RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Register-based observational study of associations between inflammatory remission, formal treatment targets and the use of disease-modifying antirheumatic drugs among patients with early rheumatoid arthritis

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To cite: Lindqvist J, Askling J, Lampa J. Register-based observational study of associations between inflammatory remission, formal treatment targets and the use of disease-modifying antirheumatic drugs among patients with early rheumatoid arthritis. *RMD Open* 2023;**9**:e003111. doi:10.1136/rmdopen-2023-003111

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2023-003111).

Received 18 May 2023
Accepted 9 October 2023

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ABSTRACT

Objective To assess associations between inflammatory remission, formal treatment targets and the likelihood of starting a new disease-modifying antirheumatic drug (DMARD), among patients with early rheumatoid arthritis (RA).

Methods Patients newly diagnosed with RA were identified in the Swedish Rheumatology Quality Register (n=11 784). Disease Activity Score 28 (DAS28) and DMARD-treatment were assessed at RA diagnosis and 3, 6, 12 and 24 months thereafter. Inflammatory remission was defined as: swollen joints (0–28)=0 and C reactive protein <10 mg/L and normal erythrocyte sedimentation rate. The primary treatment target was DAS28 remission (<2.6). The proportion of patients in inflammatory remission who failed to reach DAS28 targets was assessed at each follow-up visit, and their likelihood of starting a new DMARD was compared with patients in inflammatory remission who reached the treatment target. rate ratios (RR) and 95% CIs were estimated with modified Poisson regression.

Results Overall, 34%, 39%, 44% and 47% were in inflammatory remission at 3, 6, 12 and 24 months. Among these, 20%, 22%, 20% and 19%, respectively, failed to reach DAS28 remission. Patients who failed to reach DAS28 remission despite being in inflammatory remission were more likely to start a new DMARD treatment (RR (95% CI) at 6 months=1.59 (1.29 to 1.96), 12 months=1.52 (1.23 to 1.87)) and 24 months=1.47 (1.20 to 1.80).

Conclusion Failing to reach formal treatment targets, despite being in inflammatory remission, is common among patients with early RA, and is associated with an increased likelihood of starting a new DMARD-treatment.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Management of rheumatoid arthritis (RA) aims to achieve a state of clinical remission, defined as the absence of signs and symptoms of inflammatory disease activity, and treatment recommendations state that disease-modifying antirheumatic drug (DMARD)-therapy should be adjusted until the desired target is reached.

⇒ Disease activity is assessed through composite measures that include features of pain and inflammation; however, some patients may experience persistent pain, despite that the inflammation has resolved.

WHAT THIS STUDY ADDS

⇒ This study highlights that, in a subgroup of patients, persistent pain may prevent the treatment targets from being reached, even in the absence of inflammatory disease activity.

⇒ This patient group has an increased likelihood of having their DMARD therapy escalated, despite being in inflammatory remission.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The role of non-inflammatory causes of pain, and its impact on disease activity measures in RA, should be considered by health professionals in their clinical decision-making.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that may lead to irreversible joint damage and permanent functional impairment. The primary goal in the management of RA is to suppress the inflammatory process and to prevent, or at least delay, the development of structural joint damage. This approach is formally expressed in the treat-to-target recommendations of an international task force, which states that clinical remission is the primary target for treatment of RA, while low disease activity (LDA) may

be an acceptable alternative. The recommendations further state that drug therapy should be adjusted until the desired target is reached.[1]

The development of new and effective antirheumatic treatments during recent decades has made these goals achievable in a larger part of patients with RA. In the wake of this therapeutical development, however, other outcomes than inflammatory disease activity have gained increasing importance. One of these is the management of pain, which is frequently rated as a top priority for patients with RA.[2 3] For some patients, pain seems to become uncoupled from the underlying inflammatory condition during the course of the disease,[4] potentially manifesting as persistent arthralgia with high tender joint counts (TJC)[5] or as chronic widespread pain,[6 7] also in patients with low or no inflammatory disease activity. While disease-modifying antirheumatic drugs (DMARDs) are pivotal to halt the inflammatory process in RA,[8] the management of non-inflammatory pain primarily involves non-pharmacological interventions such as educational activities, exercise and psychological interventions.[9]

Disease activity in RA is commonly assessed through composite measures of subjective and (semi)objective features related to inflammation and pain. One of the most commonly used composite measures is the Disease Activity Score of 28 joints (DAS28), which is used both for monitoring of patients in clinical practice and as endpoint in clinical trials.[10] DAS28 provides an overall score of disease activity based on swollen (SJC) and TJCs, an acute phase reactant, and the patient's rating of overall health.[11] Based on the overall score, cutoffs for disease activity states have been defined.[12] One challenge with DAS28 (and other composite measures), however, is that the overall score does not indicate to what extent the score is driven by inflammatory or pain-related components. For example, it has previously been demonstrated that high levels of pain-related features may prevent the DAS28 targets of remission and LDA from being reached, also in the absence of inflammatory disease activity.[13] A strict adoption of the treat-to-target injunction of escalating treatment until targets are reached, without considering the role of non-inflammatory causes for the inability to reach treatment targets, might therefore potentially lead to overtreatment with DMARDs and to delay of interventions targeting pain management.

