1108-23.
12. Smolen JS, Landewé RBM, Bergstra SA, Kerschbaumer A, Sepriano A, Aletaha D, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Annals of the Rheumatic Diseases. 2023;82(1):3-18.
13. Rantalaiho V, Korpela M, Hannonen P, Kautiainen H, Järvenpää S, Leirisalo-Repo M, et al. The good initial response to therapy with a combination of traditional disease-modifying antirheumatic drugs is sustained over time: the eleven-year results of the Finnish rheumatoid arthritis combination therapy trial. Arthritis Rheum. 2009;60(5):1222-31.
14. Markusse IM, Akdemir G, Dirven L, Goekoop-Ruiterman YPM, Van Groenendael JHLM, Han KH, et al. Long-Term Outcomes of Patients With Recent-Onset Rheumatoid Arthritis After 10 Years of Tight Controlled Treatment. Annals of Internal Medicine. 2016;164(8):523.
15. Hammaker D, Firestein GS. Epigenetics of inflammatory arthritis. Curr Opin Rheumatol. 2018;30(2):188-96.
16. Pekarek B, Osher L, Buck S, Bowen M. Intra-articular corticosteroid injections: A critical literature review with up-to-date findings. The Foot. 2011;21(2):66-70.
17. Hetland ML, Østergaard M, Ejbjerg B, Jacobsen S, Stengaard-Pedersen K, Junker P, et al. Short- and long-term efficacy of intra-articular injections with betamethasone as part of a treat-to-target strategy in early rheumatoid

arthritis: impact of joint area, repeated injections, MRI findings, anti-CCP, IgM-RF and CRP. Annals of the Rheumatic Diseases. 2012;71(6):851-6.

18. Gvozdenović E, Dirven L, Van Den Broek M, Han KH, Molenaar ETH, Landewé RBM, et al. Intra articular injection with corticosteroids in patients with recent onset rheumatoid arthritis: subanalyses from the BeSt study. Clinical Rheumatology. 2014;33(2):263-7.
19. Sullivan MM, Pham MM, Marks LA, Aslam F. Intra-articular therapy with methotrexate or tumor necrosis factor inhibitors in rheumatoid arthritis: a systematic review. BMC Musculoskelet Disord. 2021;22(1):792.
20. Dey M, Nagy G, Nikiphorou E. Comorbidities and extra-articular manifestations in difficult-to-treat rheumatoid arthritis: different sides of the same coin? Rheumatology (Oxford). 2023;62(5):1773-9.
21. Conforti A, Di Cola I, Pavlych V, Ruscitti P, Berardicurti O, Ursini F, et al. Beyond the joints, the extra-articular manifestations in rheumatoid arthritis. Autoimmun Rev. 2021;20(2):102735.
22. England BR, Thiele GM, Anderson DR, Mikuls TR. Increased cardiovascular risk in rheumatoid arthritis: mechanisms and implications. Bmj. 2018;361:k1036.
23. England BR, Sayles H, Michaud K, Caplan L, Davis LA, Cannon GW, et al. Cause-Specific Mortality in Male US Veterans With Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2016;68(1):36-45.
24. Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. Arthritis Rheum. 2005;52(3):722-32.
25. Solomon DH, Greenberg J, Curtis JR, Liu M, Farkouh ME, Tsao P, et al. Derivation and internal validation of an expanded cardiovascular risk prediction score for rheumatoid arthritis: a Consortium of Rheumatology Researchers of North America Registry Study. Arthritis Rheumatol. 2015;67(8):1995-2003.
26. Bongartz T, Nannini C, Medina-Velasquez YF, Achenbach SJ, Crowson CS, Ryu JH, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: A population-based study. Arthritis & Rheumatism. 2010;62(6):1583-91.
27. Gabbay E, Tarala R, Will R, Carroll G, Adler B, Cameron D, et al. Interstitial Lung Disease in Recent Onset Rheumatoid Arthritis. American Journal of Respiratory and Critical Care Medicine. 1997;156(2):528-35.
28. Carmona L. Rheumatoid arthritis in Spain: occurrence of extra-articular manifestations and estimates of disease severity. Annals of the Rheumatic Diseases. 2003;62(9):897-900.
29. Norton S, Koduri G, Nikiphorou E, Dixey J, Williams P, Young A. A study of baseline prevalence and cumulative incidence of comorbidity and extra-articular manifestations in RA and their impact on outcome. Rheumatology (Oxford). 2013;52(1):99-110.
30. Fragoulis GE, Conway R, Nikiphorou E. Methotrexate and interstitial lung disease: controversies and questions. A narrative review of the literature. Rheumatology. 2019;58(11):1900-6.
31. Jani M, Hirani N, Matteson EL, Dixon WG. The safety of biologic therapies in RA-associated interstitial lung disease. Nature Reviews Rheumatology. 2014;10(5):284-94.
32. Roubille C, Haraoui B. Interstitial lung diseases induced or exacerbated by DMARDS and biologic agents in rheumatoid arthritis: a systematic literature review. Semin Arthritis Rheum. 2014;43(5):613-26.
33. Manfredi A, Cassone G, Luppi F, Atienza-Mateo B, Cavazza A, Sverzellati N, et al. Rheumatoid arthritis related interstitial lung disease. Expert Rev Clin Immunol.

