RHEUMATOLOGY

Rheumatology 2023;62:124–134
https://doi.org/10.1093/rheumatology/keac294
Advance access publication 18 May 2022

Original article

ACPA-negative and ACPA-positive RA patients achieving disease resolution demonstrate distinct patterns of MRI-detected joint-inflammation

Marloes Verstappen[1], Xanthe M. E. Matthijssen [1], Sean E. Connolly[2], Michael A. Maldonado[2], Tom W. J. Huizinga[1] and Annette H. M. van der Helm-van Mil[1,3]

Abstract

Objectives. Although sustained DMARD-free remission (SDFR; sustained absence of clinical-synovitis after DMARD-discontinuation) is increasingly achievable in RA, prevalence differs between ACPA-negative (40%) and ACPA-positive RA (5–10%). Additionally, early DAS remission ($DAS_{4months}<1.6$) is associated with achieving SDFR in ACPA-negative, but not in ACPA-positive RA. Based on these differences, we hypothesized that longitudinal patterns of local tissue inflammation (synovitis/tenosynovitis/osteitis) also differ between ACPA-negative and ACPA-positive RA patients achieving SDFR. With the ultimate aim being to increase understanding of disease resolution in RA, we studied MRI-detected joint inflammation over time in relation to SDFR development in ACPA-positive RA and ACPA-negative RA.

Methods. A total of 198 RA patients (94 ACPA-negative, 104 ACPA-positive) underwent repeated MRIs (0/4/12/24 months) and were followed on SDFR development. The course of MRI-detected total inflammation, and synovitis/tenosynovitis/osteitis individually were compared between RA patients who did and did not achieve SDFR, using Poisson mixed models. In total, 174 ACPA-positive RA patients from the AVERT-1 were studied as ACPA-positive validation population.

Results. In ACPA-negative RA, baseline MRI-detected inflammation levels of patients achieving SDFR were similar to patients without SDFR but declined 2.0 times stronger in the first year of DMARD treatment [IRR 0.50 (95% CI; 0.32, 0.77); $P<0.01$]. This stronger decline was seen in tenosynovitis/synovitis/osteitis. In contrast, ACPA-positive RA-patients achieving SDFR, had already lower inflammation levels (especially synovitis/osteitis) at disease presentation [IRR 0.45 (95% CI; 0.24, 0.86); $P=0.02$] compared with patients without SDFR, and remained lower during subsequent follow-up ($P=0.02$). Similar results were found in the ACPA-positive validation population.

Conclusion. Compared with RA patients without disease resolution, ACPA-positive RA patients achieving SDFR have less severe joint inflammation from diagnosis onwards, while ACPA-negative RA patients present with similar inflammation levels but demonstrate a stronger decline in the first year of DMARD therapy. These different trajectories suggest different mechanisms underlying resolution of RA chronicity in both RA subsets.

Key words: RA, anti-citrullinated protein antibodies, DMARD-free remission, drug-free remission, imaging

CLINICAL SCIENCE

Rheumatology key messages

- ACPA-negative RA patients achieving SDFR demonstrate a stronger decline in MRI-detected joint inflammation after DMARD start.
- ACPA-positive RA patients achieving SDFR have significantly lower MRI-detected inflammation scores from diagnosis onwards.
- Distinct MRI patterns in ACPA-negative and ACPA-positive RA patients achieving SDFR suggest different mechanisms underlying disease resolution.

[1]Department of Rheumatology, Leiden University Medical Centre, Leiden, The Netherlands, [2]Bristol-Myers Squibb, Princeton, NJ, USA and [3]Department of Rheumatology, Erasmus Medical Centre, Rotterdam, The Netherlands

Submitted 4 March 2022; accepted 7 May 2022

Correspondence to: Marloes Verstappen, Department of Rheumatology, Leiden University Medical Centre, P.O. Box 9600, 2300 RC Leiden, The Netherlands. E-mail: m.verstappen@lumc.nl

Introduction

Sustained DMARD-free remission (SDFR), the sustained absence of clinical synovitis after complete discontinuation of all DMARDs, is currently the best proxy for cure in RA. It has been observed that, in response to improved treatment strategies during the last two decades, SDFR prevalence increased among ACPA-positive RA patients, whereas prevalence remained similar in ACPA-negative RA [1]. Nonetheless, absolute SDFR percentages remain significantly higher within ACPA-negative RA (40%) compared with ACPA-positive RA (5–10%) [2]. The mechanisms underlying this disease resolution are unknown.

