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A large, stylized sunburst or fan-like graphic in a lighter shade of green, positioned on the left side of the cover. It has a central vertical stem and multiple curved, radiating segments that resemble the petals of a flower or the rays of a sun.

FACTORS ASSOCIATED WITH IMPROVED OUTCOMES IN INTENSIVELY TREATED EARLY RHEUMATOID ARTHRITIS

Laura Kuusalo



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ABSTRACT

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Factors associated with improved outcomes in intensively treated early rheumatoid arthritis

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The cornerstone of the treatment of early rheumatoid arthritis (RA) is intensive, clinical remission targeted treatment with disease-modifying antirheumatic drugs (DMARDs). The aim of the present study was to elucidate factors which are, in addition to the drug treatment, associated with improved outcomes in early RA.

In the New Finnish Rheumatoid Arthritis Combination Therapy (NEO-RACo) trial, 99 patients with early RA were treated with three DMARDs, low-dose oral prednisolone, and intra-articular glucocorticoid injections (iaGCs) to swollen joints for 2 years. They were randomized to receive either infliximab or placebo infusions for the initial six-month period, and were followed up for five years. The aim of treatment was a strict remission with no swollen or tender joints. We assessed the influence of selected physician-related (I, II) and patient-related (III, IV) factors upon outcomes. These included the physicians' adherence to targeted treatment (I), neglected iaGC injections (II), the burden of adverse events (III), and the associations between baseline patient-reported outcomes (PROs) and two-year remission (IV).

Greater physicians' adherence was associated with higher remission rates and lower disease activity during the 2–5 year follow-up period (I). Patients initially treated with greater adherence required fewer biologic DMARDs and changes in medication during the follow-up period. Patients who did not receive intra-articular GCs to all swollen joints were less likely to achieve remission, had higher disease activity, and suffered from a lower quality of life at 2 years' follow-up (II). A high burden of adverse events during the first year was associated with higher disease activity and reduced remission rates at one and two years (III). Only two of the eleven assessed PROs, the vitality and role-emotional functioning sections of the Short Form 36 questionnaire were associated with an increased likelihood of remission (IV).

In conclusion, physicians' adherence to the targeted treatment should be optimized and all swollen joints treated with iaGCs to bring as many early RA patients as possible into remission. Certain PROs and frequent adverse events may help in recognizing patients who are less likely to achieve remission.

Keywords: adherence, intra-articular, glucocorticoid, remission, rheumatoid arthritis

TIIVISTELMÄ

Laura Kuusalo

Intensiivisesti hoidetun varhaisen nivelreuman hyvään hoitotulokseen vaikuttavat tekijät

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Varhaisen nivelreuman hoidon kulmakivi on tehokas, kliiniseen remissioon tähtäävä reumalääkehoito. Väitöskirjatyön tavoittena oli selvittää, mitkä tekijät intensiivisen antireumaattihoidon lisäksi vaikuttavat hyvän hoitotuloksen saavuttamiseen.

Uusi suomalainen nivelreuman kombinaatiohoito (NEO-REKO) -tutkimuksessa 99 varhaista nivelreumaa sairastavaa potilasta hoidettiin 2 vuotta kolmen synteettisen reumalääkkeen, prednisolonin ja nivelensisäisten glukokortikoidi-injektoiden (GI) yhdistelmällä ja satunnaistettiin saamaan joko infliksimabi- tai placebo-infuusioita 6 kuukautta. Seuranta jatkui viisi vuotta ja hoidon tavoite oli koko tämän ajan tiukka remissio ilman arkoja tai turvonneita niveliä. Arvioimme lääkärin hoitoon sitoutumisen (I), kaikkien tulehtuneiden nivelten GI:lla hoitamatta jättämisen (II), ja ensimmäisen vuoden aikana koettujen haittatapahtumien aiheuttaman taakan (III) vaikutuksen useisiin päätemuuttujiin. Lisäksi tutkimme, voidaanko remission saavuttamista ennustaa diagnoosivaiheen potilaslähtöisten mittareiden avulla (IV).

Osoitimme, että lääkärin sitoutuminen hoitoprotokollaan oli yhteydessä korkeampiin remissiolukemiin, matalampaan nivelreuman aktiivisuuteen, ja pienempään lääkitystehostusten ja biologisten lääkkeiden tarpeeseen 2–5 vuoden seurannassa (I). Jos GI:t kaikkiin turvonneisiin niveliin jätettiin antamatta, saavuttivat potilaat remission epätodennäköisemmin, heidän nivelreumansa aktiivisuus oli korkeampi ja elämänlaatunsa huonompi (II). Korkea haittatapahtumataakka oli yhteydessä korkeampaan tautiaktiivisuuteen ja matalampiin remissiolukemiin 1 ja 2 vuoden kuluttua (III). Lähtötilanteessa tutkituista yhdestätoista potilaslähtöisestä mittarista kaksi, Short Form 36 kyselyllä mitatut vitaliteetti ja emotionaalinen roolitoiminta, olivat yhteydessä suurempaan remission saavuttamisen todennäköisyyteen kahden vuoden kohdalla (IV).

Varhaisen nivelreuman hoitotulosten parantamiseksi myös lääkäreiden hoitoon sitoutuminen tulee optimoida. Glukokortikoidia tulee injisoida kaikkiin tulehtuneisiin niveliin. Tietyt potilaslähtöiset mittarit ja potilaan korkea haittatapahtumataakka saattavat auttaa niiden potilaiden tunnistamisessa, joilla on alentunut remission saavuttamiset todennäköisyys.

Avainsanat: adherenssi, glukokortikoidi, nivelinjektio, nivelreuma, remissio

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ABBREVIATIONS

ACPA	Anti-citrullinated protein antibodies
ACR	American College of Rheumatology
ARA	American Rheumatism Association
AUC	Area under the curve
bDMARD	Biological disease-modifying antirheumatic drug
BeSt	Behandel Strategieën study
CDAI	Clinical Disease Activity Index
CIMESTRA	Ciclosporine, MEthotrexate, STeroid in Rheumatoid Arthritis study
CIS	Cumulative inactivity score
COBRA	Combinatietherapie Bij Reumatoïde Artritis
csDMARD	Conventional synthetic disease-modifying antirheumatic drug
DAS	Disease Activity Score
DAS28	Disease Activity Score assessing 28 joints
DMARD	Disease-modifying antirheumatic drug
DREAM	Dutch Rheumatoid Arthritis Monitoring cohort
EULAR	European League Against Rheumatism
FIN-RACo	Finnish Rheumatoid Arthritis Combination Therapy trial
GC	Glucocorticoid
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HAQ	Health Assessment Questionnaire
HCQ	Hydroxychloroquine
HDA	High disease activity
HLA	Human leucocyte antigen
iaGC	Intra-articular glucocorticoid
ICF	International classification of functioning, disability and health
IL-1	Interleukin 1
IL-6	Interleukin 6
LDA	Low disease activity
MDA	Moderate disease activity
MHAQ	Multidimensional Health Assessment Questionnaire
MRI	Magnetic resonance imaging
MTX	Methotrexate

Abbreviations

NEO-RACo	New Finnish Rheumatoid Arthritis Combination Therapy trial
OPERA	Optimized treatment algorithm in Early Rheumatoid Arthritis
PAS	Patient Activity Scale
PGA	Patient global assessment
PhGA	Physician global assessment
PRO	Patient-reported outcome
QALY	Quality-adjusted life year
RA	Rheumatoid arthritis
RAPID3	Routine Assessment of Patient Index Data 3
RF	Rheumatoid factor
SASP	Sulfasalazine
SDAI	Simplified Disease Activity Index
SvH	Sharp van der Heijde score
TICORA	TIght COntrol for Rheumatoid Arthritis study
TNF	Tumor necrosis factor
tsDMARD	Targeted synthetic disease-modifying antirheumatic drug
WD	Work disability

LIST OF ORIGINAL PUBLICATIONS

- I. Kuusalo L, Puolakka K, Kautiainen H, Blåfield H, Eklund K, Ilva K, Kaipiainen-Seppänen O, Karjalainen A, Korpela M, Valleala H, Leirisalo-Repo M, and Rantalaiho V, for the Neo-RACo Study Group. Impact of physicians' adherence to treat-to-target strategy on outcomes in early rheumatoid arthritis in the NEO-RACo trial. *Scand J Rheumatol* 2015;44:449-55.
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- III. Kuusalo L, Puolakka K, Kautiainen H, Karjalainen A, Malmi T, Paimela L, Leirisalo-Repo M, and Rantalaiho V, for the Neo-RACo Study Group. High burden of adverse events is associated with reduced remission rates in early rheumatoid arthritis. Submitted.
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1 INTRODUCTION

The management of rheumatoid arthritis (RA) has changed enormously during the recent decades. During the 1970s most, but not all, authors regarded RA as a disease with a good prognosis and suggested treatment with disease-modifying antirheumatic drugs (DMARDs) only after the occurrence of erosions or joint space narrowing (1,2). Finnish rheumatologists belonged to the minority, who promoted a more active treatment strategy and wrote in the *British Medical Journal* already in 1978: “It must be seen that we are treating not only the actual inflammation of the joints but also the quality of the patient’s life during many decades in the future” (3). It still took several decades before the benefits of intensive early treatment were better understood and more widely appreciated. This understanding became a driver for research and later development of the currently recommended intensive treatment strategies targeted to clinical remission (4-6). These treatment strategies, together with earlier initiation of treatment, and the introduction of biologic DMARDs (bDMARDs) at the end of 1990s, have all revolutionalized the treatment of RA. The introduction of intensive targeted treatment strategies and new biologic agents has made clinical remission an achievable goal also in routine clinical practice (7,8).

Despite these advances, not all patients respond well to treatment. In a minority of patients RA progresses, eventually leading to joint destruction and other complications, such as work disability. Identifying the patients least likely to reach remission is difficult; traditional baseline markers of poor prognosis, such as decreased functional ability, do not appear to be reliable predictors of outcomes in intensively treated early RA patients (9,10). In the current study, we searched for factors associated with improved treatment results in patients given intensive treatment for early RA. We explored the importance of physician’s adherence to remission targeted treatment, studied the influence of intra-articular glucocorticoid (GC) injections, and assessed the prognostic properties of patient-reported outcomes (PROs) and experienced adverse events in the New Finnish Rheumatoid Arthritis Combination Therapy (NEO-RACo) trial (11).

2 REVIEW OF THE LITERATURE

2.1 Overview of rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disease affecting mainly synovial joints, and may sometimes cause extra-articular manifestations. RA encompasses multiple forms of arthritis, ranging from mild and self-limiting disease to severe, disabling polyarthritis. Arthritis was recognized already by Hippocrates, but rheumatoid arthritis was named and distinguished from osteoarthritis and gout substantially later (12). However, defining RA has been and continues to be difficult due to the variability of the disease, and the lack of one simple diagnostic test. There is no consensus about comprehensive diagnostic criteria for RA, but multiple classification criteria have been developed, primarily for research purposes. These criteria are based on clinical, radiological and serological findings, and aim to differentiate RA from other rheumatic diseases. The American Rheumatism Association (ARA) published its first criteria in 1957 in order to increase uniformity in cases defined as RA in clinical studies (13).

During recent decades, the American College of Rheumatology (ACR, formerly ARA) 1987 revised criteria for the classification of rheumatoid arthritis have been among the most frequently used (Table 1) (14). These criteria are very sensitive and specific in differentiating RA from other rheumatic diseases. The ACR 1987 criteria include seven clinical findings, of which four are required for a definite diagnosis of RA. Erosions and rheumatoid nodules are among these seven findings, and their inclusion limits the sensitivity of these criteria for recognizing very early RA. As evidence supporting the early initiation of treatment continues to accumulate, the need for a new set of criteria was recognized (15). The ACR and the European League Against Rheumatism (EULAR) formulated these criteria in 2010 (16). They are to be applied to patients having at least one swollen joint not attributable to another rheumatic disease (Table 1). As intended, the new criteria have greater sensitivity, but this comes at the cost of a specificity lower than that of the 1987 criteria. Furthermore, when the 2010 criteria are used, RA outcomes appear to be milder than with the 1987 criteria (17). Additionally, anticitrullinated-antibody (ACPA) positive patients are more likely to fulfill the new criteria, and have fewer inflamed joints at presentation than seronegative patients (18). This is not surprising as seronegative patients require ten swollen joints in order to be classified as RA if their disease is non-erosive.

Table 1. ACR 1987 and ACR/EULAR 2010 RA classification criteria (14,16).

ACR 1987 Criteria	ACR/EULAR 2010 Criteria	Score
1. Morning stiffness > 1 hour	A. Joint involvement score	
2. Arthritis in 3 or more joints areas ¹	1 large joint	0
3. Arthritis of hand joints (PIP, MCP, wrist)	2–10 large joints	1
4. Symmetric arthritis	1–3 small joints ³	2
5. Rheumatoid nodules	4–10 small joints	3
6. The presence of rheumatoid factor	>10 joints (at least 1 small joint)	5
7. Radiographic changes in hand/wrist joints ²	B. Serology (at least one test)	
	Negative RF and ACPA	0
	Low-positive RF or ACPA	2
	High-positive RF or ACPA	3
	C. Acute phase reactants	
	Normal CRP and ESR	0
	Abnormal CRP or ESR	1
	D. Duration of symptoms	
	< 6 weeks	0
	≥ 6 weeks	1

¹Right or left proximal interphalangeal (PIP), metacarpophalangeal (MCP) joints, wrist, elbow, ankle, knee and metatarsophalangeal (MTP) joints. ²In the presence of erosions or peri-articular osteoporosis. ³With/without involvement of large joints. The 1987 criteria require that 4 of the 7 criteria are fulfilled for the diagnosis of RA. Criteria 1–4 have to be present for a minimum of 6 weeks. The 2010 criteria require a score of ≥ 6 points for the definite diagnosis of RA.

2.1.1 Etiology

The exact etiology of RA is incompletely understood, but as in autoimmune diseases in general, both genetic susceptibility and environmental factors are required for disease development. Recent genome-wide analysis studies have identified more than 100 risk loci for RA (19). Of these, the immune response controlling human leucocyte antigen (HLA) region has the strongest genetic association with RA. Furthermore, the most important genetic risk factors, variations in the shared epitope alleles of the HLA-DRB1 gene, are located in this region (20,21). Multiple other genes involved in the regulation and activation of the immune system as well as in inflammatory signaling pathways have been associated with rheumatoid arthritis (19). It has been estimated that nowadays approximately 50–60% of the risk for RA can be attributed to genetic susceptibility (19,22), but the concordance rate of RA between monozygotic twins is relatively

low. This underlines the importance of environmental factors and epigenetic modifications in the pathogenesis of RA (23,24).

Of the environmental risk factors, smoking is one of the strongest, being clearly associated with an elevated risk of RA (25,26). Smoking increases both the risk of developing anti-citrullinated protein antibodies (ACPA) dose-dependently, and increases the risk of ACPA-positive RA, especially in HLA-DRB1 shared epitope carriers (27). Furthermore, some chronic infections and bacteria may contribute to the pathogenesis of RA. Among the most interesting are oral bacteria, and especially *Porphyromonas gingivalis*, a common bacterium in periodontal disease. This bacterium can produce peptidylarginine deiminase, which promotes protein citrullination, possibly leading to the production of ACPA (28). Moreover, the Epstein-Barr virus, as well as other viral and bacterial infections, have been suggested as possible contributors to the pathogenesis of RA (29). The effect of sex and sex hormones is also undeniable. A significantly higher incidence of RA is observed in women, and amelioration of RA symptoms occurs during pregnancy (30). However, the impact of oral contraceptives, vitamin D intake, and dietary factors and many other variables remains under debate (31).

2.1.2 Pathogenesis

Current knowledge about the immunological processes leading to RA is increasing rapidly. These processes are highly complex and vary significantly among different RA subsets. This immunological variability and the classification based on the clinical phenotype have hindered advances in research on the pathogenesis of RA. The immunological process can begin and autoantibodies may be detectable in patients years before RA symptoms arise, but the triggers that finally lead to the disruption of immunological tolerance and the localized inflammation of the joints are poorly understood (32). The activation of both adaptive and innate immunity affects the development of synovitis. The immunological process begins when dendritic cells in peripheral tissues differentiate after being exposed to substances such as pro-inflammatory cytokines. The dendritic cells then migrate to the lymph nodes presenting the acquired autoantigens to naive T cells initiating T cell differentiation (33). The T cells become activated only when the antigen presenting cells deliver a second, co-stimulatory signal through their CD28 receptor, which binds to the CD80 ligand on the T-cell surface (32). If this co-stimulation takes place, activated autoreactive T cells can proliferate and start secreting multiple cytokines, and also interact with other immune cells. B cells also have an essential role in the pathogenesis of RA. They interact with other immune cells, can present antigens through their B cell receptor, secrete cytokines, and trans-

form into plasma cells producing characteristic autoantibodies like rheumatoid factor (RF) and ACPA. However, as important as T and B cells are in initiating the immunological process, the final steps leading to the inflammation of the joints remain unknown. After localization of the immunological process, joint damage seems to be orchestrated by a variety of cells like macrophages, mast cells and neutrophils. When activated, especially macrophages produce large quantities of pro-inflammatory cytokines. Of these, among the most important ones in RA are TNF, IL-1, IL-6, and GM-CSF (32,34). Drugs targeting all of these cytokines are used (35-37), or under development for the treatment of RA (38). When secreted, these cytokines can, besides macrophages, activate cells like chondrocytes, osteoclasts and fibroblast-like synoviocytes, and induce synthesis of many other cytokines and inflammatory mediators. If not stopped, this process eventually leads to destructive joint changes. (32,34)

2.1.3 Epidemiology

The latest estimate of the global prevalence of RA is 0.24 %, based on modeled data from 40 countries (39). This prevalence estimate has remained relatively constant during the past two decades. Previously, prevalences ranging from 0.2% to 1.0% have been reported in the developed countries (40). However, declining incidences between 30-45/100 000 have been seen lately in some of the higher prevalence areas, like northern Europe and North America (41,42). Both environmental factors and improving classification of arthritides have been suggested as possible causes for this decline (43). In Finland, the latest reported annual incidence of RA was in concordance with the previous reports. The incidence was 44.5/100 000 based on arthrititis medication reimbursement data (44). Recently, some later reports have shown again a modest increase as well as cyclic variation in the incidence, and even solar cycles have been suggested - but not confirmed - as a possible cause for this variability (45,46). In general, RA affects women approximately twice as often as men, and the incidence of the disease increases with age peaking in the sixth decade. Some studies have shown that the age at the time of RA onset has risen (41,42). However, it should be remembered that when diagnosed, two thirds of RA patients are still in working age (44).