In this project, we assessed the prevalence of patients who, at follow-up visits during the first 2 years of their RA disease, failed to reach formal treatment targets despite being in inflammatory remission. Among patients in inflammatory remission, we further assessed the pattern of new DMARD starts at follow-up visits, contrasting patients who reached, vs patients who failed to reach, formal treatment targets. For patients who failed to reach treatment targets despite being in inflammatory remission, we investigated whether the start of a new DMARD affected the likelihood of reaching the treatment targets at the subsequent visit.

METHODS

Study setting

This observational study used prospectively collected data on disease activity and treatment during the first 2 years of RA disease for newly diagnosed patients with RA from the Swedish Rheumatology Quality Register (SRQ), collected during 2011–2020. The SRQ is a nationwide clinical quality register with longitudinal data collected at clinical visits. It is used by rheumatological clinics throughout Sweden and includes approximately 85% of all prevalent RA in Sweden.[14] The data used in this study included measures of disease activity, pain, functional disability and DMARD treatment at diagnosis and follow-up. All patients included in this study fulfilled the 1987 American College of Rheumatology (ACR) criteria for RA,[15] and had a symptom duration before diagnosis of less than 1 year.

Variable assessment

The day of inclusion in SRQ was considered as baseline, with follow-up assessments at 3, 6, 12 and 24 months after baseline. For each visit time point, we used the closest registered visit for each patient within the following time span of days in relation to inclusion; −45 to 45, 46 to 137, 138 to 274, 275 to 548 and 549 to 913, respectively. The collected data included TJC and SJC 28-joint counts (TJC28 and SJC28), erythrocyte sedimentation rate (ESR), C reactive protein (CRP), the patient's global assessment of health (PGA) on Visual Analogue Scale (VAS), VAS pain, the Swedish version of the Stanford Health Assessment Questionnaire (HAQ)[16] and the physician's evaluation of disease activity on a 0–4 Likert scale (0: remission, 1: low, 2: moderate, 3: high and 4: extreme disease activity). The VASs were scaled from 0 to 100 mm, with 0 indicating the best possible outcome and 100 indicating worst possible outcome. The overall DAS28 was computed according to established formula, based on SJC28, TJC28, ESR and PGA.[11] We also computed the Simplified Disease Activity Index (SDAI),[17] and assessed the ACR/European Alliance of Associations for Rheumatology (EULAR) Boolean definition of remission.[18] For calculation of the latter two indices, the values of PGA and CRP were divided by 10, and to obtain the physician's global assessment, as part of the SDAI-score, the 0–4 Likert scale was multiplied by 2.5, as previously described.[19] The proportion of patients not reaching the Patient Acceptable Symptom State for VAS pain (≤40 mm) was assessed.[20] We also calculated the difference between the number of tender and the number of swollen joints (ΔTSJ) as an indicator of potential discordance between pain and inflammation,[21] and we assessed the prevalence of the previously proposed definition of 'fibromyalgic RA', that is, ΔTSJ≥7.[5]

Outcome assessment

We defined inflammatory remission as SJC (0–28 joints)=0, together with CRP<10 mg/L and normal ESR as defined by the reference levels used by the Karolinska

University Laboratory in Stockholm (<20 mm/hour for women <60 years, <30 mm/hour for women ≥60 years, <10 mm/hour for men <60 years, <20 mm/hour for men ≥60 years).

At each follow-up visit during the first 2 years of disease, we assessed the proportion of patients who were in inflammatory remission, and the proportion among these patients who failed to reach the treatment targets. Conversely, we also assessed the proportion of patients who failed to reach the treatment targets and the proportion among these patients who were in inflammatory remission. As primary treatment targets, we used DAS28 remission (<2.6) and DAS28 LDA (≤3.2), and for these groups we assessed clinical characteristics at follow-up visits. Secondary treatment targets included SDAI remission (≤3.3), SDAI LDA (≤11.0)[17] and ACR/EULAR Boolean definition of remission.[18]

Disease-modifying antirheumatic drugs

Comparing patients in inflammatory remission who reached, versus failed to reach, the treatment targets we made the following three assessments: First, for each follow-up visit, we assessed the likelihood of starting a new DMARD at that specific visit. Second, we assessed the cumulative number of unique DMARDs used during the period from RA diagnosis and up until each follow-up visit in question. Third, we assessed the average number of new DMARD starts per visit during the whole follow-up period by assessing the total number of visits and the total number of new DMARD starts at these visits.