In order to understand which RA patients are most likely to achieve SDFR, measures of inflammation (number of swollen/tender joints, acute-phase reactants, imaging) at the time of diagnosis have been studied in relation to SDFR development, while none appeared to be associated with this outcome [2–4]. A recent study which stratified for ACPA status and studied the course of swollen joint counts (SJC) and disease activity after DMARD-initiation in relation to SDFR, demonstrated that ACPA-negative RA patients achieving SDFR were characterized by early DAS remission, predominantly caused by a stronger decline in SJC [5]. In addition, these patients also had a stronger decline in serum levels of serum amyloid A (SAA), CRP, matrix-metalloproteinase (MMP)-1 and MMP-3 after DMARD start [5, 6]. In contrast, in ACPA-positive RA, these associations were not found. These findings possibly suggest that mechanisms underlying disease-resolution in both types of RA might be inherently different. More specifically, the more prominent decline in SJC as well as in serum markers derived from joint tissue (MMP-1, MMP-3), may imply differences at joint level in ACPA-negative RA patients achieving SDFR compared with those who do not. Although serial histological or tissue-based sequencing studies in relation to this disease outcome could be informative to further unravel the etiopathology of SDFR, this is currently not feasible as biopsy of small joints is clinically challenging and the burden for patients undergoing repeated biopsies is high. Moreover, for ACPA-positive RA, so far, no associations with achieving SDFR have been identified that can generate a specific hypothesis.

MRI is sensitive in detecting inflammation of synovium, tenosynovium and bone [7–9], and is feasible for longitudinal studies. To date, serial MRI studies in relation to SDFR development have not been performed. With the ultimate aim being to increase understanding of disease resolution in RA, we studied the course of MRI-detected inflammation in RA patients who did and did not achieve SDFR in both ACPA-positive and ACPA-negative RA. We hypothesized that the trajectories of local MRI inflammation over time differ in RA patients achieving SDFR compared with those who do not, and that these trajectories might also be different in ACPA-positive and ACPA-negative RA patients achieving SDFR.

Methods

Patient population

For this study, RA patients were retrieved from two patient populations: the Leiden Early Arthritis Clinic (EAC) (an observational inception cohort), and the AVERT-1 (a randomized controlled trial population) which served as validation population.

Leiden early arthritis cohort

In short, the Leiden-EAC is an inception cohort including all patients presenting with recent-onset arthritis with a symptom duration $\leq$2 years and has been previously described [10]. From all consecutive RA patients included in the Leiden EAC between August 2010 and February 2015 ($n = 408$), and treated with DMARDs, 198 RA patients underwent repeated MRIs during follow-up and were selected for this study (Supplementary Fig. S1, available at *Rheumatology* online). RA was stringently defined by a clinical diagnosis of RA by an experienced rheumatologist, plus fulfilment of the 1987 and/or 2010 criteria for RA [11, 12]. Patients diagnosed with conditions other than RA (e.g. reactive arthritis/psoriatic arthritis/inflammatory osteoarthritis), or who had a high suspicion on these diagnoses, were excluded. Baseline characteristics of RA patients who did and did not undergo repeated MRIs in this specific inclusion period did not remarkably differ (Supplementary Table S1, available at *Rheumatology* online).

Research visits took place at baseline, after 4 months and annually thereafter. During these visits, joint counts were performed, disease-activity scores calculated, laboratory measurements were performed and questionnaires filled out. Visits to the treating rheumatologists were more frequent, as often as it was found necessary.

Treatment strategies in the Leiden EAC have been previously described [1]. In brief, RA patients were promptly treated with conventional synthetic DMARDs (csDMARD) after diagnosis, in which MTX was first choice. Subsequently, DAS-steered treatment adjustments were made. When initial treatment failed, another csDMARD was initiated or added. A biological DMARD (bDMARD) was allowed when RA patients failed $\geq$2 csDMARDs. When low disease activity (DAS44 $<$2.4) was sustained, and clinical synovitis was absent, treatment could be tapered and eventually discontinued. Guidelines were to taper DMARDs in case of DAS44 $<$2.4 in subsequent visits to the rheumatologist; decisions on DMARDs cessation were taken in shared decision making between rheumatologists and patients.

