

# Remaining Pain in Early Rheumatoid Arthritis Patients Treated With Methotrexate

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**Objective.** To investigate the frequency of remaining pain in early rheumatoid arthritis (RA) after 3 months of treatment with methotrexate as the only disease modifying antirheumatic drug, with a special focus on patients with a good clinical response.

**Methods.** The study base was cases reported to a population-based early RA cohort who had followup data from the Swedish Rheumatology Quality Register (n = 1,241). The Disease Activity Score in 28 joints European League Against Rheumatism (EULAR) response criteria were used to evaluate clinical response to treatment as good, moderate, and no response. The primary end point was remaining pain at the 3-months followup visit, defined as pain >20 mm on a 100-mm visual analog scale (VAS).

**Results.** Remaining pain in spite of a EULAR good response at followup was associated with higher baseline disability, using the Health Assessment Questionnaire (adjusted odds ratio [OR] 2.2 [95% confidence interval (95% CI) 1.4–3.4] per unit increase), and less baseline inflammation, using the erythrocyte sedimentation rate (adjusted OR 0.81 [95% CI 0.70–0.93] per 10-mm increase). Similar associations were detected for remaining pain at followup in spite of low inflammatory activity, defined as a C-reactive protein level <10. Increase in VAS pain during the treatment period was observed in 19% of the whole cohort, with frequencies in the EULAR response groups of 9% (good response), 15% (moderate response), and 45% (no response).

**Conclusion.** These results are in line with the hypothesis that a subgroup of early RA patients exhibits pain that is not inflammatory mediated, where alternative treatment strategies to traditional antiinflammatory medications need to be considered.

## INTRODUCTION

Rheumatoid arthritis (RA) is an inflammatory disease associated with joint destruction, functional impairment, and chronic pain (1). In spite of effective immune-suppressive therapies, observational studies show that a large number of patients continue to have significant pain,

which is known to affect both quality of life and work capacity (2). In an international observational study of patient-reported outcomes, the majority of the cohorts with established RA in Europe (60%) and the US (65%) reported discontent with pain management (3). In early arthritis, active joint inflammation causes a significant burden of pain. However, several earlier observations indicate an uncoupling of pain and joint inflammation during the disease course and show that pain may persist in inflammatory remission (4,5). These findings indicate that pain, not directly related to inflammation, may be insufficiently

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## Significance & Innovations

- Remaining pain is common in early rheumatoid arthritis (RA).
- Remaining pain affects almost one-third of early RA patients with a good clinical response to methotrexate.
- Remaining pain in spite of good clinical response is predicted by high disability and low baseline inflammation.

controlled by antirheumatic drugs, and there is a lack of earlier studies of the pain pattern related to treatment response in early RA. In a population-based cohort of incident RA cases receiving standard care, we have investigated the frequency and possible predictors of remaining pain after 3 months of treatment with methotrexate (MTX) initiated at the time of diagnosis, with special focus on patients with a good clinical response.

## PATIENTS AND METHODS

The Epidemiological Investigation of RA (EIRA) study is a population-based case-control study covering parts of middle and southern Sweden, including cases of newly diagnosed adult RA patients, on average within 10 months of symptom onset (6,7). All cases of RA were diagnosed by a rheumatologist and fulfilled the American College of Rheumatology 1987 criteria for RA (8). This study was approved by the Ethical Review Board at the Karolinska Institute. All participants gave their informed consent.

**Capture of clinical data.** The Swedish Rheumatology Quality Register (SRQ) is a web-based national surveillance system started in the mid-1990s. SRQ is used by rheumatologists to follow incident RA cases longitudinally, as a part of standard care. Information about disease activity, disability, and treatment are registered at each visit, which, at the beginning of treatment, occurs at predefined time points. By virtue of their early RA, patients are invited to participate in both EIRA and SRQ; over 95% of patients accept both of these invitations. The base of the current study was cases reported to the EIRA cohort in 1996–2009 who had followup data in SRQ from diagnosis with at least 1 year of followup (1996–2010). Overall, 1,640 of the 2,567 patients included in EIRA during this time period were included in SRQ and started followup at diagnosis, with available disease activity parameters for the current analyses. Of those, 1,241 patients (76%) received MTX as the only disease-modifying antirheumatic drug (DMARD) at diagnosis.