2.1.4 Course of the disease

Usually RA begins insidiously and the signs and symptoms of the disease develop slowly within weeks or months. At times disease onset can also be acute, and rarely RA starts as spontaneously resolving attacks of arthritis called palindromic

arthritis. Hallmark symptoms of RA include symmetrical swelling, tenderness, and morning stiffness of the small and medium sized peripheral joints. Distal interphalangeal (DIP) joints are usually spared. Often, swelling can be seen also in the tendon sheaths and the bursae. Further, pain is usually present during movement, but not at rest. Non-specific systemic symptoms include fatigue, weight loss, and sometimes low-grade fever. (47)

Besides joint symptoms, RA causes also extra-articular manifestations. Some of these, like rheumatoid nodules, can be present at the time of the diagnosis, but are more common in advanced RF positive disease (48). Other organ specific extra-articular manifestations include pulmonary disease (e.g. interstitial lung disease and pulmonary nodules), heart disease (e.g. pericarditis and myocarditis) and eye disease (e.g. secondary Sjögren's syndrome and episcleritis). Further, anemia of chronic disease is common, whereas systemic extra-articular manifestations of RA, like rheumatoid vasculitis, are rare. (49,50) Currently the incidence of extra-articular RA is decreasing, most likely due to improved treatment (51,52). In addition to the possible extra-articular manifestations, chronic systemic inflammation increases the risk of reactive AA amyloidosis (49,50). Fortunately, this is nowadays a rarity. Inflammation also contributes significantly to the development of atherosclerosis (53).

The clinical course of RA is variable and ranges from mild and self-limiting disease to progressive polyarthritis (54,55). Usually RA presents as chronic arthritis with fluctuating disease activity over time, but sometimes spontaneous remission is seen within the first six months (56). If RA is not treated effectively, the inflammation and the joint changes progress and lead to permanent damage of the affected joints in most cases. This damage can be portrayed using radiographs. In early disease, a typical radiographic finding is soft tissue swelling, which can without active treatment progress into periarticular osteoporosis, juxta-articular erosions and narrowing of joint spaces (57). What is more, inflammation may cause the joints and tendons lose their shape and alignment, which can e.g. lead to characteristic deformities of the fingers, like boutonnière and swan neck deformities. Radiological progression is highest during the first years, and the feet are usually affected to a greater extent than the hands (58,59). Nowadays radiological progression can be halted and long periods of remission are achieved with modern, intensive treatment (60,61). Further, especially if treatment is started after short symptom duration, it has been suggested that autoimmunity may still be reversible, making drug-free remission possible for a small subset of patients (62).

2.1.5 Co-morbidity in RA

In RA, substantial comorbidity is detected already at disease onset and the number of comorbidities increases with time (63-65). Detecting and treating comorbidities is important, because their impact on RA outcomes is significant (66). Patients' disability and mortality increase together with the number of comorbidities, and they also have negative impact on patients' quality of life (66-68). Compared to the general population, RA patients are more likely to suffer e.g. from osteoporosis, bacterial infections, and gastrointestinal ulcerations. These are all associated with RA, but also RA treatment may increase the risk of these diseases. For example, the use of glucocorticoids (GCs) is associated with osteoporosis, and nonsteroidal anti-inflammatory drugs are known to predispose to ulcers (64,66). Also psychiatric comorbidities are prevalent among RA patients. The significance of these comorbidities, like depression, arises from their often profound impact on patient's functional ability (69). RA patients are also at substantially higher risk for cardiovascular events than the population in general (53,70). Therefore, RA patients' cardiovascular risk should be assessed, and if needed managed, regularly in clinical practice (53,71). Finally, also the overall prevalence of cancer is slightly increased in RA (72,73). Autoimmunity and immunomodulatory drugs used in RA have been suggested as possible causes for this increase (73). Some cancer types, like lymphoma and lung cancer, are more common, and others, like breast and colon cancer, are less common in RA patients compared to the general population.

2.1.6 Mortality in RA

Among RA patients, mortality has decreased during past decades but remains approximately 50% higher compared to the general population at least in established disease (74,75). The decrease in RA patients' mortality has not been as rapid as the decrease in general population's mortality, and some studies suggest that the mortality gap between RA patients and general population is widening (76,77). The observed excess mortality is explained by higher number of deaths due to infections, lung disease, some cancer types, and, most importantly, cardiovascular disease (76,78). In RA patients, significant comorbidity, high disability, low quality of life, and seropositive (RF and/or ACPA positive) disease have all been associated with an increased mortality risk (66,74,79,80). However, the future of RA patients seems brighter, most likely due to improved treatment. Improved treatment includes the use of targeted treatment strategies, more prevalent use of weekly methotrexate (MTX), and bDMARDs; all of these have been linked to reduced mortality (81-83). Further, two recent Finnish register studies

reported no increase in cardiovascular and overall mortality in nearly 15 000 early RA patients diagnosed between 2000-2007 and followed from one to eight years between 2000–2008 (84,85). Comparable results were yielded in Canadian RA patients diagnosed after year 2000. Lacaille et al. followed 24 914 incident RA patients for five years (86). They found that RA patients' mortality was higher compared to the general population in the earlier cohort diagnosed 1996–2000, but not in the later cohort diagnosed 2001–2006 (86). These studies show that, due to intensive, targeted treatment, the mortality gap might be after all closing in early RA patients diagnosed after the millennium shift. However, this is not currently the case in established RA, and future efforts should focus on improving their care.

2.1.7 Disability in rheumatoid arthritis

As a chronic disease with daily symptoms, often leading to permanent joint damage, RA can lead to cumulative disability, making simple every day tasks like writing difficult. This is often the case especially if the disease remains active despite treatment. In early RA reduced functional ability is conveyed by pain and inflammation, but later permanent joint damage becomes the main cause of functional disability (87,88). The Stanford Health Assessment Questionnaire (HAQ) is the most widely used tool for measuring RA related disability, or physical functioning (89). HAQ does not, however, measure only RA associated disability. HAQ answers of RA patients vary substantially, and approximately one fourth of this variability can be explained by factors like mental health, age, and education level (90). Disability, as defined by World Health Organization (WHO), covers not only physical, but also mental impairments, activity limitations, and problems in involvement in different life situations (91). RA often profoundly influences all of these by affecting patients' activities of daily life from dressing and performing household chores to socializing. What is more, co-existing comorbidities often complicate the situation even further by increasing the burden of disability (66).

2.1.8 Work disability

In general, the working ability of RA patients is decreased, and work disability (WD) remains a significant problem from the start of the disease, increasing with time (92). Working ability comprises of multiple individual and work-related factors. In RA, the most important predictors of working ability are age, education level, functional capacity, physical demands of the work, and disparity be-

tween individual's working capacity and work demands (93,94). In earlier cross-sectional and longitudinal studies permanent work disability has ranged from 10–30% in early RA, increasing up to 30-80% after disease duration of 10–20 years (92). However, like mortality, also RA-related WD has been declining in patients diagnosed after the beginning of the new millennium (95,96). This decline can be, at least partly, attributed to earlier and more intensive treatment; changes have occurred after the introduction of increasingly active treatment strategies. Despite these advances, WD remains a central problem in RA. This is one of the reasons why achieving early remission is currently considered extremely important (97,98).

2.1.9 Economic burden of RA

The economic impact of RA to both society and individual is substantial (99,100). Compared to many other chronic conditions like osteoarthritis and ankylosing spondylitis, annual costs associated with RA are higher (101,102). The majority of these costs have traditionally accumulated from indirect costs, especially reduced productivity, but nowadays a significant proportion of these costs cumulate from medication. Medication costs have risen substantially since the introduction of bDMARDs. Huscher et al. have estimated the average annual costs of RA per patient in Germany, including sick leaves and pensions, at approximately 15 000 euros in 2002 and at 18 000 euros in 2011 (103,104). They showed that the increase in the costs was driven by increased use of bDMARDs. The indirect costs associated with RA did not decrease enough to compensate this change. Naturally, these costs differ greatly between countries due to differences in the social security and in the use of expensive drugs (105).

Substantial savings are possible if only patients not responding to conventional synthetic DMARDs (csDMARDs) are treated with biologics, as is required by funders in many countries (105-107). This is a reasonable approach as previous studies have shown that combination therapy of csDMARDs, compared with monotherapy, is cost-effective, as well as targeted treatment and early suppression of disease activity (108,109). In addition, despite their radiological superiority, bDMARDs have not been clearly associated with reduced work disability rates, and have not therefore been cost-effective compared to csDMARDs (110-113). This may change in the future with the increasing use of low-priced biosimilars. Further, it should be remembered that even costly bDMARD treatment is worthwhile if it enables maintaining or restoring patient's working capacity, thereby reducing the long-term costs of RA.

2.2 Assessment of RA

2.2.1 Overview

Unfortunately, in the same way as the diagnosis, RA patient's assessment cannot be simplified into a single "gold standard" test or one simple question. Therefore, a need for multiple different outcome measures, like radiological progression and physical function, exists. In early 1990s it became evident that different outcomes and endpoints were used in European and North American RA clinical trials (114). This made comparison of clinical trial results extremely difficult, and led to international collaboration and development of the American College of Rheumatology (ACR) core set of disease activity measures (115). These measures were presented to the rheumatology community in the first meeting of the international Outcome Measures in Rheumatology (OMERACT) network, which aims at improving outcome measurement in rheumatology (114). The ACR core set consists of 8 valid and reliable disease activity measures, including an inflammatory marker [C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)] and two outcome measures [Health Assessment Questionnaire (HAQ) and radiographic progression]. All included measures are at least moderately sensitive to change, making detection of clinical improvement possible. However, these measures have been developed for clinical trials, not for everyday clinical work. Therefore, also numerous other disease activity indices have been developed (116). These are less comprehensive, but more feasible for use in busy rheumatology practice.

2.2.2 Assessment of tender and swollen joints

Joint assessment is the cornerstone of RA patient's clinical examination. In clinical examination, swelling, tenderness, range of motion, and possible deformities of the joints are evaluated. Depending on the joint count, the tenderness of 28 to 68 joints and the swelling in 28 to 66 joints is assessed. Joint counts are considered the "gold standard" assessment tools of RA, but like all measures, they have also limitations. These limitations have been reviewed by Sokka and Pincus, who remind that joint counts are poorly reproducible, and should therefore be performed always by the same observer in clinical trials (117). Further, it is important to remember that if 28 joint count evaluating the joints of the upper limbs and knees is used, substantial disease activity in the feet may remain undetected (118). In addition, joint counts are not free from placebo effect – joint counts improve with placebo treatment as much as other non-radiological core data set

measures (117). Joint counts are as valuable as other core set measures in distinguishing placebo from active treatment in clinical trials. Of the two joint counts, the tender joint count is more sensitive to change. However, it reflects patient's subjective experience, and is therefore more easily affected by factors like anxiety, depression, and pain (119,120). Unsurprisingly, joint counts are also less sensitive in detecting inflammation than ultrasound and magnetic resonance imaging (MRI) (117). Despite these issues joint counts are likely accurate enough. This was demonstrated by a recent randomized trial in which achieved remission rates did not differ between two treatment arms targeted to ultrasound remission and clinical remission (121).

2.2.3 Pain

Pain is usually reported as the most debilitating symptom by RA patients, and it is often associated with fatigue and psychological distress (122). In the core set, pain is assessed using a 100 mm visual analogue scale (VAS), a horizontal line where 0 corresponds with no pain and 100 with the most severe imaginable pain (123). In clinical trials, also more comprehensive instruments, like McGill pain questionnaire, are sometimes used (124).

2.2.4 Patient global assessment and physician global assessment

Patient global assessment (PGA) belongs to the patient-reported outcomes (PROs), which are valuable measures in providing patients' perspective on their health status. PGA is usually assessed using a 100 mm VAS, but sometimes alternative approaches like a VAS consisting of 21 circles are used (125). PGA can be used for assessing patients' overall health status, like in the 28-joint disease activity score (DAS28), or RA disease activity, as when ACR responses (see 2.2.9) are measured (126,127). Attention should be paid to the wording of the question as it influences the responses (128-130). When assessing disease activity, the ACR/EULAR 2011 remission criteria for RA propose the following phrasing: "Considering all the ways your arthritis has affected you, how do you feel your arthritis is today?" (131). Further, studies have shown that PGA is a reliable measure, sensitive to change, and has a good test-retest reliability (116,132,133). It is also included as the only PRO in many composite disease activity indices like the DAS28 (116). However, PGA has also limitations. One of these is PGA's discordance with objective disease activity measures, detected in 36-49% of the cases (130,134,135). This can be explained by factors that are known to influence PGA, like depression, anxiety, fatigue and pain (134,136).

Especially pain influences PGA strongly, possibly increasing it up to 75%, which shows that PGA is a good descriptor of patients' overall well-being. Despite abovementioned limitations, PGA is among the most important and the most feasible RA outcome measures.

Also physician's global assessment (PhGA) is measured using a 100 mm VAS. Unlike patient's assessment, physicians estimate is mostly affected by number of swollen and tender joints, and inflammatory markers (134). Therefore, PhGA can be considered a true composite measure as physicians usually take into account the available clinical information, and also the results of patient questionnaires.

2.2.5 Disease activity indices

The first composite disease activity measure for RA was created as early as in 1950s (137). Since then, multiple different indices have been developed. These combine different disease activity assessments and usually present the results in the form of one number (116). In general, these composite indices are easier to interpret and more sensitive to change than their individual components. Among the most used indices are the Disease Activity Score (DAS) and especially its derivative, the Disease Activity Score assessing 28 joints (DAS28) (126,138). The former includes a 44 swollen joint count (the Ritchie articular index), PGA (general health), and ESR, whereas the latter combines 28 tender and 28 swollen joint counts, PGA (general health), and ESR. A commonly used modification of DAS28 includes CRP instead of ESR (DAS28-CRP), and both DAS and DAS28 are often reported also as three-variable measures excluding PGA. Further, as can be seen based on the formula, $[0.56 \times \sqrt{(TJC28)} + 0.28 \times \sqrt{(SJC28)} + 0.70 \times \ln(\text{ESR}) + 0.014 \times (\text{PGA})]$, the weight of both tender joint count and ESR is relatively high in DAS28. This should be taken into account when DAS28 values are interpreted.

More elementary, commonly used indices endorsed by both the ACR and EULAR include the simplified disease activity index (SDAI) and clinical disease activity index (CDAI). Both consist of 28 swollen and 28 tender joint counts, PGA and PhGA. CRP (mg/dl) is included in SDAI but not in CDAI, making the latter quick to fill out in clinical practice. These indices are scored simply by adding the values of all components together, hence the range of the CDAI is 0–76, and the SDAI extends from 0.1 to 86. (116)

The four abovementioned commonly used indices consist of multiple variables, like formal joint counts, and laboratory results are required for all except CDAI, which may reduce their feasibility in every day clinical practice. Some rheuma-

tology clinics, where electronic data collection is not available, prefer simple questionnaires using only patient-reported data. These questionnaires can be filled out in a few minutes. Of these, among the most often used ones are routine assessment of patient index data 3 (RAPID3) and patient activity scale (PAS) (139,140). Both of these are calculated based on patients's assessment of functional ability, pain VAS and PGA. PAS utilises the regular HAQ, and RAPID3 requires filling the multidimensional HAQ (MHAQ).

2.2.6 Radiological progression

One of the hallmarks of RA are typical erosions seen in the small joints of the feet and hands. Erosions are detected usually in more than 20% of the patients already at presentation (141-144). These changes are irreversible, and therefore retarding radiological progression is one of the most important goals of RA treatment. Multiple scoring methods have been developed for quantifying the damage in standardized radiographs of the hands and feet. The scoring methods of Larsen and Sharp, and the Sharp method with van der Heijde modification are among the most often used ones (145-147). In the Larsen method, the joints are scored from 0 to 5, zero referring to normal and five to mutilating changes. The total Larsen score of 200 is the sum of the individual joint scores. Lately, Sharp method with van der Heijde modification (the Sharp/van der Heijde or SvH) has become the most used radiological scoring system in longitudinal observational studies and clinical trials (147) and was used also in the NEO-RACo trial.

The SvH method assesses 16 joints of hands and wrists for erosions in each hand; MCP and PIP joints, and 6 areas of the wrist (147). Erosions are graded from 0 to 5 depending on the involved surface area; 0 refers to a normal and 5 to a completely collapsed joint. In feet, the five MTP joints and the interphalangeal joint of the big toe are evaluated for erosions on both sides and graded from 0 to 10. Further, joint space narrowing is assessed in 15 joints of the hand and 6 joints of the foot, and graded from 0 to 4. The erosion score (range 0–280) and the narrowing score (range 0–168) are added together for the total SvH, which ranges from 0 to 448. Compared to the Larsen method, SvH is more difficult to learn, time consuming, and less specific, but importantly more sensitive to change (148). Nowadays overall radiological changes in clinical trials are usually small due to effective treatment and relatively short follow-up times, and therefore sensitive scoring methods are needed for detecting the often minimal progression (148).

In addition to radiographs, ultrasound and magnetic resonance imaging (MRI) have become increasingly available. Compared to conventional radiographs,

these methods are more sensitive and enable more accurate assessment of the joint changes caused by RA (149). Ultrasound is already widely available in everyday clinical practice. Nonetheless, it should be remembered that ultrasound assessment is highly dependent on operator's skills. According to a recent review and meta-analysis, if RA patients are in remission, residual ultrasound synovitis predicts radiological progression and flares (150). However, according to a randomized study by Haavardsholm et al., aiming for ultrasound remission instead of clinical remission does not improve early RA patients' remission rates (121). Ultrasound still remains a valuable tool for example in cases of diagnostic uncertainty. Compared to ultrasound, the use of MRI is restricted due to its lower availability, and higher associated costs. MRI is considerably sensitive in detection of erosions, osteitis, and synovitis (151). However, small erosions are often detected by MRI even in healthy controls. Therefore, abnormalities more specific for RA have been sought, and of these, bone marrow edema has proven to be the most important one (152). Multiple studies have shown that MRI bone marrow edema is a good predictor of future radiographic progression, i.e. new erosions in plain radiographs, in early RA (151,153). Possibly, MRI scans will become a routine procedure in the future, used for detecting early RA patients most likely to progress radiographically.

2.2.7 Stanford Health Assessment Questionnaire (HAQ)

RA leads to reduced functional capacity due to active inflammation in early disease, whereas in established RA the role of permanent joint damage becomes more significant. In RA, the most frequently used measure of functional ability is the HAQ, which is included in the ACR core set (115). HAQ has been developed for use in RA patients, and it consists of 20 questions divided into 8 dimensions; dressing, arising, eating, walking, hygiene, reaching, gripping and other activities (89). Answers are scored from 0 to 3. Zero is equal to patient being able to perform the task without difficulty, 1 with some and 2 with much difficulty. Three refers to patient's inability to perform the task in question. If aids or help from another person are needed, the item is scored 2. The sum of the highest score for each dimension divided by eight is the HAQ score, which ranges from 0 to 3, i.e. from normal to very severe disability. The HAQ has been translated to multiple languages, and a Finnish version has been available since 1990s (154). Previously, HAQ has been considered as a good predictor of long-term outcomes of RA (155-157). According to some recent studies, this is not true for intensively treated early RA patients (9,10).