AVERT-1

Because SDFR prevalence in ACPA-positive RA patients is relatively low, statistical power can be limited to detect differences between ACPA-positive RA patients achieving SDFR and patients who do not. We therefore studied ACPA-positive RA patients from the AVERT-1 trial as ACPA-positive validation population [13]. The AVERT-1

is a randomized controlled-trial with a 12-month, double-blind treatment period in which ACPA-positive RA patients were randomized to receive abatacept plus MTX, abatacept monotherapy or MTX monotherapy [13]. In case of DAS28CRP <3.2 after the 12-month treatment period, patients entered a 12-month withdrawal period in which all DMARD treatment was tapered and patients were followed for 12 months (monthly visits). In case of a flare (defined as doubling of SJC and TJC relative to month 12, increase in DAS28CRP ≥ 1.2 or investigators' judgement of RA flare) patients entered the open-label treatment (abatacept + MTX) [13]. Of the 351 patients initially randomized, 174 entered the withdrawal period and underwent repeated MRIs during follow-up, thus were selected as ACPA-positive validation population for this study.

Sustained DMARD-free remission

Sustained DMARD-free remission (SDFR) was in both cohorts defined as absence of clinical synovitis (swollen joints at physical examination) for minimally one year after cessation of DMARD treatment, and the subsequent follow-up thereafter. RA patients experiencing a flare (defined as reoccurrence of clinical synovitis) after SDFR development were also included in the non-SDFR group. These stringent definitions were chosen to ensure sustainability of DMARD-free remission. Medical files of the Leiden EAC patients were studied on occurrence of SDFR during follow-up until September 2021.

MRI

In the Leiden EAC, MRIs were performed at baseline (before DMARD initiation) and after 4, 12 and 24 months. MCP (2–5) and wrist joints of the most painful side at baseline (dominant side in case of symmetric symptoms) were imaged using a contrast-enhanced 1.5 T MRI (GE Healthcare, WI, USA). Follow-up MRIs were performed at the side of the baseline MRI. MRIs were scored for synovitis, osteitis and erosions in line with RAMRIS (Rheumatoid Arthritis Magnetic Resonance Imaging Score) and tenosynovitis as described by Haavardsholm *et al.* by one reader, with known time order, blinded for any clinical data. Intrareader reliability was excellent (Supplementary Table S2, available at *Rheumatology* online) [14, 15]. Scores were summed per inflammatory feature, per patient. Total inflammation scores were calculated by the summation of the synovitis, tenosynovitis and osteitis scores. Erosion scores were also studied. Supplementary Data S1, available at *Rheumatology* online, provides a detailed scan and scoring protocol.

In the AVERT-1, MRIs were conducted at baseline (side with most clinically inflamed joints), 6, 12, 18 and 24 months. MCP (1–5) and wrist joints were imaged using a contrast-enhanced 1.5 T MRI. MRIs were scored for synovitis, osteitis and erosions by two readers also according to the RAMRIS method. Inter-reader reliability was excellent (Supplementary Data S2, available at *Rheumatology* online). Synovitis, osteitis and erosions scores were based on the average of both readers. Because the MRIs in the AVERT-1 were not scored for tenosynovitis, total MRI inflammation score included the sum of the synovitis and osteitis scores. Supplementary Data S2, available at *Rheumatology* online, provides a detailed scan and scoring protocol.

Statistical analyses

Baseline characteristics were compared using student's *t test* or Mann–Whitney *U* test, as appropriate.

The course of total MRI-detected joint inflammation, and its individual components (osteitis, synovitis, tenosynovitis) were analysed using Poisson linear mixed models considering MRI scores should be regarded as count data. MRI trajectories were compared between ACPA-positive and ACPA-negative RA patients who did and did not achieve SDFR. In these models, levels of MRI inflammation over time were included as dependent variable and the grouping variable [SDFR (yes/no) and ACPA-positive (yes/no)] as covariate. Because it is known from previous research that MRI inflammation changes most during the first year after diagnosis and less during the second year [9, 16], linear splines were used to model the first and second year of follow-up separately. Poisson mixed-models incorporate log transformation, and therefore results are represented on a multiplicative scale, i.e. as incidence risk ratios (IRR) between the SDFR and non-SDFR patients. In this, an IRR below 1 indicates relatively less MRI inflammation in RA patients achieving SDFR compared with RA patients who did not achieve SDFR, whereas an IRR above 1 indicates more MRI inflammation. STATA(V16) was used. *P*-values <0.05 were considered statistically significant.