**Definition of pain and remaining pain.** We retrieved information on pain assessments from SRQ. Pain in the previous week, with reference to the rheumatic disease, was assessed at the time of diagnosis and after 3 months of treatment, according to a visual analog scale (VAS; range 0–100 mm). Significant pain was defined as VAS pain >20 mm as previously described (9). This cutoff was used

in the present study for defining remaining pain after MTX treatment.

**Definition of baseline variables.** Information on smoking status was retrieved from the EIRA questionnaire. Patients were classified according to their smoking status at the time of RA diagnosis as current or non-smokers. It was not possible to classify smoking habits into 2 categories (irregular smokers and users of other types of tobacco) in 16% of the patients. Clinical variables were captured from the SRQ. Patient global assessment (PGA) and Health Assessment Questionnaire (HAQ) were defined as previously described (10). Rheumatoid factor was determined using standard procedures, and anti-cyclic citrullinated peptide (anti-CCP) antibodies were determined by the standard enzyme-linked immunosorbent assay (Immunoscan RA Mark 2, Euro-Diagnostica).

**Definition of the disease activity and treatment response.** Disease activity was measured with the Disease Activity Score in 28 joints (DAS28). We used the European League Against Rheumatism (EULAR) response criteria (11) to define response to treatment. As a measurement of objective absence of systemic inflammation at 3-months followup, we used the parameter low inflammatory activity, defined as C-reactive protein (CRP) level <10 mg/liter.

**Statistical analysis.** The association between baseline parameters and remaining pain was evaluated by logistic regression and expressed as odds ratios (ORs) with 95% confidence intervals (95% CIs), adjusted for age at diagnosis (treatment start) and sex. We used IBM SPSS software, version 21, for all statistical analyses.

## RESULTS

**Eligibility of patients for analyses.** Patients who initiated treatment with MTX as the only DMARD and had available VAS pain and DAS28 data at baseline (n = 1,241) and at the followup visit (n = 1,063 of 1,241 who started MTX) constitute the basis for all analyses. Baseline characteristics of the study patients are shown in Table 1. Baseline characteristics did not differ between RA patients with and those without available DAS28 data at followup (data not shown).

**EULAR response and pain at 3-months followup.** The frequency of patients with a good response was 40%, with a moderate response 38%, and with no response 23% (Table 1). In the whole cohort, 58% reported remaining pain (VAS pain >20) after 3 months of treatment with MTX. Remaining pain was observed in 29% of patients with a good response, in 70% with a moderate response, and in 83% with no response.

**Predictors of remaining pain.** Remaining pain in the whole group of MTX-treated patients was associated with the following baseline parameters: age, more disability (HAQ), higher PGA, higher tender joint count in 28 joints (TJC28), higher CRP level, and higher DAS28 (Table 2). An important aim of the study was to assess predictors of

Table 1. Patient demographics and characteristics at baseline\*

Characteristics	All MTX patients	EULAR response groups		
		Good	Moderate	No response
EULAR response/total with BL pain data	1,063/1,241			
EULAR response groups, no. (%)		421 (40)	402 (38)	240 (23)
Remaining pain, no. (%)	615 (58)	123 (29)	280 (70)	198 (83)
Demographics				
Age, years	56 (46–63)	58 (47–64)	52 (44–61)	55 (46–62)
Female, no. (%)	862 (69)	278 (66)	296 (74)	170 (71)
Current smokers, no. (%)	321 (30)†	95 (26)‡	100 (28)‡	73 (37)‡
Baseline disease characteristics				
Rheumatoid factor positive, no. (%)	810 (67)§	269 (66)¶	254 (65)¶	164 (69)¶
Anti-CCP antibody positive, no. (%)	578 (47)	217 (52)	181 (45)	94 (39)
Symptom duration at start, days	166 (111–246)	160 (111–240)	165 (106–246)	177 (122–247)
DAS28	5.4 (4.6–6.2)	5.1 (4.5–5.8)	5.8 (5.1–6.5)	5.1 (3.9–6.1)
HAQ	1.0 (0.6–1.5)	1 (0.6–1.3)	1.2 (0.7–1.6)	1 (0.6–1.3)
SJC28	9 (6–13)	9 (6–13)	10 (7–15)	8 (5–12)
TJC28	8 (4–12)	7 (4–11)	10 (6–15)	7 (2–11)
ESR	28 (16–46)	26 (14–40)	34 (20–50)	25 (12–49)
CRP	16 (8–36)	15 (8–31)	18 (9–47)	14 (8–38)
PGA	52 (34–70)	50 (31–68)	59 (42–75)	47 (23–66)
Patient pain assessment	54 (35–71)	52 (34–70)	59 (40–73)	49 (28–71)
Therapy				
DMARD (MTX), no. (%)	1241 (100)	421 (100)	402 (100)	240 (100)
MTX duration, weeks	14 (13–16)	14 (13–16)	14 (13–16)	14 (13–15)
Prednisolone, no. (%)	523 (42)	208 (49)	143 (36)	73 (30)
NSAID, no. (%)	694 (56)	217 (52)	249 (62)	141 (59)