As a secondary analysis, we categorised DMARDs into conventional synthetic DMARDs, biological DMARDs and targeted synthetic DMARDs (tsDMARDs). The latter two categories were grouped together due to low number of tsDMARD starts.

Among the patients who failed to reach the treatment targets despite being in inflammatory remission at follow-up visits, 3, 6 and 12 months after diagnosis, we investigated whether the start of a new DMARD affected the likelihood of reaching the treatment targets at the subsequent visit.

Statistical analysis

Descriptive statistics was used to assess the numbers and proportions of patients who failed to reach treatment targets despite being in inflammatory remission at the same follow-up visit. For the clinical characteristics at baseline and follow-up, mean and SDs were computed for normally distributed variables and Student's t-test was used for statistical comparisons. For non-normally distributed variables, median and IQRs were computed, and Wilcoxon rank sum test was used for statistical comparisons. Binary clinical variables were displayed as numbers and proportions, and χ^2 test or Fisher's exact test (in case of cell counts below 5) were used for statistical comparisons.

Poisson regression was used to analyse the cumulative number of unique DMARDs used up until the follow-up visits. A modified version of Poisson regression with robust error estimation[22] was used to analyse the likelihood of starting a new DMARD at the specified visit and the rate of new DMARD starts per visit during the whole follow-up period. Ninety-five per cent CIs were obtained from the regression models. The regression models were adjusted for age at inclusion in SRQ, sex and time period for inclusion in SRQ (2011–2015 vs 2016–2020), except for the analysis of the cumulative number of unique DMARDs used up until follow-up visits, which was assessed by univariate analysis.

Modified Poisson regression was also used to analyse whether the start of a new DMARD affected the likelihood of reaching treatment targets at subsequent visits, among patients who failed to reach treatment targets despite being in inflammatory remission. These analyses included a univariate analysis of the effect of starting a new DMARD and a multivariate analysis adjusted for age, sex and year of inclusion in SRQ.

All statistical analyses were performed using R statistical software, V.4.1.3.[23]

RESULTS

Patient characteristics

A total of 12 896 patients with newly diagnosed RA and a symptom duration less than 1 year (median symptom duration before diagnosis=152 days (IQR: 88–236)), were identified in SRQ. Of these, 11 784 patients had at least one follow-up visit registered within 24 months of diagnosis, and thereby constituted the study population. After allocation of registered clinical visits to the predefined time intervals, clinical data were available for 11 141 patients at baseline, 7537 at 3 months, 7106 at 6 months, 8590 at 12 months and 7452 at 24 months. Clinical characteristics at baseline and follow-up are displayed in table 1.

Inflammatory remission and treatment targets

The proportions of patients who were in inflammatory remission at 3, 6, 12 and 24 months (out of all patients contributing with visit data for the time-point in question), were 34%, 39%, 44% and 47%, respectively. Among the patients who were in inflammatory remission, 20%, 22%, 20% and 19%, respectively, failed to reach DAS28 remission (figure 1A), and 8%, 9%, 7% and 8%, respectively, failed to reach DAS28 LDA (figure 1B). The corresponding figures for SDAI remission, SDAI LDA and ACR/EULAR Boolean remission are displayed in online supplemental figure 1.

Conversely, the proportion of patients who failed to reach DAS28 remission at 3, 6, 12 and 24 months, was 58%, 56%, 50% and 48%, respectively. Among these patients, 12%, 15%, 18% and 19%, respectively, were in inflammatory remission (figure 2A). The proportion of patients who failed to reach DAS28 LDA at 3, 6, 12 and 24 months, was 41%, 39%, 33% and 32%, respectively. Among these patients, 7%, 9%, 10% and 13%,