2.2.8 Health-related quality of life (HRQoL)

Significant part of the burden of a chronic debilitating disease like RA is mediated through changes in patient's physical, emotional, and social functioning. Of two patients who are "doing relatively well" and have, by objective measures, similar arthritis symptoms, one may remain active in work and social relationships, while the other may become work disabled and isolated. Capturing these differences in patients' reactions to disease and its treatment would be difficult without the use of measures like HRQoL instruments (158,159). These instruments, categorized into general and disease specific measures, are usually self-reported questionnaires. Generic HRQoL instruments are designed to allow comparisons of HRQoL across distinct medical conditions and different populations. One of the most used generic HRQoL measure is the Short Form 36 (SF-36) questionnaire, which was chosen for the assessment of HRQoL also in the NEO-RACo trial (158,160). SF-36 measures HRQoL in eight dimensions: physical functioning, physical role limitations, bodily pain, general health, vitality, social functioning, emotional role limitations, and mental health. The score for each dimension is the weighted sum of the questions in the section, and is translated into a score ranging from 0 to 100 where lower figure refers to lower QoL. Further, physical summary component of the SF-36, reflecting individual's physical HRQoL, is formed using physical functioning, role-physical, bodily pain and general health scores. The mental summary component encompasses the remaining four dimensions; vitality, social functioning, role-emotional and mental health.

Measurement of HRQoL in RA is important. RA is one of the diseases with a major impact on HRQoL (161). In studies, RA patients' HRQoL has been usually substantially lower compared with the general population (162-166). RA has greater impact on physical than mental components of HRQoL. Compared to other severe illnesses like congestive heart failure and depression, RA patients score lower in physical function, role physical and bodily pain dimensions of SF-36 (161). DMARDs and positive treatment responses improve RA patients' HRQoL, but even these improved scores are lower than general population's scores on physical dimensions of HRQoL (167,168). Further, also compared to other inflammatory arthritides, like psoriatic arthritis and ankylosing spondylitis, pain and impaired physical function seem to have larger impact on RA patients' HRQoL (166). Even though HRQoL is currently measured in most clinical trials, HRQoL measures have not been widely studied as predictors of RA outcomes in contrast to many other PROs. Thus far, only one study has assessed the utility of SF-36 dimensions, in addition to other commonly used PROs, in predicting the outcomes of early RA (10).

2.2.9 Remission and improvement criteria

In modern clinical practice, the treatment of RA is targeted to remission, and if this is not achievable, to low disease activity. It has become evident that this strategy leads to improved long-term outcomes (5,15). In clinical practice, the absence of swollen and perhaps also tender joints is a sufficient definition of remission, preferably together with normal inflammatory markers and the absence of radiological progression (169). However, for clinical trials this definition is not detailed enough, and thus numerous definitions of remission have been developed (56). Among the most frequently used are DAS and DAS28 based definitions, in which $DAS < 1.6$ and $DAS28 < 2.6$ equal remission (126). However, DAS28 remission allows substantial disease activity, as it is based on a 28-joint count excluding the feet. On the other hand, achieving a stringent remission according to the 1981 ACR criteria has proven to be difficult (170). The 1981 ACR criteria require patients to have met the following for at least two months: 1) morning stiffness less than 15 minutes, 2) no fatigue, 3) no joint pain (by history), 4) no joint tenderness or pain in motion, 5) no swelling in joints or tendon sheaths, and 6) normal ESR (171). A modified version of the ACR remission was used in the NEO-RACo trial; the patient was considered to be in remission if no swollen or tender joints were present, and five out of six ACR remission criteria, omitting the duration criteria, were fulfilled (11). Multiple factors unrelated to RA can contribute to joint pain and fatigue, making achievement of ACR remission difficult. The fact that 1981 ACR remission is rarely reached was one of the reasons why new ACR/EULAR remission criteria for clinical trials were created in 2011 (131). These criteria include two definitions of remission; a Boolean definition and an index based definition. For Boolean remission the following are required: Tender and swollen joint count ≤ 1 , CRP ≤ 1 mg/dl, and PGA ≤ 1 on a 0 to 10 scale. The second, index-based definition of remission requires the Simplified Disease Activity Index (SDAI) to be ≤ 3.3 or the Clinical Disease Activity Index (CDAI) to be ≤ 2.8 . These criteria are more stringent than DAS28 remission, but permit still some disease activity mostly because only 28 joints are assessed. Finally, as implied, the probability of reaching remission depends on the definition of remission. Sokka et al. showed in a large multinational, cross-sectional study in 2008 that fewer than 10% of RA patients were able to achieve 1981 ACR remission, approximately 15% reached CDAI remission, and almost 20% were in DAS28 remission (170).

Remission in RA is defined as an achieved state of no (or minimal) disease activity at a specific point of time, possibly followed by a relapse later. Thus, remission is a dichotomous status measure, which has or has not been achieved. Remission does not reflect changes in disease activity over time, and is therefore not a sufficient outcome for clinical drug efficacy trials. Consequently, response

measures for RA have also been developed. The most commonly used response measures are the ACR improvement criteria published in 1995, and the EULAR improvement criteria from 1996 (127,172). The ACR20 response criteria require 20% improvement in 5 out of the 7 core set variables, excluding radiological progression. Improvement in tender and swollen joint counts is mandatory, and no measures are allowed to worsen. Respectively, for ACR50 and ACR70 responses 50% and 70% improvement is required. The EULAR response criteria are based on DAS28 change (Table 2). These two criteria perform comparably in clinical trials, and one of these is usually reported as the primary outcome in DMARD development trials (173). However, the current system of reporting continuous measures as a dichotomous response, i.e. achieving or not achieving ACR20, reduces statistical power. Reporting continuous measures instead would help in reducing the required study population size in efficacy trials.

Table 2. EULAR response criteria using DAS28 (172).

DAS28 at endpoint	Improvement in DAS28 from baseline		
	>1.2	>0.6 and ≤1.2	≤0.6
LDA ≤3.2	Good	Moderate	None
MDA >3.2 and ≤5.1			
HDA >5.1			

DAS28, 28-joint disease activity score; LDA, low disease activity; MDA, moderate disease activity; HDA, high disease activity

2.2.10 The ICF framework

The WHO defines the impact of chronic diseases on individual's life using International Classification of Functioning, Disability and Health (the ICF framework, WHO 2001). This framework has been designed to describe individual's current level of functioning as a dynamic interaction between health conditions, environmental and personal factors, integrating social and medical models of disability (Figure 1). The ICF framework is divided into two parts: 1) function and disability, which includes the components of b) body functions, s) structure, and d) activity and participation, and to 2) contextual factors including e) environmental and personal factors, of which personal factors have not been classified. What is more, to help the rheumatologists, also an ICF core set for RA has been developed (174). The ICF coding is started with the letter of the category (b, s, d, or e), followed by the chapter number. Within each chapter, there are two to four level categories. For example, the code for pain is b280, and pain in the upper limb is coded b28014. Thus, functioning, as defined by the ICF, is a very wide concept. Therefore, ICF is capable of covering many factors not included in other measures of RA patient's functioning, like environmental and social factors, in

depth. ICF can be described as a framework for thinking; it enables including all factors that possibly influence the misfit between environmental demands and individual's capability.

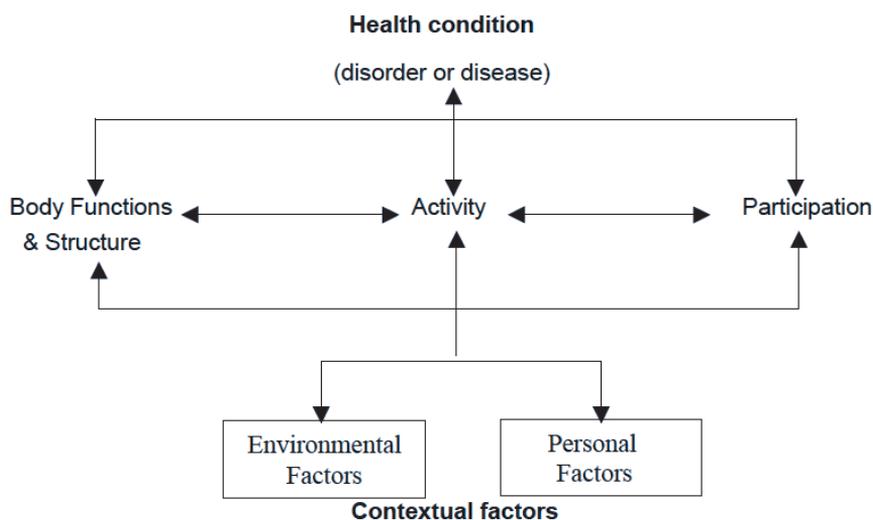


Figure 1. The International Classification of Functioning, Disability, and Health. Reprinted with permission from the WHO (2002).

2.3 Management of rheumatoid arthritis

2.3.1 Overview and current recommendations

The international rheumatology community agrees that the treatment of RA should be targeted to remission, and if this is not achievable, to low disease activity (5,15,97). Currently, multiple equally effective medication options are available. Therefore, shared decision making between the patient and the rheumatologist is important, and is stressed in the treatment recommendations (15). Nevertheless, experts' views on the best treatment for remission induction in early RA differ significantly. The latest 2015 ACR recommendations suggest starting MTX if no contraindications are present, and moving to csDMARD combinations or bDMARDs if remission is not achieved with the initial treatment (97). Further, low-dose glucocorticoids (GCs) are recommended only for patients with moderate to high disease activity. In the 2016 EULAR recommendations, GCs are positioned as short-term bridging therapy when initiating and changing csDMARDs (98). In earlier EULAR 2013 recommendations, MTX monotherapy

and csDMARD combinations were equal as initial treatment options (5). However, the 2016 update states only “MTX should be part of the first treatment strategy” (98). Initial csDMARD combinations are not recommended, but can be used at physician’s discretion. If target has not been achieved in six months adding a bDMARD is suggested in the presence of prognostically unfavorable factors, like autoantibodies and high disease activity. This is an interesting recommendation considering the increased costs without proven increased efficacy associated with bDMARDs. As Misra et al. suggest in their commentary, it seems reasonable and cost-effective to consider bDMARDs or targeted synthetic DMARDs (tsDMARDs) for patients who do not achieve remission with csDMARD combinations at 3–6 months (175). Further, in many countries, bDMARDs are reimbursed only if remission has not been achieved with multiple consecutive csDMARDs or their combinations, making it impossible to follow these recommendations (107). Both latest international recommendations also suggest that DMARDs should be tapered in sustained remission. However, according to ACR recommendations, not all DMARDs should be discontinued due to the high risk of flares.

In the recommendations the use of monotherapy is justified by patients’ lower adherence to combination treatment, and by higher toxicity of csDMARD combinations (98). Interestingly, as evidence towards excess toxicity, the latest EULAR recommendations refer only to 16 and 52-week results of one study (176,177). However, the toxicity profiles of csDMARD combinations, MTX monotherapy, and bDMARD combination therapy with MTX have been comparable in multiple previous studies (4,175,178,179). In addition, it is known that only 20–30% of patients respond well to MTX monotherapy (180,181). Despite this fact many rheumatologists prefer monotherapy, and find the use of csDMARD combinations challenging (182,183). In addition to the international recommendations, this predilection for monotherapy may be derived from rheumatologists’ unfamiliarity with combination therapy. Further, in many countries rheumatologists’ income is based on the number of patient contacts, which possibly increases the use of simpler treatment regimens, like monotherapy (183).

Compared to the abovementioned international recommendations, the 2015 update of Finnish current care guidelines for RA propose taking a clearly more active stance (6). These guidelines state that, in addition to injecting all swollen joints with glucocorticoids, early RA patients should start MTX based triple therapy of csDMARDs and oral low-dose prednisolone. Proceeding to bDMARDs is recommended if good response is not achieved within 3–6 months. This strategy has led to excellent results in clinical practice. Rannio et al. reported that 71% of incident early RA patients treated in their clinic 2008–2011 were in DAS28 remission at 12 months (8). More than 50% of these patients received combinations

of csDMARDs, 4 out of 5 were prescribed oral low-dose GCs, and more than 90% had received one or several iaGG injections. Further, fewer than 3% of the patients required bDMARDs during the first 12 months.

2.3.2 Disease-modifying antirheumatic drugs

Disease-modifying antirheumatic drugs (DMARDs) decrease pain and inflammation, and reduce joint damage in RA. These drugs can be divided into conventional synthetic DMARDs (csDMARDs), targeted synthetic DMARDs (tsDMARDs), and biologic DMARDs (bDMARDs). MTX, one of the csDMARDs, is “the anchor drug” of RA. It was originally developed for the treatment of cancer, but acts, at substantially lower dosages, as an effective anti-inflammatory agent (184,185). MTX is taken once a week, either orally or subcutaneously. Folic acid supplementation is usually coadministered in order to reduce adverse effects. Compared to oral administration, subcutaneous use of MTX has been associated with fewer side effects, improved bioavailability, and increased efficacy (186). Therefore, subcutaneous MTX should be prescribed primarily or at least tried in non-responders and patients not tolerating oral MTX before moving to bDMARDs. In addition to being efficacious, MTX has been shown to reduce cardiovascular mortality of RA patients (184,187). Other commonly used csDMARDs include sulfasalazine (SASP) and hydroxychloroquine (HCQ), which are especially beneficial in combination with MTX. In addition, leflunomide, azathioprine, cyclosporine, and gold compounds are used (47). Novel oral treatments include tsDMARDs, like oral Janus kinase (JAK) inhibitors tofacitinib and baricitinib, and numerous other small molecules are being investigated for the treatment of RA (188,189).

The improved appreciation of the underlying mechanisms behind joint inflammation in RA led to development of first bDMARDs, tumor necrosis factor (TNF) inhibitors, which became available in the late 1990s (190,191). Thereafter, the armamentarium of available bDMARDs has increased steadily, and currently, in addition to the TNF inhibitors, therapies targeting B-cells, IL-1, IL-6, and T-cell costimulation are available for the treatment of RA (190,191). These biologic DMARDs are large protein molecules, and cannot therefore be administered orally in contrast to csDMARDs and tsDMARDs. Hence, they are given as intravenous infusions or subcutaneous injections. Complicated manufacturing process, in addition to the costs associated with drug development, makes bDMARDs significantly more expensive than csDMARDs.

2.3.3 Glucocorticoids

Despite the introduction of new, targeted bDMARDs glucocorticoids (GCs) remain an important part of the treatment of RA. GCs suppress inflammation rapidly and effectively, but prolonged GC treatment is associated with multiple detrimental effects. These include e.g. hyperglycemia, osteoporosis, skin thinning, cataract, glaucoma, gastrointestinal ulcerations, infections, and weight gain (192-195). However, based on most recent clinical trials, the short-term adverse events associated with low-dose GCs, i.e. max. 7.5 mg prednisone or prednisolone daily, seem mild and comparable to placebo, except for glaucoma and weight gain (196). In addition, even low-dose GCs are possibly associated with an increased risk of cardiovascular disease, and future placebo controlled clinical trials with sufficient duration are needed in order to make definite conclusions about their safety (193,196). Currently, due to limited long-term safety data, EULAR recommendations state that GCs should be considered as part of the initial treatment strategy, but the treatment should be tapered as rapidly as clinically feasible (98).

2.3.3.1 High dose glucocorticoids

Three studies have used high-dose GCs in early RA for remission induction (197-199). Of these studies, in the Dutch The Combinatietherapie Bij Reumatoïde Artritis (COBRA) early RA patients were randomized to either monotherapy or combination therapy including oral prednisolone starting from 60 mg/day, tapered off in 28 weeks (197). At 56 weeks, a significant difference in radiological progression, but not in clinical outcomes, was seen in favor of the combination group. Radiological benefit of early combination treatment was seen also in the 5- and 11-year extensions of the study (81,200). In the Behandel-Strategieën (BeST) study, 508 early RA patients were randomized to four different treatment regimens targeting low disease activity (198). At two years, compared with monotherapy or step-up treatment, clinical outcomes were better and radiological progression rate was lower in the groups randomized to either initial high-dose prednisolone with three csDMARDs or MTX-infliximab combination. In the latest study, Infliximab as Induction Therapy in Early Rheumatoid Arthritis, MTX and 6-month induction treatment with infliximab was not superior to MTX in combination with a single 250 mg infusion of methylprednisolone at baseline when outcomes were assessed at 50 weeks (199). In these studies, the duration of the high-dose GC treatment was short, and the treatment was well tolerated with an acceptable adverse effect profile. However, in routine clinical practice patients' co-morbidities, and patients' and physicians' concerns towards GCs may reduce the feasibility of this approach. Further, similar results are

achieved with the use of low-dose oral GCs, which reduces the appeal of the abovementioned high-dose regimens.

2.3.3.2 Low-dose oral glucocorticoids

During recent decades, the beneficial effect of oral low-dose glucocorticoids in relieving RA symptoms rapidly and reducing radiological progression has been demonstrated in multiple studies (201-205). In 1990s, Kirwan et al. showed that, compared to placebo, prednisone 7.5 mg/day reduced radiological progression significantly (201). After 2000s, multiple studies presented similar results (202,205,206). Wassenberg et al. reported that only 5 mg of prednisolone daily was enough to retard radiological progression in early RA in addition to DMARD treatment after multiple trials using higher dosages (207). In more established disease low-dose oral GCs are not clearly beneficial (208,209). These studies have shown that in early RA, low-dose GC treatment does, in addition to relieving RA symptoms and clearly reducing radiological progression, also improve functional status and quality of life. Thus, GCs have disease-modifying properties, and they fulfill the conventional definition of a DMARD. However, the optimal length and dosage of low-dose oral GC treatment remains undetermined.

2.3.3.3 Intra-articular glucocorticoids

2.3.3.3.1 Single-joint injections

The use of intra-articular GCs (iaGCs) instead of oral GCs may be less detrimental due to cumulative doses remaining lower as injections are administered only in the presence of swollen joints. Therefore, injections may be less likely to cause adverse events in long-term. Furthermore, injection-associated adverse events are usually mild and transient. The only exception is bacterial arthritis, an often feared, but extremely rare complication (210,211). However, compared with oral GCs, data on the impact of iaGCs is surprisingly scarce. Current evidence supports the efficacy of single-joint iaGCs in the treatment of RA (212-215). Unfortunately, most studies have assessed only knee synovitis. One randomized double blind trial has assessed the difference between intramuscular and intra-articular GC administration in RA knee arthritis, finding the latter to be more efficient (216).

2.3.3.3.2 Polyarticular injections

Literature on polyarticular GC injections is scarce. One randomized trial has focused on comparing intramuscular and polyarticular administration of GCs in RA (217). In this study, Furtado et al. randomized 75 patients with established RA, stable DMARD treatment, and 6–12 swollen joints into polyarticular (6–8 joints) triamcinolone treatment or intramuscular triamcinolone treatment with equivalent dosage, and followed them for six months. Compared to intramuscular treatment, ACR20 and ACR50 response rates were significantly higher in the iaGG group at one and four weeks after the intervention, but not later. Ia administration was also associated with fewer adverse effects. In addition to Furtado et al., one Indian randomized trial has examined the benefits of polyarticular iaGCs in early RA. Early RA patients were treated with MTX and sulfasalazine and were randomized to two groups (218). One of these groups received iaGCs to all swollen joints, whereas the other was treated only with MTX and sulfasalazine combination. Cumulative triamcinolone dose per patient ranged from 80 mg to 640 mg. At 3 months, the patients who had received iaGCs had significantly lower DAS28 levels. ACR50 and ACR70 response rates were 60% and 36% in the iaGC group, and 20% and 0% in the control group, respectively. These two studies suggest that iaGCs are effective in both established and early RA, at least in short-term.