\* Values are median (interquartile range), unless indicated otherwise. EULAR = European League Against Rheumatism; MTX = methotrexate; BL = baseline; anti-CCP = anti-cyclic citrullinated peptide; DAS28 = Disease Activity Score in 28 joints; HAQ = Health Assessment Questionnaire; SJC28 = swollen joint count in 28 joints; TJC28 = tender joint count in 28 joints; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; PGA = patient global assessment; DMARD = disease-modifying antirheumatic drug; MTX = methotrexate; NSAID = nonsteroidal antiinflammatory drug.

† Missing data for current smoking (n = 171); EULAR response/total no. with baseline data (n = 921/1,070).

‡ Missing data for current smoking in EULAR response groups: good response (n = 53), moderate response (n = 49), no response (n = 40).

§ Missing data for rheumatoid factor (n = 31); EULAR response/total no. with baseline data (n = 1,042/1,210).

¶ Missing data for rheumatoid factor in EULAR response groups: good response (n = 11), moderate response (n = 8), no response (n = 2).

remaining pain despite a good clinical response to treatment (Table 2). In the EULAR good-responder group (n = 421), more disability at baseline was associated with remaining pain (HAQ; adjusted OR 2.2 [95% CI 1.4–3.4] per unit increase), as was less inflammation at baseline (erythrocyte sedimentation rate [ESR]; adjusted OR 0.81 [95% CI 0.70–0.93] per 10-mm increase). In addition, higher PGA was associated with remaining pain, whereas swollen joint count in 28 joints (SJC28), TJC28, CRP level, current smoking, rheumatoid factor, and anti-CCP antibody positivity were not associated with remaining pain (Table 2).

Since EULAR response criteria are based on the DAS28, which in turn includes the TJC28 and may thus correlate with pain measurements, it is of value to confirm possible associations between baseline parameters and remaining pain, in addition to having an outcome measure that is independent of pain. At followup, CRP levels did not correlate with levels of pain or PGA on VAS scales (results not shown). Thus, we performed similar analyses as for EULAR good response, using low inflammatory activity, defined as a CRP level <10 mg/liter, at 3-months followup. The combination of VAS pain >20 mm concomitant with low inflammatory activity at 3-months followup was found in

37% of all patients. In this group, remaining pain was significantly associated with baseline HAQ (OR 1.45 [95% CI 1.17–1.79]) and baseline ESR (OR 0.86 [95% CI 0.81–0.91]), adjusted for age and sex. In addition, remaining pain was significantly associated with the following baseline parameters: CRP level (adjusted OR 0.83 [95% CI 0.79–0.88]), PGA (adjusted OR 1.1 [95% CI 1.05–1.16]), and TJC28 (adjusted OR 1.04 [95% CI 1.01–1.06]). No association was found between remaining pain and baseline SJC28, current smoking, DAS28, rheumatoid factor, or anti-CCP antibody positivity.

**Predictors of increased pain.** Increased pain during the treatment period was defined as a higher VAS pain value at 3-months followup compared to baseline. In the whole cohort, 19% reported increased pain overall, with 9% in the good-response group, 15% in the moderate-response group, and 45% in the no-response group.

Increased pain in the whole cohort was associated with the following baseline parameters: lower disability (HAQ), lower ESR, lower PGA, current smoking, lower SJC28, lower TJC28, and lower DAS28 (Table 3). Risk factors for increased pain at followup within the EULAR good-response group are shown in Table 3.