Table 1 Patient characteristics at baseline and follow-up visits

Characteristic	Baseline	3 months	6 months	12 months	24 months
N	11 141	7537	7106	8590	7452
Age at inclusion (years)	62 (50 – 71)	62 (50 – 71)	62 (49 – 71)	62 (49 – 71)	62 (49 – 70)
Female, %	68	68	69	68	69
DAS28–mean (SD)	4.83 (1.46)	3.03 (1.34)	2.98 (1.35)	2.81 (1.31)	2.72 (1.31)
DAS28 remission, %	8	42	44	50	53
DAS28 low disease activity, %	14	59	61	67	68
SDAI	24.1 (15.7 – 34.4)	7.9 (3.7 – 14.6)	7.7 (3.5 – 14.5)	6.7 (2.9 – 12.8)	6.2 (2.4 – 11.8)
SDAI remission, %	3	23	24	28	32
SDAI low disease activity, %	14	64	65	69	73
ACR/EULAR Boolean remission, %	3	21	21	24	26
Inflammatory remission, %	6	34	39	44	47
CRP (mg/L)	10 (4 – 26)	4 (2 – 8)	4 (1 – 7)	4 (1 – 6)	4 (1 – 6)
ESR (mm/hour)	25 (13 – 43)	13 (7 – 24)	12 (6 – 23)	12 (6 – 22)	12 (6 – 21)
Swollen joint count (0–28)	5 (2 – 10)	1 (0 – 3)	0 (0 – 2)	0 (0 – 2)	0 (0 – 1)
Tender joint count (0–28)	5 (2 – 10)	1 (0 – 3)	1 (0 – 3)	0 (0 – 3)	0 (0 – 2)
PGA (VAS, 0–100 mm)	50 (30 – 71)	23 (8 – 46)	25 (8 – 50)	24 (7 – 48)	23 (7 – 49)
Physician's rating (0–4)	2 (2 – 3)	1 (0 – 1)	1 (0 – 1)	1 (0 – 1)	1 (0 – 1)
Pain (VAS, 0–100 mm)	54 (30 – 73)	20 (6 – 43)	23 (7 – 47)	23 (7 – 47)	22 (6 – 48)
Unacceptable pain, %	66	27	30	31	32
HAQ	0.88 (0.50 – 1.38)	0.38 (0.00 – 0.88)	0.38 (0.00 – 0.88)	0.38 (0.00 – 0.88)	0.38 (0.00 – 0.88)
ΔTSJ	0 (–1 – 2)	0 (0 – 1)	0 (0 – 1)	0 (0 – 1)	0 (0 – 1)
Fibromyalgic RA, %	7	5	5	4	4

Values are stated as median (IQR) unless otherwise noted.
Inflammatory remission: Swollen joint count (28 joints)=0 and CRP<10 mg/L and normal ESR (<20 mm/hour for women <60 years, <30 mm/hour for women≥60 years, <10 mm/hour for men<60 years, <20 mm/hour for men ≥60 years).
Physician's rating: The physician's rating of disease activity on a 5-level scale (0: remission, 1: low, 2: moderate, 3: high, 4: extreme), unacceptable pain: VAS pain >40 mm, ΔTSJ: difference (Delta) between tender and swollen joint counts (0–28), fibromyalgic RA: ΔTSJ≥7.
ACR, American College of Rheumatology; CRP, C reactive protein; DAS28, Disease Activity Score of 28 joints; ESR, erythrocyte sedimentation rate; EULAR, European Alliance of Associations for Rheumatology; HAQ, (Stanford) Health Assessment Questionnaire; PGA, patient global assessment.; RA, rheumatoid arthritis; SDAI, Simplified Disease Activity Index; TSJ, tender and the number of swollen joints; VAS, Visual Analogue Scale.

respectively, were in inflammatory remission (figure 2B). Corresponding figures for SDAI and ACR/EULAR Boolean remission are displayed in online supplemental figure 2.

The proportion of patients who failed to reach DAS28 remission despite being in inflammatory remission, out of the total number of patients contributing with visit data at 3, 6, 12 and 24 months was 7%, 9%, 9% and 9%, respectively. For patients who failed to reach DAS28 LDA despite being in inflammatory remission, the corresponding proportions were 3%, 3%, 3% and 4%. Of all the patients who failed to reach DAS28 remission despite being in inflammatory remission at 3, 6, 12 and 24 months, a total of 4 patients met this definition at all four follow-up time points, 40 patients met the definition at three time points, 269 patients at two time points and 1372 patients met the definition at one follow-up time

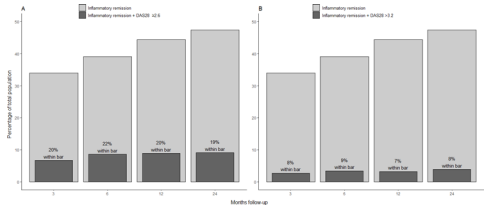

Figure 1 Bar charts displaying the proportion of patients who were in inflammatory remission at follow-up visits (light grey bars in A and B), and the proportion of the patients in inflammatory remission who failed to reach the treatment targets: (A) DAS28 remission (<2.6) and (B) DAS28 low disease activity (≤3.2). DAS28, Disease Activity Score 28.

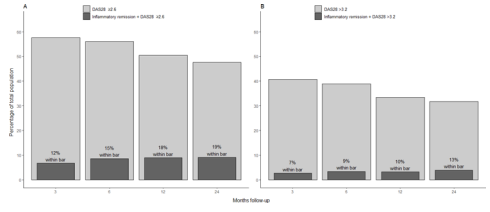

Figure 2 Bar charts displaying the proportion of patients who failed to reach DAS28 targets at follow-up visits, and the proportion of the patients who failed to reach DAS28 targets who simultaneously were in inflammatory remission. DAS28, Disease Activity Score 28.

point. Of all the patients who failed to reach DAS28 LDA despite being in inflammatory remission, no patient met the definition at all four follow-up time points, 10 patients met the definition at three time points, 83 patients at two time points and 619 patients met the definition at one time point.