2021;17(5):485-97.

34. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. N Engl J Med. 2019;381(18):1718-27.
35. van Nies JA, Brouwer E, van Gaalen FA, Allaart CF, Huizinga TW, Posthumus MD, et al. Improved early identification of arthritis: evaluating the efficacy of Early Arthritis Recognition Clinics. Ann Rheum Dis. 2013;72(8):1295-301.
36. Hazes JM, Luime JJ. The epidemiology of early inflammatory arthritis. Nat Rev Rheumatol. 2011;7(7):381-90.
37. Zaripova LN, Midgley A, Christmas SE, Beresford MW, Baildam EM, Oldershaw RA. Juvenile idiopathic arthritis: from aetiopathogenesis to therapeutic approaches. Pediatr Rheumatol Online J. 2021;19(1):135.
38. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004;31(2):390-2.
39. Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet. 2007;369(9563):767-78.
40. Magni-Manzoni S, Rossi F, Pistorio A, Temporini F, Viola S, Beluffi G, et al. Prognostic factors for radiographic progression, radiographic damage, and disability in juvenile idiopathic arthritis. Arthritis Rheum. 2003;48(12):3509-17.
41. Ravelli A, Consolaro A, Horneff G, Laxer RM, Lovell DJ, Wulffraat NM, et al. Treating juvenile idiopathic arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2018;77(6):819-28.
42. Onel KB, Horton DB, Lovell DJ, Shenoi S, Cuello CA, Angeles-Han ST, et al. 2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Oligoarthritis, Temporomandibular Joint Arthritis, and Systemic Juvenile Idiopathic Arthritis. Arthritis Rheumatol. 2022;74(4):553-69.
43. Ringold S, Angeles-Han ST, Beukelman T, Lovell D, Cuello CA, Becker ML, et al. 2019 American College of Rheumatology/ Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis. Arthritis Rheumatol. 2019;71(6):846-63.
44. Goekoop-Ruiterman YPM, De Vries-Bouwstra JK, Allaart CF, Van Zeben D, Kerstens PJSM, Hazes JMW, 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 & Rheumatism. 2005;52(11):3381-90.
45. Akdemir G, Heimans L, Bergstra SA, Goekoop RJ, van Oosterhout M, van Groenendael J, et al. Clinical and radiological outcomes of 5-year drug-free remission-steered treatment in patients with early arthritis: IMPROVED study. Ann Rheum Dis. 2018;77(1):111-8.
46. Hissink Muller P, Brinkman DMC, Schonenberg-Meinema D, van den Bosch WB, Koopman-Keemink Y, Brederije ICJ, et al. Treat to target (drug-free) inactive disease in DMARD-naive juvenile idiopathic arthritis: 24-month clinical outcomes of a three-armed randomised trial. Ann Rheum Dis. 2019;78(1):51-9.
47. van Aken J, van Bilsen JH, Allaart CF, Huizinga TW, Breedveld FC. The Leiden Early Arthritis Clinic. Clin Exp Rheumatol. 2003;21(5 Suppl 31):S100-5.