**Table 2. Risk factors for remaining pain after 3 months of initial methotrexate therapy among all RA patients and among the subset fulfilling EULAR good response\***

Baseline factors	All patients†			EULAR good response‡		
	OR	95% CI	P	OR	95% CI	P
Sex (female/male)	0.87	(0.67–1.13)	0.309	0.70	(0.45–1.01)	0.108
Age, years	0.98	(0.97–0.99)	< 0.001§	0.99	(0.97–1.01)	0.140
HAQ (per unit increase)	2.17	(1.74–2.71)	< 0.001§	2.2	(1.4–3.4)	< 0.001§
ESR (per 10-mm increase)	0.92	(0.7–1.2)	0.533	0.81	(0.70–0.93)	0.022§
PGA (per 10-mm increase)	1.02	(1.01–1.02)	< 0.001§	1.15	(1.05–1.27)	0.003§
CRP level (per 10-mg/dl increase)	1.05	(1.02–1.10)	< 0.001§	0.90	(0.81–1.00)	0.061
Anti-CCP antibody positivity (yes/no)	0.84	(0.66–1.07)	0.149	1.16	(0.72–1.86)	0.54
RF positivity (yes/no)	1.00	(0.77–1.29)	0.986	1.09	(0.65–1.81)	0.752
SJC28 (per 1 joint increase)	1.01	(0.99–1.03)	0.38	1.00	(0.95–1.04)	0.86
TJC28 (per 1 joint increase)	1.05	(1.03–1.07)	< 0.001§	1.01	(0.97–1.06)	0.63
Current smoking (yes/no)	0.86	(0.65–1.15)	0.31	0.62	(0.33–1.16)	0.13
DAS28 (per unit increase)	1.32	(1.19–1.48)	< 0.001§	0.95	(0.76–1.19)	0.642

\* Odds ratio (OR) with 95% confidence interval (95% CI) for each variable is adjusted for age and sex. RA = rheumatoid arthritis; EULAR = European League Against Rheumatism; HAQ = Health Assessment Questionnaire; ESR = erythrocyte sedimentation rate; PGA = patient global assessment; CRP = C-reactive protein; anti-CCP = anti-cyclic citrullinated peptide; RF = rheumatoid factor; SJC28 = swollen joint count in 28 joints; TJC28 = tender joint count in 28 joints; DAS28 = Disease Activity Score in 28 joints.  
† Remaining pain no./total (%): 615/1,063 (58).  
‡ Remaining pain no./total (%): 123/421 (29).  
§ Significant.

## DISCUSSION

In this study on an unselected early RA population, we found that a majority of patients receiving standard care with MTX monotherapy initiated at diagnosis have remaining pain 3 months later, despite the fact that 40% had a good clinical response. Moreover, remaining pain was present in one-third of patients with a good EULAR response to therapy and in two-thirds of patients with moderate or no response. These data show that significant pain after good clinical response is common in early RA and support the need for more intensive pain control early in the disease.

Our first aim was to assess the presence of remaining pain in RA after the initial antirheumatic treatment. Earlier investigations defining significant pain in RA are scarce, but a previous study by Wolfe and Michaud (9), in a large cohort of patients using a multivariate regression analysis, concluded that the best cutoff point for having pain above an acceptable level on the VAS scale was >2.0 cm (20 on a 100-mm scale). A higher cutoff, defined as the level of definite unacceptable pain, was described by Tubach et al (12) (patient-acceptable symptom state [PASS]; VAS pain >41 mm) and validated after 4 weeks of nonsteroidal antiinflammatory drug treatment in RA and

**Table 3. Risk factors for increased pain after 3 months of initial methotrexate therapy among all RA patients and among the subset fulfilling EULAR good response\***

Baseline factors	All patients†			EULAR good response‡		
	OR	95% CI	P	OR	95% CI	P
Sex (female/male)	0.78	(0.56–1.08)	0.135	0.47	(0.23–0.98)	< 0.05§
Age, years	0.99	(0.98–1.01)	0.59	1.0	(0.98–1.03)	0.77
HAQ (per unit increase)	0.57	(0.43–0.75)	< 0.001§	0.25	(0.12–0.54)	< 0.001§
ESR (per 10-mm increase)	0.90	(0.84–0.97)	0.006§	0.88	(0.72–1.08)	0.22
PGA (per 10-mm increase)	0.83	(0.77–0.88)	< 0.001§	0.79	(0.68–0.92)	0.003§
CRP (per 1-mg/dl increase)	0.97	(0.92–1.01)	0.23	0.95	(0.80–1.12)	0.57
Anti-CCP antibody positivity (yes/no)	0.97	(0.71–1.31)	0.82	1.36	(0.66–2.72)	0.39
RF positivity (yes/no)	0.91	(0.66–1.26)	0.56	0.68	(0.34–1.37)	0.28
SJC28 (per 1 joint increase)	0.96	(0.93–0.99)	0.004§	0.94	(0.87–1.01)	0.09
TJC28 (per 1 joint increase)	0.97	(0.95–0.99)	0.037§	0.90	(0.83–0.99)	0.02§
Current smoking (yes/no)	1.54	(1.09–2.18)	0.015§	1.94	(0.90–4.18)	0.91
DAS28 (per unit increase)	0.71	(0.62–0.81)	< 0.001§	0.53	(0.36–0.79)	0.002§