Clinical characteristics of patients who failed to reach DAS28 targets despite being in inflammatory remission

The clinical characteristics at follow-up visits for patients who were in inflammatory remission, stratified by DAS28 treatment targets, are displayed in online supplemental tables 1–4. The proportion of women was consistently higher, at all follow-up time points, among the patients in inflammatory remission who failed to reach DAS28 targets. Patients who failed to reach DAS28 remission at 3 months, and patients who failed to reach DAS28 LDA at 3 and 6 months, were significantly younger.

For patients in inflammatory remission who failed to reach DAS28 remission, the median VAS pain levels ranged from 32 mm at 3 months to 44 mm at 24 months (vs 7 mm and 10 mm for those who reached DAS28 remission), the proportion of patients with unacceptable pain (VAS pain>40 mm) was 40% at 3 months and 56% at 24 months (vs 7% and 12% for those who reached DAS28 remission), and the proportion of patients who met the definition of 'fibromyalgic RA' was 19% at 3 months and 17% at 24 months (vs 0% and <1% for those who reached DAS28 remission).

For patients in inflammatory remission who failed to reach DAS28 LDA, the median VAS pain levels ranged from 45 mm at 3 months to 50 mm at 24 months (vs 9 mm and 12 mm for those who reached low DAS28), the proportion of patients with unacceptable pain was 57% at 3 months and 68% at 24 months (vs 10% and 16% for those who reached low DAS28), and the proportion of patients who met the definition of 'fibromyalgic RA' was 37% at 3 months and 35% at 24 months (vs 1% at both time points for those who reached low DAS28).

Although that all patients who were in inflammatory remission had ESR-levels within the normal range, those who failed to reach DAS28 targets had significantly higher ESR levels at all follow-up visits, compared with those who reached DAS28 targets. Similar patterns were seen for CRP levels, except for at 6 and 12 months, where no difference was seen between patients in inflammatory remission who reached, versus failed to reach, DAS28 LDA (online supplemental tables 1–4).

Patterns of DMARD consumption

Among patients in inflammatory remission, those who failed to reach DAS28 remission were more likely to start a new DMARD at 6 months (rate ratio, RR (95% CI))=1.55 (1.25 to 1.91), 12 months=1.51 (1.22 to 1.86) and 24 months=1.47 (1.20 to 1.81), but not at 3 months=1.14 (0.95 to 1.38), compared with patients who reached DAS28 remission (table 2). Correspondingly, patients in inflammatory remission who failed to reach DAS28 LDA were more likely to start a new DMARD at 3 months=1.33 (1.05 to 1.69), 6 months=1.74 (1.34 to 2.26), 12 months=1.63 (1.23 to 2.16) and 24 months=1.68 (1.31 to 2.17) compared with patients who reached DAS28 LDA (table 2). Similar patterns were seen for treatment targets based on SDAI and ACR/EULAR Boolean remission (table 2). The corresponding likelihoods of starting either a csDMARD or b/tsDMARD, are presented in online supplemental tables 5–6.

The cumulative number of unique DMARDs used up until 3 and 6 months did not differ between patients in inflammatory remission who reached, versus failed to

Table 2 Table displaying the likelihood (risk ratio) of starting a new DMARD at the respective follow-up visits, comparing patients in inflammatory remission who reached, versus failed to reach, the treatment targets: (a) DAS28 remission=<2.6, (b) DAS28 low disease activity (LDA)=≤3.2, (c) SDAI remission=≤3.3, (d) SDAI LDA=≤11.0 and (e) ACR/EULAR Boolean remission

Patients in inflammatory remission	3 months RR (95% CI)	6 months RR (95% CI)	12 months RR (95% CI)	24 months RR (95% CI)
DAS28 non-remission versus DAS28 remission	1.14 (0.95 to 1.38)	**1.55 (1.25 to 1.91)**	**1.51 (1.22 to 1.86)**	**1.47 (1.20 to 1.81)**
DAS28 non-LDA versus DAS28 LDA	**1.33 (1.05 to 1.69)**	**1.74 (1.34 to 2.26)**	**1.63 (1.23 to 2.16)**	**1.68 (1.31 to 2.17)**
SDAI non-remission versus SDAI remission	**1.27 (1.09 to 1.50)**	**1.29 (1.04 to 1.58)**	**2.01 (1.63 to 2.48)**	**1.55 (1.29 to 1.88)**
SDAI non-LDA versus SDAI LDA	1.21 (0.93 to 1.58)	**2.23 (1.75 to 2.85)**	**2.14 (1.66 to 2.77)**	**1.77 (1.36 to 2.29)**
Boolean non-remission versus Boolean remission	**1.28 (1.08 to 1.50)**	**1.42 (1.14 to 1.77)**	**1.77 (1.42 to 2.20)**	**1.50 (1.23 to 1.82)**