2.3.3.3.3 Polyarticular injections as a part of the treatment strategy

In addition to the abovementioned two studies, iaGCs have been used actively as a part of the treatment strategy in multiple trials. Design of these studies is shown in Table 3 (4,11,219–224). In Ciclosporine, Methotrexate, Steroid in RA (CIMESTRA) and Optimized treatment algorithm in early RA (OPERA) trials, iaGCs were injected to swollen joints at all visits, but the number of injections was limited to four per visit (222,224). Hetland et al. also analyzed the efficacy of iaGCs in CIMESTRA separately, and found that injections (n=1373) led to rapid and long-lasting control of inflammation in the injected joints (225). Injections were well tolerated, and more than 50% of the injected joints remained synovitis free throughout the two-year follow-up. The percentages were lower for joints injected two or three times, but 43% and 31% of these joints, respectively, were synovitis free at two years.

Proudman et al. allowed methylprednisolone injections up to 15 joints or a maximum of 160 mg per visit in the combination group (Table 3), but in the monotherapy group only significantly painful and swollen joints were injected (219).

In addition, if ACR20 response had not been achieved at three months, the patient received also an intra-muscular GC injection. In their more recent study, all patients were treated with triple combination of csDMARDs and fish oil, but injections were recommended only to persistently swollen joints (221). Saunders et al. allowed a maximum of 80 mg of triamcinolone acetonide per visit. This had to be given into swollen joints which had not been injected during the previous 3 months (223). In addition, intramuscular GCs were allowed up to 80 mg if less than this amount was injected within 3 months and low disease activity had not been achieved.

In the four abovementioned trials, oral GCs were not allowed. Of the strategy trials using iaGCs, only in Finnish Rheumatoid Arthritis Combination treatment strategy (FIN-RACo) and NEO-RACo both low-dose oral and intra-articular GCs were used actively (4,11). In the TIGHT CONTROL for Rheumatoid Arthritis (TICORA) trial, the treatment was gradually intensified, and up to 3 joints or 120 mg of triamcinolone acetonide per visit were injected (220). If low disease activity had not been achieved earlier, oral GCs were added as the fifth treatment step. However, during the 18-month study, only 7 patients (6%) received oral GCs in addition to iaGCs. In contrast, in NEO-RACo all, and in FIN-RACo at some point 82% of the patients received oral GCs during the study. Therefore, in comparison to other trials mentioned in Table 3., cumulative daily doses of prednisolone were significantly higher in these two studies. In addition to these trials, iaGCs were allowed, but not encouraged in the BeSt study, in which only a small proportion of patients, less than 20%, received injections (198).

The achieved remission rates in the studies using iaGCs actively are not directly comparable for multiple reasons, including differing definitions of remission. Nevertheless, in these studies the highest reported remission rates, achieved in most cases in the intensive or combination treatment groups, were 13% by Proudman in 2000 (ACR remission), 37% in FIN-RACo and 66% in NEO-RACo (modified ACR remission), 65% in TICORA and 51% in CIMESTRA (DAS remission), 53% by Proudman in 2007, 45% by Saunders et al., 82% in NEO-RACo, and 74% in OPERA (DAS28 remission).

Based on these studies, used with or without oral GCs, iaGCs are clearly useful as a part of the targeted treatment of RA, and most likely associated with fewer side-effects compared to systemic administration. In the current EULAR recommendations, iaGCs are recommended for optimizing the treatment in the presence of one or few swollen joints, i.e. only for patients suffering from mono- or oligoarticular synovitis (98). Direct evidence on iaGCs is scarce; no studies have compared oral and intra-articular administration of GCs, and only one study has compared intra-articular and intra-muscular administration (217). Thus, more

Table 3. Studies using polyarticular injections as a part of the treatment strategy.

Author and year (ref)	RA duration	Patients and follow-up	DMARD treatment	Intra-articular (ia) GCs to swollen joints	Daily GC dose, prednisolone equivalents
Hørslev-Petersen et al. 2014 (224)	<6 months	180 patients 1 years	MTX + placebo or adalimumab	Triamcinolone max. 4 ml/visit, 0-4 joints, all visits	<1 mg/day
Leirisalo-Repo et al. 2013 (11)	<12 months	99 patients 2 years	Triple+pred+pla vs Triple+pred+infl	Any iaGC, all swollen joints, all visits	Triple+pla 7.9 mg/day, Triple+infl 7.7 mg/day
Saunders et al. 2008 (223)	<5 years	96 patients 1 years	Step-up vs. triple	Triamcinolone, 0-4 joints, 3-monthly if DAS28 _{3,2} ≥3.2	Step-up 1.3 mg/day, triple 1.2 mg/day
Helland et al. 2008 (222)	<6 months	160 patients 2 years	MTX + placebo or cyclosporine	Betamethasone max. 4 ml, 0-4 joints, all visits	<2 mg/day 1st year, <0.5 mg 2nd year
Proudman et al. 2007 (219)	<12 months	61 patients 3 years	Triple+fish oil	Methylprednisolone max. 160 mg per visit for persistently swollen joints, im GCs if needed	0.1 mg/day
Grigor et al. 2004 (220)	<5 years	110 patients 1,5 years	Step-up; SASP > triple > triple+pred	Triamcinolone, 0-3 joints, max. 120 mg/3 months, balance up to 120 mg im 3 monthly	<1,5 mg/day
Proudman et al. 2000 (221)	<12 months	82 patients 1 year	SASP vs MTX+cyclosporine	Methylprednisolone, painful vs swollen joints (max. 160 mg per visit), 120 mg im if no ACR20	Mono <0.1 mg/day, combi 0.2 mg/day
Möttönen et al. 1999 (4)	<2 years	199 patients 2 years	SASP +/- pred vs triple+pred	Any iaGC, all swollen joints, all visits	Mono 5.2 mg/day, triple 5.1 mg/day

RA, rheumatoid arthritis; DMARD, disease-modifying antirheumatic drug; GC, glucocorticoid; MTX, methotrexate; Triple, triple therapy of DMARDs; Pred, prednisolone; Pla, placebo; Infl, infliximab; Step-up, initial monotherapy and step-up to combination therapy if required; DAS28, 28-joint disease activity score; SASP, sulfasalazine; ACR20, American college of Rheumatology 20% improvement; Mono, monotherapy.

studies exploring the benefits of iaGCs are needed, and barriers to effective use of injections should be recognized. Surveys have shown that many, but not all, rheumatologists find the use of csDMARD combinations challenging (182,183). This may be true also concerning polyarticular, potentially time-consuming, administration of iaGCs.

2.3.4 Adverse events

An adverse event can be defined as any undesirable medical event temporally associated with the use of medication, which may or may not have a causal relationship to the used medication. All medications, even placebo, are associated with adverse events (226). With current tight reporting requirements, modern efficacy trials report adverse events in majority of patients (11,189). Adverse events may influence treatment results and lead to discontinuation of medication or reduced adherence. In RA studies, inefficacy and adverse events have been the two leading causes for drug discontinuation (227-230). Adverse events caused by DMARDs are variable. CsDMARDs can cause a plethora of subjective symptoms, of which gastrointestinal complaints are most common. In addition, csDMARDs sometimes cause elevation of liver enzymes or blood count changes, and can influence renal function therefore requiring regular safety monitoring. Compared to csDMARDs, bDMARDs are more pronouncedly associated with an increased risk of severe infections. (47) Patients do not always recognize this inflated infection risk. A study analyzing data from the German bDMARD register found that physicians reported three times more infections than patients, and patients often failed to associate even severe infections with their bDMARD treatment (231).

Two meta-analyses have focused on retention rates and toxicity of DMARDs. Maetzel et al. analyzed the withdrawal rates of csDMARD monotherapy before the era of bDMARDs, and Choy et al. assessed the toxicity of DMARD combinations, including TNF inhibitors (232,233). According to Maetzel et al., MTX had the best 5-year survival, 65%, when only toxicity was taken into account. Respective figures for sulfasalazine and intramuscular gold were 48% and 36%. Choy et al. found that the risk of toxicity was slightly higher for DMARD combinations, including bDMARDs, than for monotherapy (RR 1.37, 95% CI 1.16–1.62). However, this increase risk of toxicity not seen with MTX in combination with sulphasalazine, anti-malarials or both.

In addition to abovementioned meta-analyses, five studies have focused on adverse events or predictors of DMARD discontinuation. Aletaha et al. analyzed 2376 patient years of DMARD use in 593 RA patients treated in two Austrian

hospitals during the last third of the 20th century (227). They found that adverse events, of which 70% were subjective and 9% laboratory abnormalities, caused 42% of the DMARD discontinuations. In more recent early RA studies DMARD discontinuation rates caused by toxicity have been slightly lower, ranging from 34% to 38% after a follow-up of 2–3 years (229,230,234). In the Early RA Network cohort adverse events caused 34% of csDMARD discontinuations, and baseline disability, extra-articular disease, and worse mental health predicted DMARD failure (229). The results of Listing et al. were in concordance with the previous study showing that patient's psychological well-being and baseline disease activity predicted DMARD survival (235). Further, Cummins et al. studied the tolerability of triple therapy of csDMARDs in 119 early RA patients (230). After a median follow-up of 104 weeks, adverse event led to cessation or replacement of one of the drugs in 38% of the patients. One-year remission rates did not differ between patients who stayed (43%) and did not stay on triple therapy (41%; i.e. continued with one or two DMARDs), but complete DAS28 data were available only for 60% of the patients at this time point. In addition, Wabe et al. reported that during a 3-year follow-up, 37% of the patients withdrew at least one DMARD, and found that these withdrawals were associated with fewer improvements in function (HAQ), pain, fatigue and PtGA, but not HRQoL (234).

In conclusion, adverse events, most of which are subjective, lead to cessation of 34–42% of the DMARD courses in RA. Of the csDMARDs, MTX has the best survival due to its tolerability and efficacy (5,236). Multiple factors including disease activity, disability and mental health, may predict DMARD survival at baseline.

2.3.5 Non-pharmacological treatment

In addition to drug treatment, the optimal care of RA requires a multidisciplinary team of health professionals. Person-centered, empowering patient education based on dialogue is one of the cornerstones of RA treatment. Patient education is usually given by a rheumatology nurse, and has been shown to improve medication adherence (237). It aims at teaching the patient what RA encompasses, how it is treated, and what are its consequences without treatment. It should be stressed that remission is a realistic goal in early disease, but will not be achieved without conscientious use of medication. Further, occupational therapy improves patients' functional ability, and individually tailored physical therapy may benefit especially patients, who have developed substantial disability (238). Research does not support the use of inpatient rehabilitation in the treatment of RA (239). However, there is strong evidence suggesting that the effects of exercise are ben-

official, and both aerobic and muscle strength training should be routinely recommended for RA patients, preferably instructed by a physiotherapist (240,241). Nowadays, surgery is required seldom due to the improved treatment (242). However, timely surgical treatment improves functional ability in selected cases, and multiple surgical options, including joint replacement, are available for RA patients (243).

2.4 How are good treatment results achieved and improved?

2.4.1 Evolution from no treatment to targeted treatment

In 1980s, it became evident that RA is not a mild disease with a good prognosis (244,245). This led to growing interest in more effective treatment, and into the introduction of the saw tooth strategy by Fries in 1990 (246). This strategy encouraged to early DMARD use, and switching to another DMARD in case of suboptimal clinical response or adverse events. Still, for many patients, DMARD monotherapy did not offer sufficient disease control. Therefore, rheumatologists and researchers started exploring also DMARD combinations. The first combination treatment trials did not, however, demonstrate significant improvements in efficacy compared to monotherapy (247). Popularity of combination therapy grew when later studies yielded clearly positive results with an acceptable toxicity profile (4,248). Also, the popularity of MTX increased, and in the late 1990s most rheumatologists preferred MTX monotherapy as the first line option (249). MTX became the “anchor drug” of RA, and continues to be the initial choice for the treatment of early RA among most rheumatologists. Some started to prefer combination therapy, which is reasonable, as only 20–30% of patients achieve remission with MTX monotherapy (181,250). Further, the therapeutic armamentarium of RA broadened in the end of 1990s when first bDMARDs became available. However, due to their high price, bDMARDs are rarely a part of the initial treatment strategy. bDMARDs are, together with tsDMARDs like JAK-inhibitors, currently recommended by EULAR as second line treatment in active, ACPA positive RA if remission is not reached with MTX monotherapy. Contrastingly, many studies have shown that csDMARD combinations and bDMARDs in combination with MTX are equally effective (251,252).

Most rheumatologists around the world agree that MTX should be part of the initial treatment strategy. However, there’s no unanimous opinion on what - if anything - should be combined with it. Perhaps agreement on the best initial treatment strategy is not even needed, as the choice of DMARD(s) does not sole-

ly determine the outcome of early RA. Researchers started to comprehend this in 1990s, when they discovered that the early institution of therapy led to improved treatment results (253). What is more, later multiple trials showed that, compared to routine clinical practice, treatment results improved significantly when tight-control treatment strategies targeting remission or low disease activity were used (220,254,255). Finally, these advances led to the publication EULAR's treat-to-target manifesto in 2010, and its later update (15,256). This manifesto states that the treatment aim of RA should be remission, or alternatively in established disease, low disease activity. Regular follow-up visits every 1–3 months are recommended in active disease, as well as use of composite measures of disease activity including joint counts. In addition, the manifesto states that treatment choices should be based on shared decision between the patient and the rheumatologist, taking into account also patient's views on different treatment options. The content of the treat-to-target manifesto and the evidence supporting it are reflected on current treatment recommendations, all of which target remission (5,6,97). Contemporary evidence also suggests that, instead of a specific DMARD or DMARD combination, the favorable results of RA treatment strategy trials can be largely attributed to the use of tight-control treatment strategies (177,223,257,258).

2.4.2 Targeted treatment in clinical practice

Rheumatologists have understood and accepted the importance of early institution of targeted treatment. However, even professionals' adherence to guidelines tends to be limited in the treatment of chronic conditions (259,260). Treat-to-target recommendations are no exception. When rheumatologists from 14 countries were surveyed, physicians mostly agreed with treat-to-target recommendations (261). Nevertheless, only 67% of their patients were prescribed DMARDs early, during the first four weeks after diagnosis, and data on composite measures of disease activity were available for only approximately 50% of the patients. Another survey analyzed barriers reducing the use of intensive csDMARD combinations with glucocorticoids among Belgian rheumatologists (262). According to this survey, patient related factors, like patients' reluctance to start a multi-drug regimen and contraindications to csDMARDs, were among the most important barriers to the use of intensive treatment strategies. In addition, many physicians found prescribing a multi-drug regimen difficult.

Despite the abovementioned survey results, multiple cohort studies have shown that intensive treatment strategies can be applied into clinical practice with good results. Rantalaiho et al. analyzed medications of 14 878 newly diagnosed RA

patients in a Finnish nationwide cohort between 2000 and 2007, and showed that the use of DMARD combinations as the initial treatment strategy increased from 38% to 55%, MTX became the most commonly started DMARD, and approximately 95% of the patients bought DMARDs during the first three months after diagnosis (106). Interestingly, these changes in DMARD strategies coincide with a reduction in RA related work disability pensions among incident RA patients in Finland, possibly caused by the intensification of initial treatment strategies (96). In the Canadian Early Arthritis Cohort 1138 early RA patients in 8 rheumatology centers were followed between 2007 and 2011 (143). Depending on the study site, 35–75% of the patients achieved DAS28 remission at 12 months. Highest remission rates were reported at sites using more subcutaneous MTX and triple therapy of csDMARDs. Also RA patients (n=1202) at Leiden University Medical Center 2008–2013 were treated with good results (263). In clinical practice, during 69% of the visits patients' disease activity was low, and respectively, DAS remission was recorded during 39%. Rannio et al. reported even higher remission rates in two Finnish studies (8,144). They followed 406 early RA patients treated in a single rheumatology clinic 2008–2011 and studied a multicenter cohort of 506 early RA patients recruited 2011–2014. Of these patients, 71% and 75% reached DAS28 remission at 12 months, respectively. The abovementioned studies differ in many aspects; some are nationwide register studies, others report the treatment results of one clinic. However, when summarized, the results of these studies suggest that remission, at least DAS28 remission, is indeed a realistic treatment target in modern rheumatology clinical practice.

2.4.3 Influence of adherence

2.4.3.1 Patient adherence

Multiple terms have been used in the literature to describe medication-taking behaviours. Adherence and compliance to medications are usually defined as the extent to which patients take their medications as prescribed by their health care provider (264). Adherence has become the preferred term, stressing the importance of shared decision making between the patient and the physician, whereas compliance refers more to passively obeying physician's orders. Non-adherence is a significant public health problem. According to an estimate by WHO, only 50% of patients suffering from chronic conditions are adherent in developed countries (264). This lack of adherence has a substantial impact on health outcomes, as medications are only effective when taken. In addition to

higher health care costs, nonadherence to medication has been associated with increased morbidity and mortality (264-268).

Multiple factors, related to patient, society, health care system, therapy and the disease itself all influence adherence. Nonadherence can be intentional or unintentional. Patients can, for example, decide not to start the prescribed treatment, or forget to take their medication regularly. Further, health care associated factors, like medication costs, are a barrier to adherence for many. According to WHO, adherence is also strongly related to patients' knowledge and beliefs concerning their illness and its treatment, and their level of health-literacy. The importance of health literacy arises from its strong influence on patient's self-management skills and understanding of the possible consequences of non-adherence. (264)

Also many physician-related factors contribute to medication nonadherence. These include prescribing complex drug regimens without explaining possible adverse effects and benefits thoroughly, failing to recognize nonadherence in patients, and not taking into account the financial burden of the prescribed treatment to the patient (266,269). Physician's good communication skills are essential in improving patient adherence (270). Successful communication is required for asking non judgementally about possible adverse effects and nonadherence (266). The latter should always be addressed due to its high prevalence, as medication nonadherence is more prevalent than physicians tend to believe, and cannot be improved if it remains unrecognized (266,269)

2.4.3.2 DMARD adherence

Nonadherence is prevalent among RA patients. Studies have shown that RA patients' DMARD adherence ranges from 10% to 107%, with an overall adherence rate of 66% (271-274). A recent meta-analysis demonstrated that adherence to bDMARDs is also incomplete, and ranges from 32% to 91% after one year of treatment (275). MTX persistence, a marker of adherence, efficacy and toxicity, ranged from 50% to 94% at 1 year and 25% to 79% at 5 years in a recent meta-analysis by Curtis et al., whereas another meta-analysis by Hope et al. reported a MTX adherence range of 59% to 107% where the latter figure refers to overuse (236,276). In addition, according to Curtis et al., adherence to both MTX and bDMARDs may be higher compared with other csDMARDs although, due to different study designs and possible biases, direct comparisons between studies are difficult (236).