\* Odds ratio (OR) with 95% confidence interval (95% CI) for each variable is adjusted for age and sex. See Table 2 for additional definitions.  
† Increased pain no./total (%): 204/1,063 (19).  
‡ Increased pain no./total (%): 36/421 (9).  
§ Significant.

other rheumatic diseases. For the current study, the intention was to use a simple, clinically measurable cutoff reflecting significant remaining pain, sensitive enough to reflect potential pain above an acceptable level, also present in patients with a good clinical response in early RA. Therefore we chose to use the cutoff described by Wolfe and Michaud (9). The proportion of patients in the present study fulfilling PASS 41 and VAS 20 pain cutoff is shown in Supplementary Table 1 (available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.22790/abstract>). There have also been other reports using specifically designed indices to discriminate between inflammation and pain impact on disease activity and clinical response. McWilliams et al (13) used a newly developed index called the DAS28-P, which includes only the patient-reported components of the DAS28 (TJC28 and PGA) as a marker of patient-reported pain. Using this index, they found incomplete improvement in pain in a majority of the patients with early RA at 12-months followup (13), which is in line with our results, although our followup time was shorter.

Our finding that 58% of early RA patients have remaining pain after 3 months of standard treatment provides an important message concerning the limitations of the present treatment strategies. In this respect, our data confirm and extend previous data from Taylor et al (3), who reported in 2010 that a majority of the RA patients studied in Europe (60%) and the US (65%) reported discontent with pain management. That study notably included both established and early RA, whereas our patient cohort consisted only of early RA patients included at diagnosis and who thereafter received their first DMARD treatment with MTX. Thus, directly comparing results from the 2 different cohorts of patients is difficult. Nevertheless, the similar frequencies of pain with the earlier investigations indicate that our cutoff is adequate and may mirror a general manifestation of remaining pain after use of modern antirheumatic treatment and that these manifestations are present both early and late during treatment.

We also wanted to determine whether or not there is a discrepancy between decrease of inflammation during treatment and change of concomitant pain. In this regard, we aimed to isolate the remaining condition of pain in spite of a clinically well-defined good effect of the treatment. In order to increase the homogeneity of the studied patient cohort, we included only patients from the early arthritis register who were initially treated with the first-line DMARD, MTX. We chose 3 months as a followup, since this time period was earlier defined as adequate time for assessment of relevant clinical response after MTX treatment in RA (14), and we note in this observational cohort (EIRA) that nonresponders at 3 months often receive other or additional treatment at that time point, while most good responders remained on the same treatment (15). The rates of EULAR clinical good response in the present study were in line with earlier investigations (14,15). Since the data were collected in a register in an unselected population of early RA patients, as part of standard care, this study should reflect the clinical setting and have a high external validity. Thus, relating to a clinical good response at the 3-month evaluation, the rheumatolo-

gist's decision of further treatment should probably be to continue with the current therapy and not change the antirheumatic treatment.

Interestingly we found that in spite of a good inflammatory response to MTX after 3 months, almost one-third of these patients reported remaining pain to an extent that has previously been defined as above an acceptable level to the individual. This finding is important, and consistent with the notion that even after a good clinical response, rheumatologists may face several challenges in how to optimally treat the patient with RA to achieve good health and quality of life. Today, the aim for inflammatory control has been a hallmark for all newly developed antirheumatic therapies and has also shown association with a better long-term outcome and less functional impairment. The observational data from the present and other studies indicate that emphasis should also be laid on better strategies for treatment of concomitant pain during the course of arthritis. Moreover, these results emphasize that the impact on disease activity and pain do not necessarily occur in parallel, and that the effects of RA and treatments for RA on pain have to be evaluated separately.