The RR and 95% CIs are analysed by modified Poisson-regression, adjusted for age, sex and year of inclusion in SRQ (2011–2015 vs 2016–2020). The RR refers to the multiplicative effect on the 'risk' of starting a new DMARD at the follow-up visit for patients in inflammatory remission who failed to reach treatment targets, in reference to patients in inflammatory remission who reached the corresponding targets.
ACR, American College of Rheumatology; CI, confidence interval; DAS28, Disease Activity Score 28; DMARD, disease-modifying antirheumatic drug; EULAR, European Alliance of Associations for Rheumatology; RR, risk ratios; SDAI, Simplified Disease Activity Index; SRQ, European Alliance of Associations for Rheumatology.

Table 3 Table displaying (1) the accumulated number of visits during the follow-up period where patients were in inflammatory remission, stratified by treatment targets, (2) the total number of new DMARD starts during these visits, (3) the average rate of new DMARD starts per visits and (4) the rate ratio comparing visits with patients in inflammatory remission who failed to reach, versus reached, the treatment targets

Visits with patients in inflammatory remission, stratified by treatment targets:	Total no of visits during follow-up period, 3–24 months	Total no of DMARD starts during follow-up, 3–24 months	Rate of DMARD starts per visit, mean (SD)	RR (95% CI)
DAS28 non-remission versus DAS28 remission	2046 vs 8121	405 vs 1307	0.22 (0.45) vs 0.16 (0.40)	**1.36 (1.22 to 1.51)**
DAS28 non-LDA versus DAS28 LDA	815 vs 9352	218 vs 1539	0.27 (0.48) vs 0.17 (0.41)	**1.56 (1.35 to 1.80)**
SDAI non-remission versus SDAI remission	4676 vs 4861	977 vs 660	0.21 (0.45) vs 0.14 (0.37)	**1.48 (1.34 to 1.64)**
SDAI non-LDA versus SDAI LDA	732 vs 8805	221 vs 1416	0.30 (0.50) vs 0.16 (0.40)	**1.72 (1.49 to 1.98)**
Boolean non-remission versus Boolean remission	6104 vs 4063	1211 vs 546	0.20 (0.43) vs 0.13 (0.38)	**1.41 (1.28 to 1.56)**

The RRs are analysed by Poisson regression, adjusted for age, sex and year of inclusion in SRQ (2011–2015 vs 2016–2020).
DAS28, Disease Activity Score 28; DMARD, disease-modifying antirheumatic drug; LDA, low disease activity; RR, rate ratio; SDAI, Simplified Disease Activity Index; SRQ, Swedish Rheumatology Quality Register.

reach, the DAS28 and SDAI treatment targets (online supplemental tables 7–11). At 12 and 24 months, patients in inflammatory remission who failed to reach the DAS28 and SDAI treatment targets had used a slightly higher number of DMARDs compared with patients in inflammatory remission who reached the targets. For example, patients in inflammatory remission who failed to reach DAS28 remission at 24 months had on average used 1.42 (SD=0.71) unique DMARDs compared with 1.34 (SD=0.64) for patients in inflammatory remission who reached DAS28 remission, RR=1.06 (95% CI=1.01 to 1.11) (online supplemental table 7).

The average number of new DMARD starts per visit during the follow-up period, for all patient visits in the study population, was 0.26 (8098 DMARD starts in 30 685 visits). For visits where patients were in inflammatory remission, the average number of new DMARD starts was 0.18 (1893 new DMARD starts in 10 732 visits). For visits where patients were in inflammatory remission but failed to reach DAS28 remission, the average number of new DMARD starts was 0.22 (405 DMARD starts in 2046 visits), and for visits where patients were in inflammatory remission and reached DAS28 remission, the number of new DMARD starts was 0.16. This difference was statistically significant, RR 1.36 (95% CI 1.22 to 1.51) (table 3). The corresponding numbers of new DMARD starts for visits where patients who were in inflammatory remission failed to reach, vs reached DAS28 LDA, was 0.27 (218 DMARD starts in 815 visits) compared with 0.17 (1539 DMARD starts in 9352 visits), RR 1.56 (95% CI 1.35 to 1.80) (table 3). Similar patterns were seen for treatment targets based on SDAI and ACR/EULAR Boolean remission (table 3).