Multiple studies have associated higher DMARD adherence with lower disease activity (277-280). Contreras-Yanes et al. showed that nonadherence and non-persistence were associated with flares in early RA patients with low disease activity, and good persistence during the first four years of treatment was associated with lower disease activity and lower HAQ during the fifth year (277,279). Waimann et al. monitored 107 established RA patients drug intake electronically using Medication Event Monitoring System (MEMS) for 2 years and determined adherence as the percentage of correctly taken doses (278). Adherence to DMARDs was 64%, and 70% for prednisone, and only one fifth of the patients had an adherence rate of 80% or higher. Adherent patients had better mental health, significantly lower DAS28 levels throughout the follow-up, and less radiological progression. In early RA, nonadherence seems to have similar influence on disease activity. This was demonstrated by Pasma et al., who followed 120 early RA patients starting their first DMARDs for a year and assessed their adherence using MEMS (280). They found that adherence, excluding prednisolone, decreased over time and nonadherence was associated with higher disease activity during the first six months, but not later. Treatment modifications according to treat-to-target principles may explain this; if remission was not achieved, treatment was intensified despite possible nonadherence.

2.4.3.3 Interventions for improving adherence

Nonadherence is a well-acknowledged problem. However, influencing adherence has proven to be very difficult. Adherence interventions have been assessed in two Cochrane reviews (281,282). The earlier review by Haynes et al. showed that simple interventions often improved short-term adherence successfully (281). Long-term interventions in chronic conditions were less successful, and improved adherence in approximately half of the studies. Improvement in clinical outcomes was detected in only 30% of these studies (281). Seventeen randomized, controlled trials with a low risk of bias were analyzed in the update of this review in 2014. These studies used complex multi-component interventions for improving adherence. Interventions included education, counseling (e.g. motivational interviewing, cognitive behavioural therapy) given by health professionals, and daily treatment support. However, both adherence and clinical outcomes improved in only five out of 17 studies underscoring that current interventions for improving adherence are, unfortunately, not effective (282).

Medication adherence in rheumatic diseases has also been reviewed recently. Galo et al. found 23 studies, which reported direct or indirect adherence interventions (283). Thirteen randomized, controlled studies underwent further analy-

sis. Seven studies assessed RA patients, and four of these reported improvements in adherence. However, only one study demonstrated significant improvements in outcomes like DAS, pain, physical function, and quality of life. Overall, the reviewed studies showed that some interventions may improve medication adherence in rheumatic diseases slightly, but are unlikely to improve outcomes (283).

2.4.3.4 Physician adherence

2.4.3.4.1 Surveys concerning physicians' guideline adherence

Evidence-based guidelines are essential for high-quality management of diseases, but their implementation requires overcoming multiple barriers. Physicians' agreement with guidelines does not automatically translate to following the guidelines in clinical practice (259,260,284). This is true also concerning treat-to-target recommendations. Surveys have shown that majority of rheumatologists agree with the recommendations (261,285,286). However, this is not always reflected in the way they actually treat their patients. The International Recommendation Implementation Study (IRIS) recruited 132 rheumatologists from 14 countries and measured their adherence to treat-to-target recommendations (261). Rheumatologists received education concerning treat-to-target and RA treatment recommendations. Later, they answered a questionnaire about their agreement with the recommendations. Each rheumatologist recruited 5–10 early RA patients, who were followed for 1–2 years. Of the physicians, 98% and 96% agreed with the following recommendations: DMARD treatment should be initiated early, and MTX should be a part of the initial treatment strategy. Further, 83% agreed that measures of disease activity should be recorded regularly. However, of the 378 patients included in the study only 253 (67%) received DMARDs within four weeks, 225 (60%) were initially prescribed MTX, and composite measures of disease activity were recorded regularly in only 134 (54%). Not using composite measures of disease activity including joint counts is unsurprising; surveys have shown that this recommendation is the one that rheumatologists are least likely to apply into clinical practice (285,286). Some rheumatologists find also adjusting the drug treatment difficult if remission has not been achieved, often due to lack of time (286). Evidence-based guidelines aim to incorporate the latest evidence, expert opinion, and patients' preferences. Nevertheless, it should be remembered that guidelines remain only consensus recommendations. Therefore, it is unrealistic to expect 100% guideline adherence as individual patient's

optimal treatment may, for multiple reasons, require deviating from the recommendations.

2.4.3.4.2 Physicians' adherence in clinical trials and clinical practice

Four studies have examined physicians' protocol adherence in the targeted treatment of early RA. These studies are highlighted in Table 4 (287-290). Vermeer et al. reviewed the medication charts of 100 randomly selected early RA patients from the Dutch DREAM remission induction cohort (287). The patients were assessed 1–2 monthly during the first six months, and every three months thereafter. If needed, the treatment was intensified according to a predefined protocol. Physician's adherence was evaluated at all visits. Physicians were adherent to treat-to-target during 69% of the 1092 visits. The most common cause for non-adherence was discordance between DAS and rheumatologist's assessment of disease activity. The impact of nonadherence on RA outcomes was not assessed.

Wabe et al. followed RA patients at an early arthritis clinic for three years after RA diagnosis (288). All patients started combination therapy of csDMARDs, and their treatment was modified according to treat-to-target principles. Protocol deviations and their causes were assessed retrospectively. Wabe et al. found that treatment advice was followed during 75% of the visits, a figure comparable to the 69% adherence rate reported by Vermeer et al (287). In addition, Wabe et al. and Vermeer et al. reported a protocol deviation during at least one clinic visit in 90% and 91% of the patients, respectively. In both of these studies, compared with patients who reached remission, deviations were significantly more frequent during the visits of patients who did not reach remission. Interestingly, Wabe et al. reported that 20% of protocol deviations were caused by comorbidities and 23% by DMARD toxicity, whereas toxicity caused only 6% of the deviations in the DREAM cohort. Difference in reporting protocol deviations likely explain this; Wabe et al. reported, on average, more than two causes for each protocol deviation whereas Vermeer et al. reported only the main cause.

Markusse et al. studied physicians' adherence to treat-to-target during the BeST study and its 10-year follow-up (290). In contrast to the abovementioned studies, physicians had to fill an adherence questionnaire at all 3-monthly visits. Protocol adherence was 79% over time, comparable with Wabe et al. and Vermeer et al. However, Markusse et al. reported 100% adherence at baseline, which decreased to 60% over time. In concordance with Vermeer et al., rheumatologist's disagreement with DAS increased the risk for protocol deviations in this study. Further, also rheumatologist's dissatisfaction with the level of disease suppression,

Table 4. Studies assessing physicians' adherence to targeted treatment

Author and year (ref)	Patients and follow-up	Study type, treatment strategy and target	Adherence measure	Outcome
Markusse et al. 2016 (290)	508 patients 10 years	Best trial, treatment arms: mono/step-up/combi/MTX +infliximab, DAS remission	Protocol adherence questionnaire to physicians 3-monthly	Adherence present during 79% of the visits, from 100% to 60% over time
Wabe et al. 2015 (288)	198 patients 3 years	Early RA cohort, initial triple, DAS28 remission	Retrospective assessment of medical charts	Protocol deviations during 24.5% of the visits
Rantalaho et. al 2014 (289)	199 patients 2–5 years	FINN-RACO trial (SASP monotherapy vs triple), ACR remission	Protocol adherence yes/no based on a retrospective nonadherence score	Best outcomes (WD, ACR remission) when treated adherently with triple
Vermeer et al. 2012 (287)	100 patients 28 months (mean)	DREAM early RA cohort, initial MTX step-up, DAS28 remission	Retrospective assessment of medical charts	Adherence present during 69% of the visits

Mono, monotherapy; Step-up, initial monotherapy, and step-up to combination therapy if required; Combi, combination treatment ; MTX, methotrexate; DAS, disease activity score; DAS28, 28-joint disease activity score; SASP, sulfasalazine; Triple, combination of MTX, SASP, and hydroxychloroquine; ACR, American College of Rheumatology; WD, work disability.

and discordance between patient's and rheumatologist's assessment of disease activity increased the risk of nonadherence.

Rantalaiho et al. studied protocol adherence in the FIN-RACo trial and assessed physicians' adherence retrospectively (289). Patients were scored points from protocol deviations, which included not injecting iaGCs into all swollen joints, not filling out the study forms properly, and not intensifying medication in case of non-remission. Based on the score, patient's treatment during the first two years was categorized as adherent or nonadherent. After a follow-up of 2–5 years, physicians' adherence had a significant impact on disease outcomes. Actively treated patients in the combination therapy group were most likely to reach remission at 2 years and had least cumulative WD days during 5-year follow-up, whereas the patients treated inactively with monotherapy had the worst outcomes. Rantalaiho et al. concluded that in order to bring most patients into remission, both active targeted treatment and DMARD combinations should be used.

In all of the abovementioned studies, excluding BeSt, adherence was assessed retrospectively and physicians were unaware of this assessment while making treatment decisions. Therefore, the results of these three studies likely describe physician's true protocol adherence. Of the two clinical trials, all physicians were adherent to treatment advice at baseline in BeSt, perhaps due to the adherence questionnaire, but not in the FIN-RACo, in which adherence was assessed retrospectively. Both Wabe et al. and Markusse et al. described how adherence changed over time; Wabe et al. reported that the mean time to first protocol deviation was 30 months, whereas in the BeSt adherence decreased from 100% in the beginning to 60% over time. Based on these studies it seems that physicians' adherence is comparable to patients' adherence; it is incomplete, decreases over time, and may influence the outcomes of early RA.

3 AIMS OF THE STUDY

The aim of the present study was to elucidate factors that, in addition to intensive remission targeted DMARD treatment, are associated with improved outcomes in early RA. The following research questions were formulated:

1. Does physicians' adherence to the treatment protocol and to the targeted treatment affect the outcomes?
2. Does neglecting intra-articular glucocorticoids have an impact on treatment results?
3. How do adverse events influence remission rates?
4. Are patient-reported outcome measures (PROs) useful as predictors of remission in intensively treated early RA patients?

4 MATERIALS AND METHODS

4.1 Patients

The trial enrolled 99 working age (18–60 years) patients at 15 rheumatology centers in Finland between March 2003 and April 2005. The patients had to fulfill the ACR 1987 classification criteria for RA (14), and have active RA with at least 6 swollen and 6 tender joints, and one or more of the following: duration of early morning stiffness ≥ 45 min, ESR ≥ 30 mm/h, and CRP ≥ 20 mg/l. The patients were required to be DMARD naive and have early RA defined as duration of symptoms ≤ 12 months. Furthermore, the patients also had to be working or available for work. Among the exclusion criteria were treatment with oral GCs within 6 months, iGCs within 1 month, contraindications to study medications, a history of tuberculosis or malignancy within 5 years, and current active infection.

4.2 Study design

The NEO-RACo (New Finnish Rheumatoid Arthritis Combination treatment strategy) trial was an investigator initiated, randomized, controlled, double-blind trial. The study aimed to compare the efficacy of infliximab versus placebo induction treatment of 6 months in addition to openly administered triple therapy of csDMARDs and low-dose oral prednisolone. IaCGs to all swollen joints were strongly recommended as a part of the treatment strategy. The patients were randomized to receive infliximab or placebo infusions at weeks 4, 6, 10, 18, and 26. The FIN-RACo combination treatment consisted of MTX (started 10 mg/week, increased up to 25 mg/week or the highest tolerated dose in 14 weeks), sulfasalazine (SASP, 1 g/day, increased up to 2 g/day in 2 weeks), hydroxychloroquine (HCQ, 35 mg/kg/week), and prednisolone (7.5 mg/day). In addition, the patients were prescribed folic acid (5 mg/week), calcium (1000 mg/day), and vitamin D3 (800 IU/day) supplementation. In case of adverse events, MTX could be administered in the subcutaneous form using the same maximum tolerated dose. Throughout the study, the treatment was targeted to a modified ACR remission, named NEO-RACo remission, and defined as no swollen (66 joint count) or tender joints (68 joint count) and presence of 5 out of the 6 following criteria: 1) morning stiffness < 15 minutes, 2) no fatigue, 3) no joint pain, 4) no tender joints, 5) no swelling in joints or tendons, and 6) erythrocyte sedimentation rate < 30 mm/h in women and < 20 mm/h in men.

Further, if remission was not achieved after using the maximum tolerated doses of study medication for 3 months, the csDMARDs were changed aiming towards a better response as follows: MTX was substituted with azathioprine (50 mg/day, max. 2,5 mg/kg/day), sulfasalazine with cyclosporine (2,5 mg/kg/day, max. 4 mg/kg/day), and HCQ with auranofin (6mg/day, max. 9 mg/day). The combinations had to include at least one of the following: MTX, leflunomide, azathioprine, and cyclosporine at all times. However, if remission or at least ACR50 improvement was not achieved after week 26 at two consecutive visits, this was regarded as a treatment failure (127). Thereafter treatment was at physician's discretion including the possibility to use TNF-blockers. However, the patient continued in the study until the 5-year visit, and the randomization code was not opened.

If remission was reached, the study medication was continued until the 2-year visit. Thereafter, in sustained remission, defined as continuous remission after the 24-month visit, medication could be tapered in the following order: First, prednisolone dosage was decreased 2,5 mg every 3 months. If prednisolone was tapered and the patient was still in remission, sulfasalazine was reduced by 500 mg every 3 months, and thereafter MTX by 2,5 mg/week every 3 months. If remission was lost, the previous drug was added back to the regimen.

4.3 Assessments and follow-up

The patients were assessed clinically at weeks 0, 4, 6, 10, 14, 18, 22 and 26, at months 8, 10, 12. Thereafter assessments were 3-monthly until the 5-year visit. The evaluation consisted of the number of swollen (66) and tender (68) joints, patient's assessment of pain (100 mm VAS), patient's and physician's global assessment of disease activity (100 mm VAS), assessment of physical function (HAQ), and acute phase reactants (C-reactive protein and ESR). Radiographs of the hands and feet were taken at baseline, and at 2 and 5 years. Quality of life was assessed with the Short Form 36 (SF-36) questionnaire at baseline, and at 8, 12, and 24 months, and yearly thereafter (160). The SF-36 scores were converted into Short-Form Six-Dimension scores for calculating quality-adjusted life years (QALYs). The medications used, iaGCs given, and adverse events experienced were carefully elucidated at each visit.

4.3.1 Assessment of physicians' adherence (I)

We formulated a score to study the physicians' (n=30) adherence to the treatment protocol on all 15 study visits during the first two years of the study. Two reviewers gathered the data from the case report forms. Points for nonadherence were scored as follows: 0.2–0.4 points, if the patient had inflamed joints which were not treated with iaGCs (depending of the number of non-injected joints); 0.4 points if remission had not been achieved but the DMARD treatment was not modified; 0.2 points if the study forms were inadequately filled in; 0.5 points if a study visit was replaced by a phone call; and 1.0 points if a study visit was cancelled. The cumulative inactivity score (CIS) was the sum of points for non-adherence. The maximum score was 1 point/visit, and 15 points for the 2-year follow-up. Of note, DMARD modifications were not considered necessary if adverse events prevented the adjustment of medication, or non-remission was due to subjective symptoms (i.e. high patient global or tender joints without objective signs of inflammatory activity), or if the medication had been modified within 2 weeks. Possible disagreement between reviewers was discussed and resolved by consensus.

4.3.2 Assessment of neglected intra-articular GC injections (II)

We quantified the impact of the missed iaGCs. All given injections on each of the study visits during the first 2 years were carefully elucidated and scored by 2 reviewers. If injections were neglected, points were scored irrespective of the reason (i.e. patient refusal/physician's decision) as follows: Not injecting swollen large joint(s) or not injecting more than 2 small swollen joints was considered a gross negligence (0.4 points). Not injecting 1-2 small joints was considered a minor negligence (0.2 points). Points for negligence were not given if ≥ 2 ml of glucocorticoids were injected, because in Finland it has been recommended to avoid injecting larger amounts in order to avoid systemic adverse effects. Further, points were not given if joints seldom affected by RA (like distal interphalangeal joints of hands) were not injected, injections were repeated three or more times without improvement, and if the treating physician reported that the joint effusion was caused by osteoarthritis (OA). The maximum score for the neglected injections was 0.4 points/visit, and 6 points for the 2-year follow-up.

4.3.3 Assessment of the burden of adverse events (III)

We analyzed all adverse events during the first year of the study. The treating physicians scored the events from one to four based on their severity: 1) mild; hardly notable/requires no measures, 2) moderate; possibly causes dose changes in study medication, 3) severe; may cause temporary or permanent discontinuation of study medication, and 4) serious; any event leading to hospitalization, death, or causing permanent or significant damage. We changed the scoring of the adverse events only if the forms clearly stated that the patient had been hospitalized but the event in question had not been scored as a serious one. We defined the burden of adverse events per patient as the sum of scores (from 1 to 4) of all individual events. The highest classification was used in case the same adverse event was reported on multiple visits.

4.3.4 Assessment of patient-reported outcomes as predictors of remission (IV)

We used the baseline measurements of the eight dimensions of the SF-36 (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health), and the three ACR core data set PROs [patient's global assessment (PGA) on VAS of 10 cm, patient's assessment of pain on VAS of 10 cm, and patient's assessment of physical function with HAQ] (115,160). For the PGA, following wording was used: "How would you estimate your rheumatoid arthritis disease activity today?".

4.4 Outcomes

4.4.1 Physicians' adherence to a treat-to-target strategy (I)

As outcomes we assessed the impact of physicians' adherence on NEO-RACo and DAS28 remission rates, disease activity, radiological changes, cumulative days off work, and the use of anti-rheumatic medication during follow-up of 2 to 5 years (126).

4.4.2 *Neglecting intra-articular GCs (II)*

Disease activity (DAS28) over time, NEO-RACo remissions, health-related quality of life (SF-36), and radiological progression (modified SvH score) at 24 months were used as outcome measures (147).

4.4.3 *Burden of adverse events (III)*

We used the 28-joint disease activity score (DAS28) remission rates and disease activity at 12 and 24 months as outcomes.

4.4.4 *Patient-reported outcomes as predictors of remission (IV)*

We aimed to identify baseline PROs associated with increased odds of the NEORACo trial's primary outcome, NEO-RACo remission, at 2 years.

4.5 Ethical considerations

The study protocol was approved by and was in accordance with the ethical standards of the ethics committee of the Hospital District of Helsinki and Uusimaa. The protocol was also approved by the ethics committees of the participating hospitals. The study was conducted according to the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all patients. The study has been registered at <http://www.ClinicalTrials.gov> (NCT00908089).

4.6 Statistical methods

The results are presented as means with standard deviations (SD), as counts with percentages, or as medians with interquartile range (IQR). The 95 % confidence intervals (CI) are given when appropriate. In three out of four original publications (I, III, III), we divided the patients into tertiles for analysis. The normality of the variables was evaluated with either the Shapiro-Wilk test (I, II, IV) or the Shapiro-Francia test (III). Due to the unknown theoretical or skewed distribution (i.e. non-normality) of the test statistic, and the small sample size, bias-corrected bootstrapping was used for obtaining 95% CIs (I, II, III, IV) when appropriate.