Given the above, we then investigated possible predictors for remaining pain in spite of a good clinical response. The strong association between remaining pain and functional impairment at baseline was not a surprising finding, as disability and pain are very strongly correlated (16). Previous data have implicated disability as a strong marker for chronic pain (17), and research earlier showed that RA patients with concomitant fibromyalgia display increased disability compared to patients without fibromyalgia (18,19). From our data, we could not detect prevalence of fibromyalgia, which was not in the scope of the study, but earlier investigations have shown that the prevalence of chronic widespread pain may be increased by 10-fold in RA (18).

Furthermore, there was an inverse association between remaining pain and baseline level of the objective parameter ESR, indicating that patients with low systemic inflammation at baseline may differ from patients with initially high inflammation concerning the ability to respond to DMARD treatment with decreased pain. Baseline pain and PGA were also predictive for remaining pain, and a substantial portion of these patients may already have widespread pain at the time of diagnosis. This pain will be to a large extent independent of systemic and joint inflammation and therefore not expected to decrease with DMARD treatment. Similar findings that high baseline pain predicts later development of widespread pain in RA was reported recently (17). In addition, and in line with our findings, there were lower baseline levels of the ESR and CRP level in the RA group that had developed widespread pain, compared to other RA patients (17). Whereas the remaining pain patients of the present study may exhibit several features for concomitant widespread pain, they also displayed significant decrease of the ESR, SJC28, and TJC28 at 3 months (results not shown), confirming the presence of a reversible joint inflammation at diagnosis. Moreover, anti-CCP antibodies and rheumatoid factor status of the remaining pain patients were not different from other good responders, making a potential misdiagnosis

between RA and fibromyalgia (for discussion, see reference [20]) in patients with chronic pain and joint tenderness less likely in this context.

Due to the involvement of subjective symptoms and pain on disease activity and the DAS28, we sought to challenge our results using a CRP level <10 mg/liter, together with remaining pain at 3 months as an objective marker of resulting inflammation after treatment. Also this definition of remaining pain was significantly associated with baseline high disability and low systemic inflammation, as measured both with the CRP level and ESR, as well as a high number of tender, but not swollen, joints. Altogether, these data confirm the results from good responders and strengthen the potential discrepancy between therapy-induced changes in inflammation on one hand, and pain on the other.

It has been suggested previously that the development of generalized and widespread pain in RA may be in large part related to the inflammatory impact on the peripheral nerves (21). Thus, inflammatory actions on nerve endings, including nociceptive fibers, may result in long-term sensitization, which contributes to chronic pain conditions. Proinflammatory cytokines like tumor necrosis factor (TNF) and interleukin 6 (IL-6) are both of specific importance in RA pathogenesis, and specific cytokine blockade has been shown beneficial (22,23). Both TNF and IL-6 also affect pain thresholds in experimental arthritis (24,25), as well as long-term sensitization of joint nociceptors (26). In RA, general hyperalgesia to mechanical and thermal stimuli have been reported (27), and decreased pain thresholds over nonpainful areas were also shown in established RA, but not in early disease, suggesting the impact of long-term inflammation in this context (28). Also in the present study, inflammation-induced changes on pain regulation may be of importance for the results.

Another potential explanation for remaining pain in RA may be subclinical inflammation resulting in persistent joint pain. In the present study, a clear distinction between generalized pain due to peripheral and central sensitization, and subclinical inflammatory pain after treatment, was not possible, but our data indicate that the latter should not contribute substantially to the remaining pain in the group with good clinical response. The median SJC28 after treatment in this group was very low, and the data clearly showed that overall higher baseline inflammation correlated to higher inflammation after treatment (results not shown). We would then expect that subclinical inflammatory pain after treatment should also be predicted by high baseline inflammation. However, remaining pain in the good-response group was associated with low, not high, inflammation at baseline.

Thus, our data instead indicate that patients who will later develop a remaining pain phenotype may be more sensitive to the influence of inflammation on baseline pain features, i.e., a low grade of general inflammation can result in high pain levels. Hypothetically, in these patients, possible inflammatory actions on nociceptive fibers may lead to sensitization, which may be long-lasting and further contribute to development of a chronic pain condition. The antirheumatic treatment suppresses joint inflammation, and systemic inflammatory parameters

decrease in general. However, if dysregulated pain thresholds, hyperalgesia, and allodynia have been established, these conditions are usually not reversible by immune suppression. Notably, similar patterns have been shown in models of transient experimental arthritis, where the initial joint inflammation caused a long-lasting pain-like behavior, persisting after the inflammation had resolved and also unresponsive to antiinflammatory drugs (29). Likewise, remaining pain based on peripheral sensitization in RA patients is a challenge for therapy, where further immune suppression is unlikely to have pain-relieving effects.