As described above, patients in inflammatory remission who failed to reach DAS28 targets had higher levels of ESR and CRP at follow-up visits, compared with the patients who reached DAS28 targets (online supplemental tables 1–4). To assess if higher levels of acute phase reactants were associated to the likelihood of starting a new DMARD, we performed univariate modified Poisson regression analyses for the association between the individual clinical characteristics and the likelihood of starting a new DMARD among all the patients who were in inflammatory remission at follow-up visits. We found no association between higher levels of ESR or CRP and the increased likelihood of starting a new DMARD at any follow-up visit, while the pain-related variables VAS Pain, PGA and TJC28 were all individually significantly and positively associated with the likelihood of starting a new DMARD at all follow-up visits (online supplemental tables 12–15).

Among patients who failed to reach the treatment targets despite being in inflammatory remission at the same follow-up visits, the patients who started a new DMARD generally tended to be younger, display higher levels of pain and pain-related features, and receive higher physician ratings of disease activity, compared with the patients who did not start a new DMARD (online supplemental tables 16–45). The patients who did not start a new DMARD displayed higher levels of CRP and ESR on several occasions (online supplemental tables 18, 20, 24, 28 and 40). The start of a new DMARD at month 3, 6 and 12, respectively, did not affect the likelihood of reaching the treatment targets at the subsequent visit at month 6, 12 and 24, respectively, among the patients who failed to reach the treatment targets despite being

in inflammatory remission (online supplemental tables 16–45).

DISCUSSION

In this study, we show that a substantial proportion of patients who are in inflammatory remission at follow-up visits during the first 2 years of RA fail to reach formal treatment targets. These patients were more likely to be started on a new DMARD compared with patients in inflammatory remission who reached the treatment targets.

Our findings support the notion that factors other than inflammatory disease activity may influence disease activity measures and prevent formal treatment targets from being reached, also in patients without apparent signs of inflammatory disease activity. We also found that the start of a new DMARD at follow-up visits for these patients did not affect the likelihood of reaching the treatment targets at subsequent visits. Taken together, these findings are compatible with the hypothesis that factors other than inflammatory disease activity may influence the decision to initiate new DMARD treatments, which potentially could lead to overtreatment with DMARDs in this patient category.

The treat-to-target recommendations advocate that drug therapy should be adjusted at least every 3 months until the desired treatment target, remission or LDA, is reached.[1] The recommendations also state that the target value and clinical decision-making should take comorbidities, including chronic pain, in consideration. In other words, if the target fails to be reached because of factors other than inflammatory disease activity, escalated antirheumatic treatment may not be advisable. The role of pain in RA can, however, be ambiguous since pain might occur both as a symptom of ongoing inflammation (nociceptive pain) and as a consequence of altered neural pain processing (nociplastic pain),[24] the latter of which may be regarded as a disease entity in itself.[25] Nociceptive and nociplastic pain mechanisms may coexist to a varying degree in the same patient,[26] posing a challenge for clinical decision-making. Thus, a patient with chronic nociplastic pain may benefit from escalated DMARD treatment if there is any level of inflammation contributing to the pain experience, while a patient with nociplastic pain in the absence of inflammatory disease activity will probably not benefit from escalated DMARD treatment. In the latter case, the decision to escalate treatment based on symptoms of pain might lead to overtreatment with DMARDs. This may lead to otherwise avoidable side effects as well as increased individual and societal costs. It may also result in the discontinuation of DMARDs that are actually working well—in suppressing the inflammation. Furthermore, mistaking and treating chronic pain as a symptom of inflammatory disease activity might delay well-needed pain management interventions.

The treat-to-target recommendations state that the primary target for treatment of RA should be a state of clinical remission, and that clinical remission is defined as the absence of signs and symptoms of significant inflammatory disease activity.[1] As we and others have shown,[5] the use of composite measures to assess inflammatory disease activity can be challenging in patients with high levels of pain or other comorbidities, which can affect the composite measure primarily through PGA. A study that evaluated the presence of sonographic signs of inflammation in patients with high PGA who were otherwise in remission found that PGA-levels did not reflect inflammatory activity.[27] High levels of PGA have on the contrary predominantly been associated with pain, fatigue and features of mental ill health.[28] In our data, 10%–17% of the patients who failed to reach DAS28 LDA, and 17%–26% of the patients who failed to reach DAS28 remission, displayed no signs of inflammatory activity, based on joint assessment and laboratory findings. In these patients, the composite measures may not provide adequate ground for treatment decisions, which is also acknowledged in the treat-to-target recommendations.[1]

It has previously been reported that involvement of joints in the feet may be present in patients who are classified as being in remission based on the 28 joints included in DAS28 (and SDAI).[18 29 30] The presence of feet involvement has also been linked to increased levels of PGA.[30 31] It is, therefore, possible that active arthritis in the feet may contribute to elevated levels of PGA and thereby to the failure of reaching treatment targets, in which case escalated treatment may indeed have been motivated. However, the proportion of patients without swollen joints in the 28 joint count who have swollen joints in the feet has been reported to be low, around 3%–6%.[31 32]