We made statistical comparisons using the chi-square test (I, II, IV) Cochran-Armitage trend test (III), the Fisher-Freeman-Halton test (I), the Kruskal-Wallis test (II), the Mann-Whitney U test (IV), the student's t-test (IV), and analysis of variance (ANOVA) (I, II, III). We analyzed repeated measures for continuous and binary variables with logistic regression models (I), generalized estimating equations models (III), and generalized linear models with appropriate distribution and link function (II), when appropriate. The selection of determinants for multivariable analysis was based on statistical significance, clinical relevance and knowledge of common confounding factors.

When studying physicians' adherence (I), we estimated the internal consistency of the scoring system by calculating Cronbach's alpha with 95% CIs. When we examined the burden of adverse events (III), we handled missing data by carrying the last observation forward. For analyzing PROs as predictors of remission (IV), due to the high multicollinearity, we used generalized maximum entropy estimation methodology for discrete choice models for estimating odds ratios for remission. In addition to working well with a limited sample size, this novel method avoids strong parametric assumptions, and performs well even when covariates are highly correlated. STATA 13.1, StataCorp LP (College Station, TX, USA) statistical package was used for the analyses.

5 RESULTS

The NEO-RACo trial yielded excellent results. As previously reported, 66% and 53% of the patients randomized to either infliximab or placebo treatment in addition to a combination of 3 csDMARDs, oral low-dose prednisolone, and intra-articular GCs were in NEO-RACo remission at 2 years. DAS28 remission rates were 82% in both groups. (11) Furthermore, NEO-RACo remission rates at 5 years were 60% and 61% for the infliximab and placebo groups, and the respective DAS28 remission rates were 84% and 89% (61). At 2 years, the patients in the infliximab group had slightly less radiological progression in the small joints of the hands and the feet compared to the placebo group, but at 5 years no significant differences were detected between the randomisation groups (11,61).

5.1 Physicians' adherence

At 3 and 24 months approximately 50% and 70% of the points for physicians' nonadherence [the cumulative inactivity score (CIS)] were given for a lack of intra-articular glucocorticoid injections in both treatment arms (Figure 2). The internal consistency value for all 4 components of the scoring system was 0.58 (95% CI 0.40–0.76). CIS ranged from 0 to 11.8 (Figure 3). The mean CIS started to differ between the treatment arms at 3 months (Figure 3). At 24 months, the mean±SD CIS was 2.1±1.7 in the FIN-RACo+INFL group and 2.7±2.3 in the FIN-RACo+PLA group ($p=0.032$ for between-group difference, adjusted for age, sex and baseline disease activity).

We had 5-year follow-up data available for 93 patients (92%). We divided the patients from both treatment arms into tertiles by physicians' adherence as follows: good adherence ($n=31$, CIS 0–1.5), intermediate adherence ($n=32$, CIS 1.6–2.6) and low adherence ($n=30$, CIS ≥ 2.7). The baseline characteristics of the patients by tertiles are presented in Table 5.

At 3 months, the mean±SD CIS was 0.8±0.6 for the patients in strict NEO-RACo remission, and 1.5±0.7 for patients not in remission ($p<0.001$, adjusted for age, sex, baseline disease activity, and the original treatment arm). The respective scores at 24 months were 1.8±1.3 and 3.3±2.6 ($p=0.003$). During the first three months of the study, 12% of the patients received intra-articular GCs into all of their swollen joints. Of these patients, 73% achieved NEO-RACo remission at 3 months. However, only 28% of the patients who had non-injected swollen joints reached remission at this time point ($p=0.014$, adjusted for age, sex and

Table 5. Baseline characteristics of the patients by tertiles of physicians' adherence (I).

Characteristic	Physicians' adherence			P
	Good (n=31)	Intermediate (n=32)	Low (n=30)	
Demographic data at baseline				
Female, n (%)	23 (74)	22 (69)	18 (60)	0.49
Age (years), mean±SD	43±11	50±7	46±12	0.017
BMI, mean±SD	25.7±4.3	25.9±4.0	26.2±4.6	0.92
Rheumatoid factor present, n (%)	25 (81)	22 (69)	22 (73)	0.55
Symptom duration (mo.), median (IQR)	4 (2, 6)	3 (2, 4)	4 (2, 6)	0.86
Measures of disease activity at baseline				
Number of swollen joints, mean±SD	15±7	16±5	16±7	0.86
Number of tender joints, mean±SD	17±11	20±9	24±12	0.086
C reactive protein (mg/L), mean±SD	41±48	23±28	27±33	0.15
ESR (mm/h), mean±SD	36±25	32±19	31±21	0.60
PGA (VAS, mm), mean±SD	46±27	48±26	53±24	0.52
Pain (VAS, mm), mean±SD	51±26	53±30	58±23	0.49
PhGA (VAS, mm), mean±SD	47±24	53±17	55±18	0.27
Physical function (HAQ), mean±SD	0.8±0.6	1.0±0.6	1.1±0.7	0.20
DAS28, mean±SD	5.4±1.6	5.6±0.9	5.7±1.0	0.55
Radiography at baseline (SvH score)				
Total score, mean±SD	2.1±4.1	2.7±9.1	1.5±3.5	0.72
Erosion score, mean±SD	1.8±3.5	2.5±7.9	1.2±3.0	
Narrowing score, mean±SD	0.5±1.4	0.2±1.2	0.3±0.8	
The initial randomization group				
FIN-RACo+Placebo, n (%)	15 (48)	13 (41)	18 (60)	0.31
FIN-RACo+Infliximab, n (%)	16 (52)	19 (59)	12 (40)	

BMI, body mass index; ESR, erythrocyte sedimentation rate; PGA, patient global assessment; VAS, visual analogue scale; PhGA, physician global assessment; HAQ, health assessment questionnaire; DAS28, 28-joint disease activity score; SvH score, modified Sharp van der Heijde – score; FIN-RACo, combination of methotrexate, sulfasalazine, hydroxychloroquine and low-dose prednisolone.

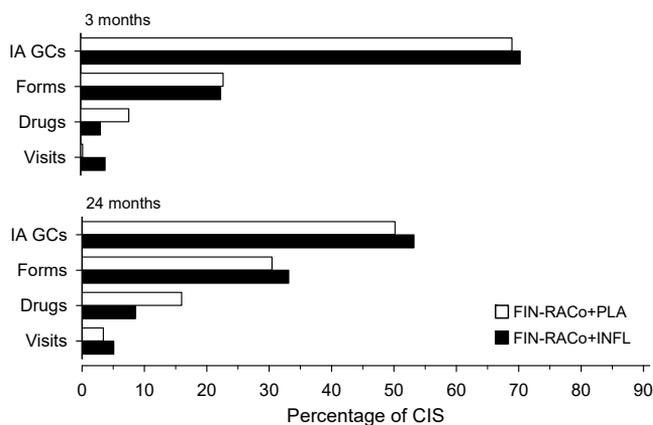


Figure 2. Cumulative inactivity score (CIS) at 3 and 24 months (I).

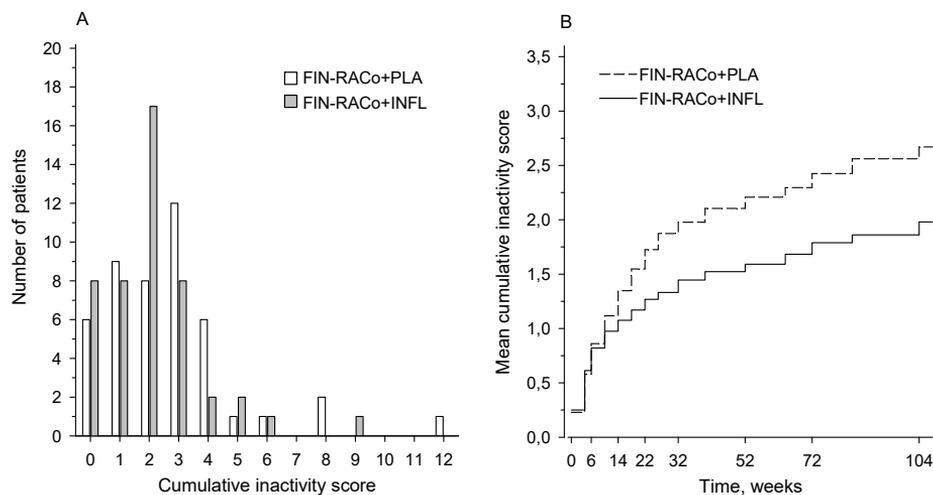


Figure 3. The distribution of the CIS (A) and the mean CIS (B) during the first 2 years of follow-up (I).

baseline disease activity, and the original treatment arm). In a multivariable logistic regression analysis physicians' adherence ($p < 0.01$), the use of infliximab ($p = 0.016$), and duration of symptoms ($p = 0.037$) before the initiation of treatment were all associated with achievement of remission at 3 months (Figure 4). However, at 24 months only physicians' adherence ($p < 0.001$) predicted reaching remission (Figure 5).

NEO-RACo remission rates of the three CIS-groups differed at 2, 3, and 4 years, but not at 5 years (Figure 6). We also found a trend favoring active treatment demonstrated by lower mean DAS28 levels in the actively treated throughout the

study (Figure 6). What is more, the mean DAS28 and its upper 95% CIs were below the DAS28

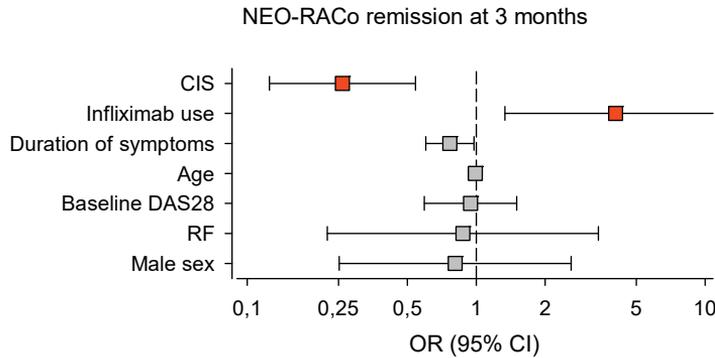


Figure 4. Multivariable analysis for the odds of being in strict NEO-RACo remission at 3 months.

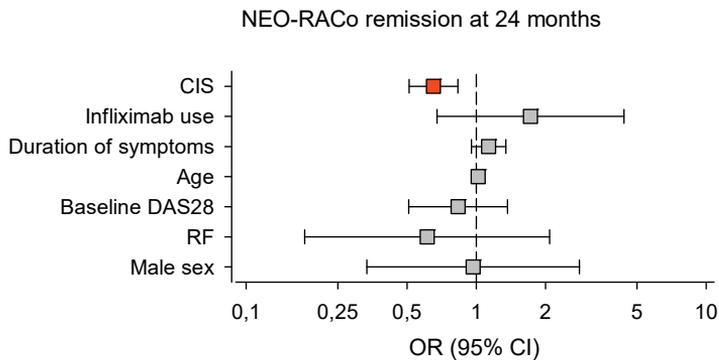


Figure 5. Multivariable analysis for the odds of being in strict NEO-RACo remission at 24 months.

remission limit (< 2.6) in all patient groups at all time points, except for the low adherence group at 5 years (Figure 6).

Radiological progression during the follow-up was marginal in most patients. We detected no differences across tertiles in radiological progression (data not shown). On average, the good, the intermediate and the low adherence groups had 17, 33, and 37 cumulative days off work per patient-year ($p=0.48$, adjusted for age and sex). Respectively, 1, 2, and 4 patients became permanently work disabled in the good, in the intermediate, and in the low adherence groups.

The number of used DMARDs between 2 and 5 years, reflecting changes in medication due to non-remission or adverse events, was lower in the good adherence group compared with the low adherence group. The mean number of

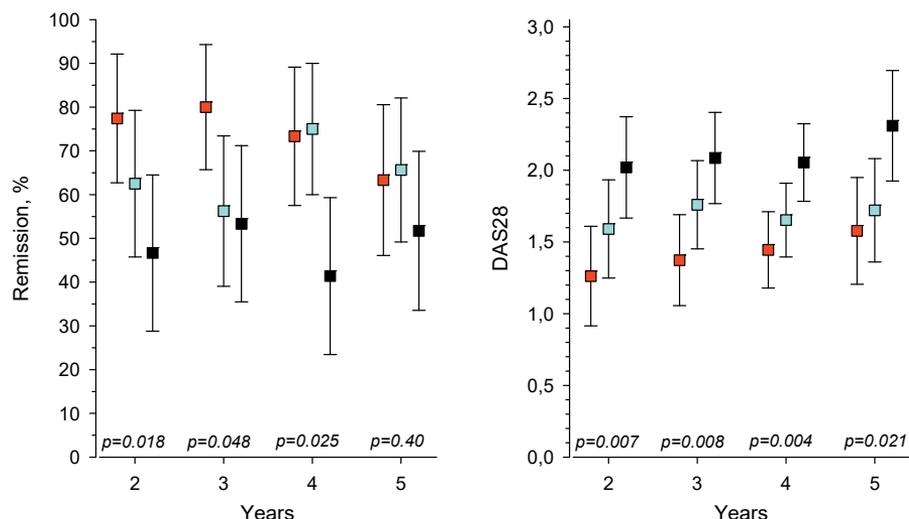


Figure 6. NEO-RACo and DAS28 remission rates of the three CIS-groups at 2, 3, 4, and 5 years. Red, blue, and black squares represent tertiles of good, intermediate, and low adherence, respectively. P values are for linearity. Adjusted for age, sex, rheumatoid factor status, baseline disease activity, duration of symptoms, and original treatment arm.

DMARDs was 3.4 ± 0.9 in the good adherence group, 3.5 ± 0.9 in the intermediate adherence group and 4.1 ± 1.3 in the low adherence group ($p=0.023$). During the follow-up from 2 to 5 years, 10 patients (11%) received biological DMARDs. 7 of these treatments (23% of 30 the patients) were initiated in the low adherence group, 1 in the intermediate adherence group (3% of the 32 patients), and 2 in the good adherence group (6% of the 31 patients, $p=0.024$).

5.2 Neglecting intra-articular GC injections

We had 24-month follow-up data for 93 of the 99 patients randomized to the study (92%). The range of points from the neglected iaGC injections per patient was from 0 to 5.2. This is shown as percentages of patients in Figure 7. We divided the patients into tertiles by the score for the neglected intra-articular GC injections. The clinical and demographic baseline characteristics of the patients by tertiles are shown in Table 6. The median number of iaGCs injections in the first, in the second, and in the third tertile was 5.5, 1.5, and 2.0 ($p=0.007$).

We found a statistically significant linear relationship across the tertiles of neglected injections and NEO-RACo remission rates, and DAS28 remission rates at 24 months (Figure 8). DAS28 at 24 months by tertiles of neglected injections behaved respectively (Figure 8). The correlation coefficient between DAS28

AUC₀₋₂₄ (area under the curve from 0 to 24 months) and neglected iaGCs was 0.51 (95% CI 0.34–0.64). DAS28 remission rates at 24 months were 90% in the first, 93% in the second, and 76% in the third tertile, and respective NEO-RACo remission rates were 74%, 77% and 39% (Figure 8).

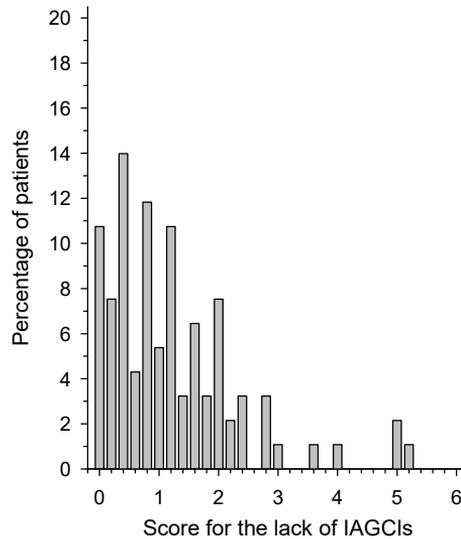


Figure 7. Range of points from the neglected iaGCs (II).

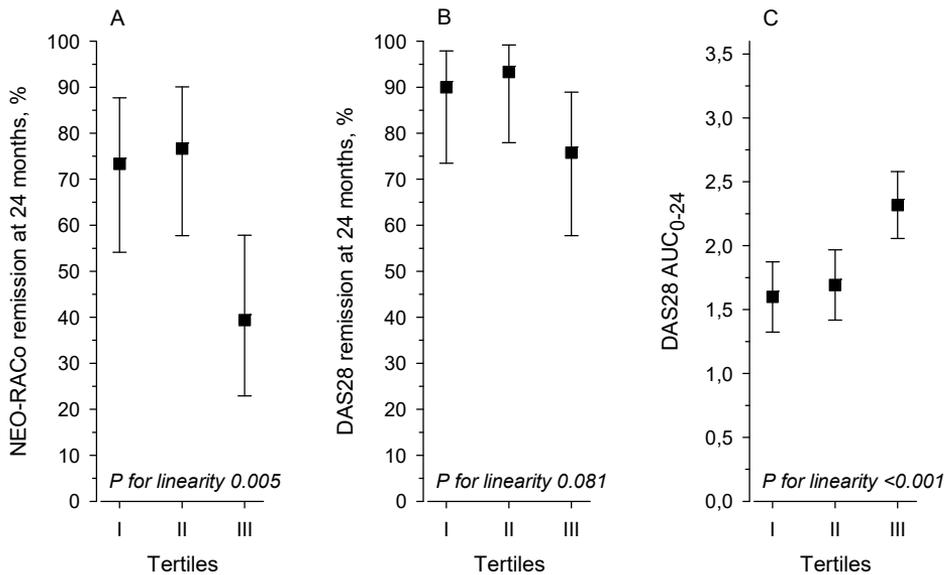


Figure 8. NEO-RACo and DAS28 remission rates at 24 months, and DAS28 AUC₀₋₂₄ by tertiles of neglected injections. Adjusted for age, sex, rheumatoid factor status, baseline disease activity, and the original treatment arm (II).

Table 6. Baseline characteristics of the patients categorised into tertiles by neglected iaGCs (II).

Characteristic	Tertiles by neglected iaGCs			P
	I (n=30) Score 0–0.4	II (n=30) Score 0.6–1.2	III (n=33) Score ≥1.4	
Demographic data at baseline				
Female, n (%)	22 (73)	23 (77)	18 (56)	0.11
Age (years), mean±SD	43±10	47±11	48±10	0.12
BMI, mean±SD	26.1±4.2	25.9±4.0	26.0±4.5	0.93
Symptom duration (mo.), median (IQR)	4 (2 , 6)	3 (2 , 5)	4 (3 , 6)	0.99
Rheumatoid factor present, n (%)	21 (70)	25 (85)	23 (70)	0.95
Measures of disease activity at baseline				
Number of swollen joints, mean±SD	14.9±7.1	14.9±5.2	16.0±7.0	0.53
Number of tender joints, mean±SD	18.3±10.6	19.0±9.4	22.5±11.2	0.12
ESR (mm/h), mean±SD	35.2±24.6	34.3±21.2	29.5±20.0	0.29
PGA (VAS, mm), mean±SD	51±27	42±22	53±25	0.77
Pain (VAS, mm), mean±SD	57±26	47±25	56±28	0.90
PhGA (VAS, mm), mean±SD	48±23	49±17	56±19	0.09
Physical function (HAQ), mean±SD	0.9±0.7	0.8±0.7	1.2±0.6	0.16
DAS28, mean±SD	5.5±1.6	5.5±0.9	5.6±1.0	0.66
Radiography at baseline (SvH score)				
Total score, mean±SD	1.1±2.0	2.4±5.0	2.7±8.9	0.32
Erosion score, mean±SD	1.0±1.9	2.2±4.4	2.3±7.7	0.35
Narrowing score, mean±SD	0.3±1.3	0.2±0.7	0.4±1.3	0.78
The initial randomization group				
FIN-RACo+Placebo, n (%)	16 (53)	9 (30)	21 (64)	0.38
FIN-RACo+Infliximab, n (%)	14 (47)	21 (70)	12 (36)	

iaGCs, intra-articular glucocorticoid-injections; BMI, body mass index; ESR, erythrocyte sedimentation rate; PGA, patient global assessment; VAS, visual analogue scale; PhGA, physician global assessment; HAQ, health assessment questionnaire; DAS28, 28-joint disease activity score; SvH score, modified Sharp van der Heijde score; FIN-RACo, combination of methotrexate, sulfasalazine, hydroxychloroquine and low-dose prednisolone.