Whereas there was a clear decrease of median VAS pain after 3 months in the whole group, we could detect an increase in pain in almost one-fifth of the patients. In these patients, there was a significant downregulation of both tender and swollen joints (results not shown), confirming that increased pain was in the majority of patients not an indication of a worse clinical response. Increased pain with no accompanying inflammation in this context may be explained by several reasons. These include early development of joint destructions, development of enthesitis, and development of widespread pain, or fibromyalgia.

Development of pain-causing early joint destructions should be marginal during the relatively short followup time of 3 months in the present study (30). Enthesitis and other complications of a higher musculoskeletal load may potentially lead to increased pain, but enthesitis-related pain is at least to some extent reversible with steroid injections and physiotherapy. Widespread pain is, as discussed earlier, quite common in RA and often causes significant impact on quality of life (18). Interestingly, both in the whole group and the patients with good clinical response in the present study, increased pain was predicted by low baseline TJC28 and low VAS for PGA. These findings indicate that patients with increased pain were unlikely to have concomitant widespread pain or fibromyalgia at diagnosis. Instead, a significant portion of these patients during disease course may have developed peripheral pain sensitization, which is refractory to both antirheumatic and antiinflammatory therapy. Another contributing factor in this respect may be maladaptive pain coping, earlier described in RA (31). Altogether, these data illustrate that not only patients with a fibromyalgia-like disease at diagnosis are at risk for development of treatment-resistant pain conditions, and rheumatologists should closely follow pain assessments in all patients with RA. Moreover, attempts to improve coping strategies for pain may be of value as additional therapeutic strategies to antirheumatic and pain treatment in early RA.

The connection between increased pain and smoking is interesting and confirms the earlier studies showing associations between smoking and pain (13,32). In line with this association, recent studies, including one based on the present study population, also show that smoking is connected with a worse EULAR response to both MTX and biologic treatment and influenced both pain-related and other DAS28 components (15,33). The lack of association between smoking and increased pain in the group with a clinical good response may be related to a lower prevalence of smoking (7% versus 25% in the whole

cohort), which is also in line with previous data (15). In addition, there was an association between increased pain and male sex. The latter may be related to lower baseline VAS pain in males, as previously shown (34).

Study limitations have to be considered when interpreting our results. Some additional confounding factors were not possible to control for, as they were not a part of the original program in the early arthritis followup. For example, depression is common in RA (35), and there is a confirmed strong association between pain and depressive symptoms (36). Moreover, several studies have shown that depression and anxiety may impact clinical response to antirheumatic treatment (37). However, the authors note that these effects could have been mainly due to parameters such as global health and pain, which comprises a large component of disease activity (37). Since we did not have any data on the prevalence of depression and anxiety in the present study, we cannot exclude an influence of these factors. However, due to the registry-based approach, we believe that a major impact of such effects on the results would be limited. Concerning potential influence of fibromyalgia at baseline on prediction of remaining pain, a sensitivity analysis excluding patients with VAS pain >70 at baseline was performed, and this adjustment did not change the results (results not shown). Thus, baseline fibromyalgia should not be a major contributing factor in this context.

Another assumption may be that prednisolone treatment could have affected the results, but adjustment for prednisolone treatment did not change any of the findings concerning predictors for remaining pain (data not shown). Likewise, smoking is a known predictor of response, but adjustment for smoking also did not alter the results (results not shown), and we could find no association between smoking and remaining pain despite good clinical response (results not shown). Taken together, we could not find evidence for smoking as an independent risk factor for remaining pain.

In conclusion, we have found a high prevalence of remaining pain in patients with early RA treated with MTX. Moreover, one-third of the patients with a clinical good response to the treatment reported remaining pain. Remaining pain in spite of good clinical response was associated with high disability and low inflammation at baseline. These results are in line with the hypothesis that a subgroup of early RA patients exhibits pain that is not inflammatory mediated, and where non-RA causes and alternative treatment strategies need to be considered.

#### AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Lampa had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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