In our study, we found that patients in inflammatory remission who failed to reach DAS28 targets had higher levels of ESR and CRP compared with patients in inflammatory remission who reached DAS28 targets, although both groups by definition had ESR levels within the normal range and CRP-levels below 10 mg/L. This finding could potentially be consistent with the presence of arthritis outside the 28 counted joints in the patients who failed to reach DAS28 targets. However, when we assessed the association between ESR and CRP, respectively, in relation to the likelihood of starting a new DMARD among patients in inflammatory remission, we found no association between higher levels of ESR or CRP and the likelihood of starting a new DMARD. On the contrary, higher ESR and CRP were negatively associated to the likelihood of starting a new DMARD at some follow-up visits. On the other hand, the pain-related variables TJC, PGA and VAS pain were all associated with increased likelihood of starting a new DMARD among these patients, at all follow-up visits.

While active arthritis may drive PGA for some patients, a thorough assessment of PGA in the context of RA have concluded that pain, fatigue and functional impairment (HAQ) are the main drivers of PGA,[33] with several studies identifying pain as the single most important contributing factor.[34–36] Inflammatory markers, such as SJC, CRP and

ESR, were consistently not more than weakly correlated to PGA.[33–35] In our study, we found that among the patients who failed to reach treatment targets despite being in inflammatory remission, the start of a new DMARD did not affect the likelihood of reaching the treatment targets at the subsequent visit. While there might be several potential explanations behind this finding, one explanation could be that non-inflammatory pain prevents the treatment targets from being reached through its influence on PGA, in which case additional DMARDs would not be expected to have a meaningful effect.

Limitations of this study include the lack of information on joint status outside the 28 counted joints, which prevented an assessment of arthritis in the feet as a potential contributing factor to the failure of reaching the treatment targets. It is also possible that residual inflammation might have been present in the joints that were clinically assessed as inactive, since sonographic signs of inflammation have previously been demonstrated in clinically inactive joints,[37] which again could contribute to the failure of reaching treatment targets. This study did not consider the use of oral and intra-articular glucocorticoids, which are medications that are less stringently reported in SRQ compared with the use of DMARDs. We can, therefore, not exclude potential influence of the usage of glucocorticoids on our findings. The potential role of comorbidities not directly associated to RA, which may influence the assessment of PGA and pain, were also not considered in this study.

In conclusion, we found that around 20% of patients in inflammatory remission fail to reach DAS28 remission, and just below 10% fail to reach DAS28 LDA, at follow-up visits during the first 2 years of RA disease. Patients in inflammatory remission who failed to reach the treatment targets were more likely to start a new DMARD, compared with patients in inflammatory remission who reached the treatment targets. These findings indicate that formal treatment targets can be prevented from being reached by factors other than inflammatory disease activity and that these factors may influence the decision to start new DMARD treatments.

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Acknowledgements The authors gratefully acknowledge the coordinating personnel at SRQ as well as all the patients and health professionals around Sweden that have contributed with data to the register. An earlier version of this manuscript is included in the corresponding author's thesis, entitled 'Pain patterns in early rheumatoid arthritis', available through the Karolinska Institute Open Archive at https://openarchive.ki.se.

Contributors JLindqvist drafted the article, and all authors critically revised the article for important intellectual content and approved the final version to be published. JLindqvist and JLampa where responsible for the study conception and design, as well as for the acquisition of data. All authors contributed to the analysis and interpretation of data. JLindqvist accepts full responsibility for the finished work and the conduct of the study, had access to the data, and controlled the decision to publish.

Funding The research leading to these results has received funding from the Swedish Research Council, the Swedish Governmental Agency for Innovation Systems (VINNOVA), the Swedish Rheumatism Association, the Swedish Heart-Lung Foundation, the Stockholm County Council and Karolinska Institutet Foundations & Funds.

Disclaimer The funding sources had no role in the designing, data collection, analysis, interpretation and writing of the study, nor in the decision to submit the study for publication.

Competing interests JA has received grants from Abbvie, BMS, Eli Lilly, Galapagos, MSD, Pfizer, Roche, Samsung Bioepis and Sanofi, as part of agreements between these entities and Karolinska Institute with JA as principal investigator. JLindqvist and JLampa declare no conflict of interest.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by The Swedish Ethical Review Authority, reference numbers 2021-05665-01 and 2022-00297-02. Written informed consent has been waivered for registration of patients in the Swedish Rheumatology Quality Register. Patients may opt-out.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Data may be obtained from a third party and are not publicly available. The data for this study consist of deidentified participant data from the Swedish Rheumatology Quality Register (SRQ). Application for data extraction from SRQ may be sent to the SRQ office, info@srq.nu. The application is examined by the Register Council of the Swedish Association for Rheumatology in consultation with the Register holder.

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