Differences in the gain of quality adjusted life years across tertiles at 24 months are shown in Figure 9. Further, the change in the quality of life was associated with DAS28 AUC_{0–24} by tertiles of neglected intra-articular GC injections (Figure 9). P-values for the difference between the first and the second tertiles in quality of life were nonsignificant, however, the differences between the first and the third, and the second and the third tertiles were significant ($p < 0.001$, and $p = 0.020$; Figure 9).

Radiological changes during the follow-up were on average marginal. We found no statistically significant linear relationship across the tertiles in radiological progression ($p=0.089$; Figure 10). Only one adverse event due to iaGCs was reported. This was a suspected septic arthritis after a carpometacarpal joint injection at 8 months.

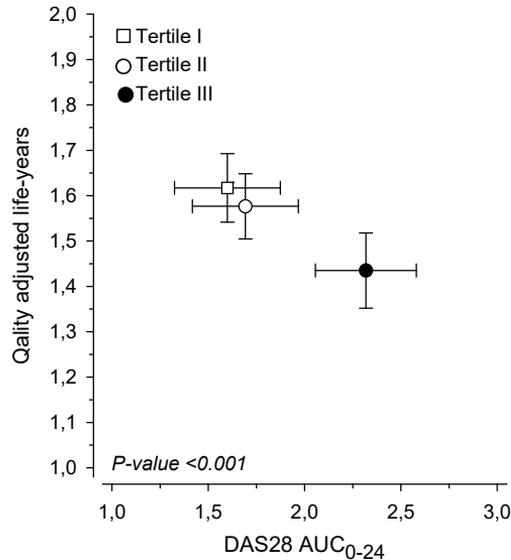


Figure 9. Gain in quality adjusted life-years and DAS28 AUC₀₋₂₄ by tertiles of neglected iaGCs. Adjusted for age, sex, rheumatoid factors status, baseline disease activity, and the original treatment arm.

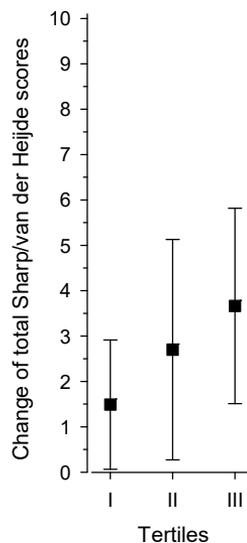


Figure 10. Change in modified Sharp van der Heijde (SvH) score by tertiles of neglected iaGCs. P for linearity 0.089. Adjusted for baseline SvH score, sum of injections and the original treatment arm (II).

5.3 Burden of adverse events

Ninety-nine patients were included in the study. During the first 12 months, 331 adverse events were reported. Of these, 11 (3%) were categorized as severe, 16 (5%) as serious, 141 (43%) as moderate, and 163 (49%) as mild. Of the adverse events experienced, 7% were classified by the attending physician as definitely connected, 27% as probably connected, and 30% as possibly connected to the medication under study. Further, 26% of the adverse events were classified as unlikely to be associated with the study medication, 9% unrelated, and data were lacking for 2%.

The mean burden of adverse events was 5.4 ± 4.3 (range 0–18). After dividing the patients into tertiles according to the burden of the adverse events, range of burden of adverse events in the first, second, and third tertiles was 0–2, 3–6, and 7–18, respectively. Of the patients, thirteen reported no adverse events. The baseline clinical and demographic characteristics of the patients are shown in Table 7. The erythrocyte sedimentation rate ($p=0.03$) and tender joint count ($p=0.001$) differed across the three tertiles.

Of the 331 adverse events, 79 (24%) led to csDMARD discontinuation. Discontinuations were either temporary 52 (66%) or permanent 27 (34%). Discontinuations were most prevalent in the third tertile (Table 7). MTX was discontinued permanently in four, sulfasalazine in ten, and HCQ in thirteen patients. An adverse event led to discontinuation of infliximab or placebo in three patients.

At 12 months, the DAS28 remission rates decreased across the tertiles, being 94%, 94%, and 76% in the first, second, and third tertiles respectively (p for linearity 0.029; Figure 11). At 24 months, the remission rates were 90%, 86% and 70% in the first, second, and third tertiles, respectively (p for linearity 0.021; Figure 11). Mean DAS28 scores at 12 months were 1.7 ± 1.0 for all, 1.5 ± 1.0 in the first tertile, 1.7 ± 0.9 in the second tertile, and 1.9 ± 1.2 in the third tertile (p for linearity 0.021). Respective mean DAS28 scores at 24 months were 1.7 ± 1.0 for all, and 1.4 ± 0.8 , 1.6 ± 1.1 , and 1.9 ± 1.1 by tertiles (p for linearity 0.007; Figure 11).

Table 7. Baseline characteristics of the patients by the burden of adverse events.

Characteristic	Tertile of Adverse Event Burden			P
	I (n=31)	II (n=35)	III (n=33)	
Demographics				
Female, n (%)	20 (65)	22 (63)	24 (73)	0.48
Age years, mean (SD)	48 (9)	47 (10)	44 (12)	0.15
Duration of symptoms (mo.), mean (SD)	4 (3)	4 (2)	4 (2)	0.99
Rheumatoid factor present, n (%)	25 (81)	27 (77)	23 (70)	0.31
Measures of disease activity				
DAS28, mean (SD)	5.7 (1.1)	5.2 (1.2)	5.7 (1.2)	0.99
ESR, (mm/h), mean (SD)	41 (22)	30 (22)	29 (20)	0.03
No. of swollen joints, mean (SD)	16.5 (5.6)	13.3 (5.7)	16.0 (7.7)	0.81
No. of tender joints, mean (SD)	17.6 (7.7)	17.2 (8.3)	24.8 (12.9)	0.005
PGA (VAS), mean (SD)	46 (24)	49 (29)	52 (24)	0.26
Pain assessment (VAS), mean (SD)	48 (29)	57 (30)	55 (21)	0.29
PhGA (VAS), mean (SD)	52 (20)	47 (21)	55 (21)	0.60
Physical function (HAQ), mean (SD)	0.9 (0.6)	1.0 (0.7)	1.1 (0.7)	0.23
Infliximab treatment, n (%)	19 (61)	15 (43)	16 (48)	0.32
Adverse events				
Number, n (% ^a)	21 (6)	111 (34)	199 (60)	
csDMARD switch, n (% ^a)	0 (0)	5 (2)	22 (7)	
Temporary csDMARD pause, n (% ^a)	1 (0)	16 (5)	35 (11)	
The initial randomization group				
FIN-RACo+Placebo, n (%)	16 (53)	9 (30)	21 (64)	0.38
FIN-RACo+Infliximab, n (%)	14 (47)	21 (70)	12 (36)	

P values are for linearity. The range of the burden of adverse events by tertiles I, II, and III was 0–2, 3–6, and 7–18. ^aPercentage of all adverse events (n=331). DAS28, 28-joint disease activity score; ESR, erythrocyte sedimentation rate; CRP, PGA, patient global assessment; VAS, visual analogue scale; PhGA, physician global assessment. HAQ, health assessment questionnaire; csDMARD, conventional synthetic disease modifying antirheumatic drug; FIN-RACo, combination of methotrexate, sulfasalazine, hydroxychloroquine and low-dose prednisolone.

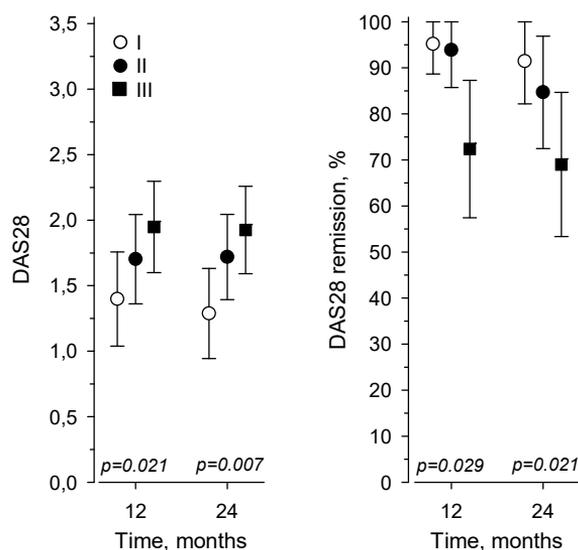


Figure 10. DAS28 levels and remission rates at 12 and 24 months by tertiles of the burden of adverse events.

5.4 Patient-reported outcomes as predictors of remission

At 24 months, we had follow-up data for 93 of the 99 patients included in the study (92%). Fifty-eight patients (62%) reached NEO-RACo remission at 24 months. The baseline characteristics of the patients by remission status at 24 months are shown in Table 8. At baseline, patients who achieved remission had lower tender joint count ($p=0.001$), lower patient's ($p=0.005$) and physician's global assessment ($p=0.019$), lower HAQ ($p=0.016$), less early morning stiffness ($p=0.009$), and higher Sharp-van der Heijde score ($p=0.04$) compared with the patients who did not reach remission. All SF-36 dimensions except mental health ($p=0.12$) were associated with remission at 24 months when this association was analyzed separately for each dimension (Table 9).

Odds ratios (OR) and 95% CIs for remission at 24 months for 1-SD increase in the eleven analyzed PROs are adjusted for age, sex, rheumatoid factor status, original treatment arm, baseline modified SvH score, baseline swollen and tender joint counts, and baseline ESR and shown in Figure 11. When ACR core dataset PROs and SF-36 dimensions were simultaneously included in the multivariate logistic model, only two SF-36 dimensions, vitality (OR 2.01; 95% CI 1.19–3.39) and emotional role functioning (OR 1.64; 95% CI 1.01–2.68) were associated with increased odds of remission.

Table 8. Baseline characteristics of the patients according to their remission status at 24 months (IV).

Patient characteristics	Remission at 24 months		P
	No (n=35)	Yes (n=58)	
Clinical and demographic characteristics			
Female, n (%)	24 (69)	39 (67)	0.89
Age (years), mean (SD)	45 (10)	47 (11)	0.61
BMI (kg/m ²), mean (SD)	26.3 (5.0)	25.8 (3.7)	0.59
Rheumatoid factor present, n (%)	26 (74)	43 (74)	0.99
Symptom duration (mo.), median (IQR)	4 (2, 4)	4 (2, 7)	0.35
Randomized to infliximab, n (%)	14 (40)	33 (57)	0.11
Measures of disease activity			
DAS28, mean (SD)	5.7 (1.3)	5.5 (1.1)	0.31
ESR (mm/h), mean (SD)	33 (24)	33 (21)	0.92
CRP (mg/l), mean (SD)	33 (45)	29 (33)	0.56
Swollen joints (66 joints), mean (SD)	16 (7)	15 (6)	0.41
Tender joints (68 joints), mean (SD)	25 (12)	17 (9)	0.001
PGA VAS (mm), mean (SD)	58 (27)	44 (23)	0.005
Pain VAS (mm), mean (SD)	59 (28)	50 (25)	0.13
HAQ, mean (SD)	1.2 (0.6)	0.8 (0.6)	0.02
PhGA VAS (mm), mean (SD)	58 (20)	48 (19)	0.02
Morning stiffness (min), median (IQR)	120 (100, 240)	90 (60,180)	0.009
Radiography (SvH score)			
Erosion score, mean (SD)	0.6 (1.2)	2.6 (6.5)	0.02
Narrowing score, mean (SD)	0.2 (0.6)	0.4 (1.4)	0.51
Total score, mean (SD)	0.8 (1.6)	2.9 (7.6)	0.04

BMI, body mass index; DAS28, 28-joint disease activity score; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; PGA, patient global assessment; VAS, visual analogue scale; HAQ, health assessment questionnaire; PhGA, physician global assessment; SvH, modified Sharp van der Heijde score.

Table 9. Baseline Short Form 36 (SF-36) dimensions by remission status at 24 months (IV).

SF-36 dimension	Remission at 24 months		P
	No (n=35)	Yes (n=58)	
Physical functioning	40 (21)	56 (27)	0.005
Role-physical	9 (20)	27 (38)	0.01
Bodily pain	28 (17)	39 (18)	0.003
General health	46 (17)	57 (17)	0.003
Vitality	36 (22)	52 (23)	0.002
Social Functioning	59 (28)	75 (24)	0.004
Role-emotional	38 (45)	63 (44)	0.01
Mental Health	68 (18)	74 (17)	0.12
Summary components			
Physical component	28 (7)	34 (10)	0.003
Mental component	46 (11)	51 (12)	0.02

Numbers are reported as mean (SD). P values are unadjusted.

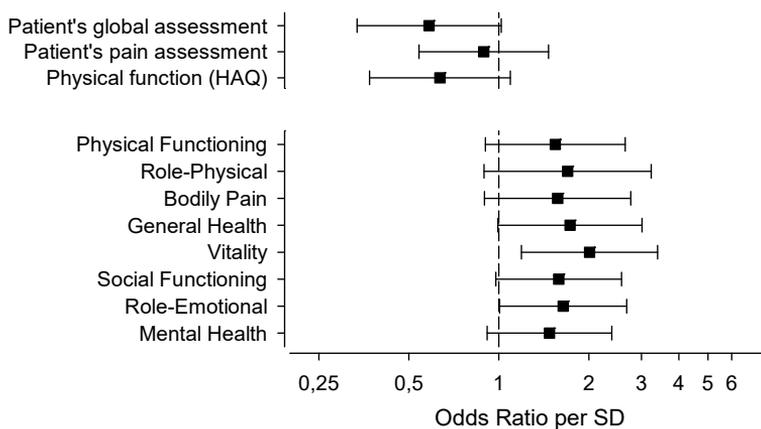


Figure 11. Odds ratios (OR) and 95% confidence intervals for remission at 24 months for 1 standard deviation (SD) change in baseline ACRC core data set PROs and SF-36 dimensions (IV).

6 DISCUSSION

The results of our study show that, in addition to patient-related factors, physicians' actions also significantly influence the outcomes of early RA during intensive, targeted treatment. We demonstrated that physicians' adherence can vary significantly even in a clinical trial with a strict, predefined treatment protocol and showed that good adherence positively influenced disease activity and remission rates. Physicians' good adherence was also associated with fewer DMARD switches during the follow-up from two to five years. Furthermore, failure, for any reason, to treat all swollen joints with iaGCs was also associated with lower remission rates, higher disease activity, and a lower quality of life at 2 years. These analyses emphasize the importance of an active role by physicians treating early RA.

In the NEO-RACo trial, nine out of ten adverse events reported during the first year were mild or moderate, and one in four led to temporary or permanent csDMARD discontinuation. Despite the low number of severe and serious adverse events, a high burden of adverse events was associated with lower likelihood of reaching DAS28 remission at one and two years. We also searched for novel predictors of remission, which would be feasible for use in everyday clinical practice. Of the eleven baseline PROs measured in the study, only two SF-36 dimensions, vitality and role-emotional functioning, but not traditional PROs like HAQ, were associated with increased odds of reaching NEO-RACo remission at two years.

To our knowledge, the intensive combination treatment used in the trial, which was targeted to a strict remission allowing no swollen or tender joints, led to the highest strict and DAS28 remission rates ever reported from an early RA trial (11,61). We found the aforementioned associations despite the stringent protocol and the excellent overall results of the study. From this we conclude that physicians' nonadherence, neglected iaGCs, and the burden of adverse events may have an even larger impact on outcomes in observational studies and in daily clinical practice.

6.1 Physicians' adherence

In this analysis, we demonstrated that physicians' adherence varies greatly, even within a clinical trial. We were able to show that differences in adherence during the first two years were associated with differences in multiple outcomes; good adherence was associated with improved remission rates, lower disease activity,

fewer csDMARD replacements, and less use of bDMARDs during the follow-up from two to five years. Physicians' adherence was also, in addition to infliximab treatment and disease duration, the most important predictor of early remission at three months, and the only independent predictor of remission at two years.

Remission rates remained high in all tertiles throughout the follow-up. As demonstrated in Figure 6, even mean DAS28 and its upper 95% CIs are below the DAS28 remission limit of 2.6 at all time points, except for the low adherence group at 5 years. Despite these high remission rates, we found a significant correlation between physicians' good adherence to protocol and higher strict remission rates at 2, 3, and 4 years and lower disease activity at all time points. This demonstrates that even the most intensively treated early RA patients clearly benefit from their physicians' active stance.

Due to the aggressive treatment strategy of our trial only few patients had inflamed joints after the first 6 months, limiting the opportunity for protocol deviations thereafter. However, minor nonadherence was very common and only four patients were treated exactly according to the protocol for two years. Approximately 50% of the points for nonadherence resulted from non-injected swollen joints. Furthermore, early remission at three months was significantly more frequent in the patients, whose all swollen joints were treated with iaGCs compared to the patients having non-injected swollen joints. Early treatment and early remissions are associated with improved long-term outcomes in RA (253,291-293). Our results emphasize the importance of strict control over treatment, particularly the physicians' adherence to protocol from the very beginning.

We were able to show that the nonadherently treated patients required more changes in their DMARD regimen between 2 and 5 years, most likely because of ongoing disease activity. During the follow-up bDMARDs were also used in this group more frequently, suggesting that it was necessary to compensate for the physicians' low adherence with an expensive bDMARD in order to achieve remission.

The intensive treatment led to minimal radiological progression in most patients, and also the number of WD days and pensions remained at a low level. Hence, we were not able to detect significant differences between the groups in these outcomes. However, the absolute number of WD days and pensions was highest in the low adherence group.

In the current analysis, outcomes were assessed at the patient level instead of at the physician level. Of the 30 physicians, each treated only one to five patients. With minor exceptions, the same physician treated the patient throughout the follow-up, and likely continued treating the patients in the same adherent or non-

adherent way after the initial two years. Our aim was not to find and name the nonadherent physicians, which could have been done using a different method of analysis. Instead, we chose to demonstrate how their adherence influenced the treatment results. In addition, our analysis can be justified based on the fact that it is very difficult, or impossible, to separate patients' and physicians' adherence from each other. Therefore, our results also stress the importance of good patient-physician relationship, or working alliance. Previous studies have shown that a good working alliance may lead to improved patient adherence and outcomes, and that efficient patient-physician communication is of key importance in creating this alliance (270,294).

Only two other studies have assessed physicians' adherence to targeted treatment in rheumatoid arthritis in relation to outcomes. Rantalaiho et al. demonstrated in a subanalysis of the FIN-RACo trial that patients treated according to the protocol had higher modified ACR remission rates at 2 years, and a lower number of cumulative WD days during the five-year follow-up period, in comparison with the nonadherently treated patients (289). In their analysis, only csDMARD combination therapy and physicians' adherence predicted remission at 2 years in multivariable models, which is in concordance with our results. The association between physicians' good adherence and higher remission rates was apparent also in the NEO-RACo trial, but differences in cumulative WD remained nonsignificant. Low prevalence of WD due to more intensive treatment in the NEO-RACo trial likely explains this; in the analysis of Rantalaiho et al. the cumulative WD days per patient-year ranged from 44 to 130 depending on the treatment group, whereas the respective range in our study was from 17 to 37.

Wabe et al. were the first to assess the association of treat-to-target adherence and outcomes in an observational cohort study (295). They showed that physicians' adherence to targeted treatment protocol was associated with higher remission rates and improved functional ability at three years, but not at one year. In their study, adherence was present on approximately 75% of the visits, and DAS28 remission was reached by 46% of the patients at three years. Compared to the NEO-RACo trial their patients were treated less intensively; the use of oral GCs was discouraged, and parenteral GCs were recommended only for temporarily reducing disease activity. In addition, the treatment was targeted to DAS28 remission, not strict remission, and these differences in addition to the differences in study design likely explain the differences in attained remission rates. Nevertheless, the main results of this study are in agreement with ours and promote the importance of physicians' adherence to protocol.

Three studies have assessed physicians' treat-to-target adherence, but not the association between adherence and outcomes; therefore comparing the results of

these studies to ours is difficult. Vermeer et al. studied adherence to treat-to-target strategy in 100 patients from the DREAM early RA cohort and treated aiming at DAS28 remission (287). Physicians adhered to the protocol during 69% of the visits and adherence was even higher, 81%, if remission was present. Markusse et al. obtained corresponding results using 10-year follow-up data of 508 patients from the BeSt study and reported an average adherence of 79% to treat-to-target advice (290). In both studies, physicians were more likely to deviate from the protocol if they disagreed with DAS/DAS28. In addition, when comparing data from two trials, BeSt and Induction therapy with MTX and prednisone in rheumatoid or very early arthritic disease (IMPROVE), Akdemir et al. found that physicians were more likely to adhere to the protocol which aimed at low disease activity, not at remission (296). This was true especially when physicians disagreed with the used disease activity measure, DAS, and when treatment intensification, instead of tapering, was needed. PGA in DAS is known to be associated not only with objective disease activity measures, but also with factors like depression and pain, and discordance between objective disease activity measures and PGA is common (130). Nevertheless, it is unfortunate that physicians were less adherent in the more recent study, which began in the same year that the treat-to-target manifesto was published. One explanation for this may be that physicians have become more aware of the caveats of composite measures of disease activity, and intensify treatment only when objective signs of RA activity are present, but not if subjective, patient-reported measures of disease activity are in discordance with their own assessment.

Our results suggest that physicians' adherence is of crucial importance for successful, remission targeted treatment of early RA. Furthermore, substantial non-adherence to the targeted treatment can also exist in a clinical trial setting. This leads us to conclude that the implementation of tight control over treatment strategies is even more challenging in everyday clinical practice. Based on these results it is clear that in order to obtain improved outcomes, efforts should be made to ensure physician's protocol adherence in addition to emphasizing patient adherence.

6.2 Neglecting intra-articular GCs

We were intrigued when we found that the lack of intra-articular GC injections comprised a significant part of physicians' nonadherence, and realized that the influence of injections warranted further research. We studied the impact of neglecting injections separately, and found that failure to treat all of the patients' swollen joints with iaGCs was associated with lower remission rates and higher

disease activity at 2 years, and with a lower quality of life. Interestingly, the effect of neglected injections was clear despite the intensive treatment with three csDMARDs, oral low-dose prednisolone, and infliximab.

Despite the high remission rates in this study, we found a trend towards lower NEO-RACo remission rates and higher disease activity in patients who were not given iaGC injections to all swollen joints. Furthermore, due to the aggressive treatment strategy of this study, most patients did not have inflamed joints after 6 months, which substantially lowered the need for iaGCs. The overall treatment responses were very good, and radiological progression was minimal in both treatment arms. No progression was detected in 80% of the patients randomized to infliximab, and in 53% of the patients randomized to placebo (23). This may explain why the trend we found in radiological progression (Figure 10) did not reach statistical significance.

It should be noticed that this study was conducted in Finland, where the liberal use of iaGCs has long been and is currently, in addition to DMARDs, a mainstay the treatment of early RA. The Finnish national Current Care Guidelines for RA state that all swollen joints of early RA patients should be injected with GCs (6). Hence, physicians are, and have been, expected to inject all or most of the swollen joints, and injecting only one or two joints is generally not considered sufficient. This is why the use of iaGCs into all swollen joints was exclusively recommended in the study; it is considered to be a self-evident part of the Finnish rheumatology clinical practice.

The literature on the impact of intra-articular GCs is surprisingly limited possibly because their use began long before the gradual acceptance of evidence based medicine (297). Different administration routes of GCs in RA have been compared in one randomized, controlled trial, which showed that intra-articular injections were more effective, and had fewer adverse effects compared to the intramuscular injections (217). Further, only one trial has focused on studying the impact of injections as a part of the combination therapy. In this Indian study patients treated with fixed dose methotrexate and sulfasalazine were more likely to achieve ACR 50 or ACR70 improvement at 3 months, if their swollen joints were injected with GCs at baseline (218).

Our results are most comparable with other treatment strategy trials, in which IaGCs have been used, like Proudman et al. in 2000 and TICORA, CIMESTRA, and OPERA trials (219,220,222,224). In these trials, GCs were administered in intra-articular and intramuscular form in TICORA and by Proudman et. al, and only intra-articularly in CIMESTRA and OPERA. Oral GCs were not allowed, and therefore cumulative daily GC doses (prednisolone equivalents) remained low, being less than 2mg/day during the first year in all trials (219,220,222,224).

However, in contrast to our study, the number of injections was limited in three of four studies to 3–4 per visit. Only Proudman et al. allowed multiarticular and intramuscular injections, but do not report the number or timing of the injections in detail. Previously, injections have been analyzed in detail only in CIMESTRA, where injections led to long-lasting remission of the individual joints, and more than third of the joints injected 2–3 times due to effusion were in remission at 24 months (225). The influence of neglecting injections to all swollen joints in early RA has not been studied earlier. Thus, comparing our results to the results of these trials is challenging. Nevertheless, these studies demonstrate the usefulness of iaGCs as a part of the treatment strategy. In the current study, oral low-dose oral prednisolone was a part of the combination treatment. This led to higher cumulative GC doses than observed in the aforementioned studies. However, injections increased the cumulative daily prednisolone dose from only 0.1 mg in the infliximab arm to 0.4 mg in the placebo arm. In the NEO-RACo trial, in order to treat the patients as intensively as possible, both oral and iaGCs were used.

Based on our results early RA patients are less likely to achieve remission, have higher disease activity, and suffer from lower quality of life if intra-articular GCs into swollen joints are neglected despite effective combinations of csDMARDs. IaGCs are well tolerated, inexpensive and feasible for the rheumatologists to use. Based on our results, we can implicitly conclude that iaGCs are very useful, and their use should be actively encouraged in the treatment of RA.

6.3 Burden of adverse events

We found that increased burden of adverse events during the first year was associated with lower DAS28 remission rates and higher disease activity at 1 and 2 years in the study population. Even though most adverse events (92%) were mild or moderate, one in four led to temporary or permanent csDMARD discontinuation. However, differences in clinical outcomes at 2 years were small, and most patients, 70–90% depending on the tertile, achieved DAS28 remission.

We were not able to find previous studies that have specifically assessed the impact of adverse events on RA outcomes. One recent study has focused on medication persistence in RA patients (279). Contreras-Yanes et al. showed in this observational cohort study that the duration of DMARD discontinuation periods during the first four years of RA treatment was associated with higher disease activity and increased disability during the fifth year in Mexican early RA patients. Interestingly, the timing of the non-persistence during the first four years did not influence the outcomes, although it is known that RA generally reacts more amenable to early treatment (253). Due to the differences in study design,

it is difficult to compare the results of this study with ours. However, a higher burden of reported adverse events could also be associated with a higher risk of decreased medication adherence and persistence also in our study.

Based on the csDMARD discontinuation rates, non-persistence caused by adverse events was most likely the primary reason for lower remission rates in the third tertile of adverse event burden in our study. The impact of drug discontinuations is accentuated by the fact that it may take two to three months to reach the peak effect of a new csDMARD (11). Thus, patients suffering from adverse events, which lead to drug switches, may be undertreated for several months, decreasing their probability of reaching remission. Further, in routine clinical practice the impact of drug discontinuations is likely more pronounced due to less intensive treatment, particularly if monotherapy is used, lower adherence, and longer control intervals.

We found only minor differences in the characteristics of the patients categorized by the burden of adverse events. The patients who experienced the most adverse events had a higher tender joint count and a lower ESR compared with the two other groups. The discordance of these measures is interesting, and could be caused by truly higher disease activity despite lower ESR or by higher prevalence of non-inflammatory joint pain in the third tertile. The latter seems more likely based on previous studies, which have shown that RA patients suffering from non-inflammatory pain, like fibromyalgia, have higher DAS28 scores and a lower likelihood of remission due to disproportionately high subjective disease activity measures compared to patients with RA alone (120,298,299).

Few studies have assessed the underlying causes for DMARD treatment failure in early RA. According to these studies, poor mental health seems to be one of the key factors associated with treatment failure and drug discontinuation, and it may also affect patient assessments by increasing DAS28 and by inflating tender joint count and patient global assessment values (119,229,235). Further, some patients may also be more prone to adverse events due to their psychological characteristics, like anxiety or depression, and negative expectations concerning medications (226). In our study, the use of a triple combination of csDMARDs was mandatory, and therefore adverse events led to alterations, but not to cessation or failure of the drug regimen. However, impaired mental health may have been one of the drivers of increased adverse event reporting in our study. Unfortunately, we were not able to test this hypothesis due to lack of instruments assessing psychological factors, apart from SF-36 questionnaire.

We conclude that in early RA, a higher burden of adverse events during the first year of treatment is associated with reduced remission rates and higher disease activity thereafter. These findings are most likely explained by temporary and

permanent DMARD discontinuations caused by adverse events. In the current study, one third of the patients experienced almost two thirds of the adverse events. Future studies are warranted to elucidate factors that influence adverse event reporting.

6.4 Patient-reported outcomes as predictors of remission

We explored the predictive value of PROs in the NEO-RACo trial, and showed that 2 dimensions of the SF-36 questionnaire, vitality and role-emotional functioning, were more accurate predictors of remission at baseline than the traditional ACR core data set PROs. In univariable analyses, PGA, HAQ, and nearly all dimensions of SF-36 predicted remission at 24 months. However, when we simultaneously analyzed all PROs in the regression models with other clinically relevant covariates, only two SF-36 dimensions, vitality and emotional role functioning, were associated with future remission.

We found only one longitudinal study focused on predicting remission in early RA using SF-36 dimensions (10). In this small, observational study of 40 RA patients none of the SF-36 dimensions predicted DAS28 remission after follow-up of three years. According to da Mota et al., only 23% of the patients achieved remission, making the study likely underpowered to examine SF-36 dimensions as predictors of outcomes. Thus, comparing the results of this study to ours is difficult.

In our study, none of the ACR core data set PROs (HAQ, PGA and pain VAS) predicted remission at 24 months after adjustment for SF-36 dimensions and other clinical covariates. HAQ has been previously considered to be one of the most important predictors of outcomes in RA (156,157). However, as confirmed by the current study, baseline HAQ has not been a strong predictor of clinical remission in early RA in patients receiving intensive, targeted treatment (9,10). PGA is appreciated as a feasible measure of disease activity. However, non-inflammatory factors, such as pain, depression, anxiety, and fatigue, can contribute significantly to the level of PGA (130,134,136). According to our findings, PGA is not a reliable predictor of future remission in early RA.

We found that a 1-SD increase in baseline vitality was associated with 2-fold greater odds of being in remission at 24 months, and better emotional role functioning also predicted remission. These measures may reflect patients' healthier psychological functioning, and possibly improve patients' ability to cope with RA and RA treatment, thereby improving outcomes. Vitality can be defined as the presence of energy, well-being, and the absence of fatigue (300). So far, only

a few studies have reported about the benefits of vitality to physical health. In these studies, higher vitality has been a protective factor against coronary heart disease and stroke (301,302). In RA studies, the vitality subscale of SF-36 has been previously used as a validated measure of RA fatigue, defined as low vitality (303). However, the connection between fatigue (or low vitality) and disease activity is still being debated as recent reports have demonstrated that fatigue may be mediated mainly through factors like pain, disability, and poor mental health (304).

Our study was the first to demonstrate that better emotional role functioning is associated with a higher likelihood of reaching remission in early RA. It may also reflect patients' healthier psychological functioning. Furthermore, previous studies have shown that RA symptoms can be alleviated with psychosocial interventions, like cognitive behavioural therapy (305,306). Thus, identifying patients, who might benefit from these interventions already at time of diagnosis, is important.

Although the SF-36 questionnaire is seldom used in everyday clinical practice, electronic collection of PRO data is increasing. At present, electronic data collection is widely used in the treatment of RA in the Nordic countries and their biologic DMARD registers (144,307,308). If future studies confirm the accuracy of vitality and role-emotional functioning in predicting remission, adding these SF-36 dimensions into patients' current electronic monitoring would be relatively easy and would enable the feasible measurement of these PROs.

6.5 Limitations of the study

Despite of its strengths such as the clinical trial design reducing the possibility of bias, and the short follow-up intervals that enabled collection of very detailed data, the results of our study should be interpreted in the context of its limitations. Without doubt, the main limitation is the small sample size. The sample size of 100 patients was calculated based on the results of the FIN-RACo study assuming a 25% strict remission rate at 6 months in the combination therapy group (4). The yielded remission rates were significantly higher, more than 45% in both groups at 6 months, which reduced the power of the study. This does not, however, reduce the significance of our results, but is likely one of the reasons why we were not able to detect significant differences in some of the outcomes, such as radiological progression.

Second, our study population consisted of intensively treated and followed working age patients with early RA, which may reduce the generalizability of these

results to other settings, like clinical practice, older RA populations, and patients with contraindications to the DMARDs used in our study or with significant comorbidities. However, it should be remembered that two thirds of patients are of working age at RA onset (44). Current international recommendations stress importance of frequent monitoring in early, active RA (256), but as intensive monitoring as in the NEO-RACo trial (8 visits during the first six months) is rarely achieved in everyday clinical practice, which slightly reduces the generalizability of our results. The fact that patient adherence was not measured systematically in the NEO-RACo trial is also a possible source of bias. However, 92% of the patients completed the 2-year study, and only 9% were lost to follow-up over 5 years, indicating good patient adherence.

We made sure that physicians' treatment decisions were not affected by adherence monitoring by analysing physicians' adherence retrospectively, which we consider a strength. Thus, our results are likely to represent physicians' true adherence to targeted treatment. To some, the scoring system for adherence may seem arbitrary. It was, however, based on our views of the best possible way of actively treating RA following the trial protocol and Finnish national recommendations. The fact that physicians had fewer opportunities for nonadherence while treating patients who responded well to treatment has the potential to cause a channelling bias. However, the majority of the nonadherence points accumulated from a lack of iaGCs. Bias caused by physicians ceasing to inject patients, who did not respond well to treatment seems unlikely.

We studied the influence of not injecting swollen joints retrospectively (II) because the NEO-RACo trial was not originally designed to investigate the efficacy of iaGCs. Proving the efficacy of iaGCs would require a placebo-controlled study with sham injections, which, from our point of view, would have been unethical. Therefore, in order to confirm the usefulness of injections, we analyzed only the effects of not injecting swollen joints, and determined the efficacy of iaGCs implicitly. Possible biases in this analysis include unreported injections by other physicians, like general practitioners, and joint effusions treated with iaGGs but not caused by RA. Frequent clinical assessments and documenting of all injections, also ones administered outside the study visits, make a significant bias in the number of injections unlikely. Patients with other inflammatory arthritides were excluded from the study, but some patients may have had joint effusions caused by OA. The differentiation between OA and RA in the study was based on the treating physician's clinical assessment. All study physicians were experienced rheumatologists, and the prevalence of significant OA was low among the working age study population making OA an unlikely cause of significant bias.

Of the adverse events, more than 90% were mild or moderate, and physicians rated approximately a third of all adverse events as unrelated or unlikely related to study medication (III). Therefore, csDMARD discontinuations are unlikely to be the only explanation for the association between the burden of adverse events and lower remission rates. Unfortunately we had no data on other factors possibly influencing the burden of adverse events, like the prevalence of psychological problems, non-inflammatory joint pain, or fibromyalgia in the study population. We can therefore only speculate that these factors might be associated with a higher burden of adverse events. Further, due to the small study sample the number of permanent csDMARD discontinuations remained low and prevented us from separately assessing the effects of discontinuation of individual csDMARDs, like MTX.

Finally, it should also be noted that the prognostic factors for RA, such as PROs (IV), are often highly interrelated, complicating statistical analysis. We tried to minimize the effects of this multicollinearity by using generalized maximum entropy estimation methodology when we analyzed PROs as predictors of remission. Due to the small study sample, the associations between the two baseline SF-36 dimensions and remission should be confirmed with larger trials.

7 CONCLUSIONS

In this study, we investigated factors that are, in addition to intensive clinical remission targeted DMARD treatment, associated with improved outcomes in early RA and arrived at the following conclusions:

1. Physicians' adherence to the treatment protocol improves the outcomes of patients with early RA. Physicians' lower adherence during the first two years was associated with lower remission rates, higher disease activity, and a higher number of DMARDs replacements during the follow-up from two to five years. To bring as many patients as possible into remission, the physicians' and the patients' adherence to the targeted treatment needs to be optimized.
2. Intra-articular GC injections to all swollen joints should not be neglected. When iaGCs were not given to all swollen joints, the patients were less likely to achieve remission, had higher disease activity, and suffered from a lower quality of life. Injections are well tolerated, inexpensive and feasible and their use should be an integral part of the targeted treatment of early RA.
3. A high burden of adverse events was associated with higher disease activity and reduced DAS28 remission rates at one and two years in the NEO-RACo trial. Despite most adverse events being mild or moderate, one in four led to temporary or permanent csDMARD discontinuation. Patients with a high burden of adverse events, and those experiencing frequent mild to moderate adverse events may thus be at risk for treatment failure.
4. Two baseline SF-36 dimensions, vitality and role-emotional functioning, were associated with achieving remission at 2 years in the study, but this association was not found for the traditional ACR core set PROs. Future studies are needed to confirm the value of these SF-36 dimensions as predictors of remission.

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