Ethics approval and consent to participate

Leiden Early Arthritis Clinic: 'Commisie Medische Ethiek' of the Leiden University Medical Centre (B19.008). All studied patients gave written informed consent. AVERT-1: The study protocol was approved by the Institutional Review Board or Independent Ethics Committee at each site of participation.

Results

Study population

In total, 198 RA patients from the Leiden EAC were studied; the mean age was 56 years, 65% were female, median symptom duration was 14 weeks and 53% were ACPA-positive (Table 1). Median follow-up was 6.1 years (IQR 4.2–7.4 years). Among the ACPA-negative RA population ($n = 94$), 51% achieved SDFR after median 3.2 years of follow-up (IQR 2.4–4.4 years). Among the ACPA-

Table 1 Baseline characteristics study populations, stratified for SDFR development

(i) ACPA-negative RA	Total ($n = 94$)	No SDFR ($n = 46$)	SDFR ($n = 48$)
Age (years), mean (S.D.)	61 (15)	57 (13)	62 (13)
Females, %	66	61	65
Symptom dur. (weeks), med (IQR)	14 (6–27)	17 (8–39)	13 (5–22)
RF-positive, %	34	50	23[a]
DAS28CRP at baseline, med (IQR)	4.6 (4.0–5.3)	4.5 (3.7–5.2)	4.6 (4.2–5.8)
SJC at baseline, (0–28), med (IQR)	6 (3–11)	4 (2–8)	6 (2–11)
TJC at baseline, (0–28), med (IQR)	9 (4–16)	7 (2–12)	7 (3–12)
CRP (ug/l), med (IQR)	28 (11–39)	7 (3–21)	18 (4–27)
VAS (0–100 mm), med (IQR)	50 (30–70)	40 (30–68)	50 (30–80)
HAQ-DI, med (IQR)	1.0 (0.6– 1.5)	1.0 (0.6–1.4)	1.1 (0.6–1.5)
(ii) ACPA-positive RA	**Total ($n = 104$)**	**No SDFR ($n = 92$)**	**SDFR ($n = 12$)**
Age (years), mean (S.D.)	55 (14)	54 (17)	51 (14)
Females, %	65	67	50
Symptom dur. (weeks), med (IQR)	15 (7–35)	15 (7–35)	15 (9–26)
RF-positive, %	85	84	92
DAS28CRP at baseline, med (IQR)	3.9 (3.3–4.7)	4.0 (3.3–4.8)	3.5 (2.9–4.2)[a]
SJC at baseline, (0–28), med (IQR)	5 (2–8)	3 (1–6)	2 (1–3)
TJC at baseline, (0–28), med (IQR)	7 (3–11)	4 (2–8)	2 (1–5)
CRP (ug/l), med (IQR)	7 (3–15)	8 (3–15)	4 (3–6)
VAS (0 -100 mm), med (IQR)	40 (20–70)	40 (20–70)	50 (10–70)
HAQ-DI, med (IQR)	0.9 (0.4–1.5)	0.9 (0.4–1.5)	0.8 (0.1–1.1)
(iii) ACPA-positive validation-population	**Total ($n = 174$)**	**No SDFR ($n = 160$)**	**SDFR ($n = 14$)**
Age (years), mean (S.D.)	46 (12)	46 (12)	46 (12)
Females, %	78	78	71
Symptom dur. (weeks)[b], med (IQR)	—	—	—
RF-positive, %	96	95	100
DAS28CRP at baseline, med (IQR)	5.2 (4.5–6.2)	5.4 (4.6–6.3)	4.4 (3.4–5.0)[a]
SJC at baseline, (0–28), med (IQR)	9 (5–17)	10 (5–18)	5 (3–6)[a]
TJC at baseline, (0–28), med (IQR)	12 (7–20)	12 (8–20)	8 (5–10)[a]
CRP (ug/l), med (IQR)	8 (2–20)	9 (3–21)	3 (1–8)[a]
VAS (0–100 mm), med (IQR)	62 (46–76)	64 (47–78)	55 (31–61)[a]

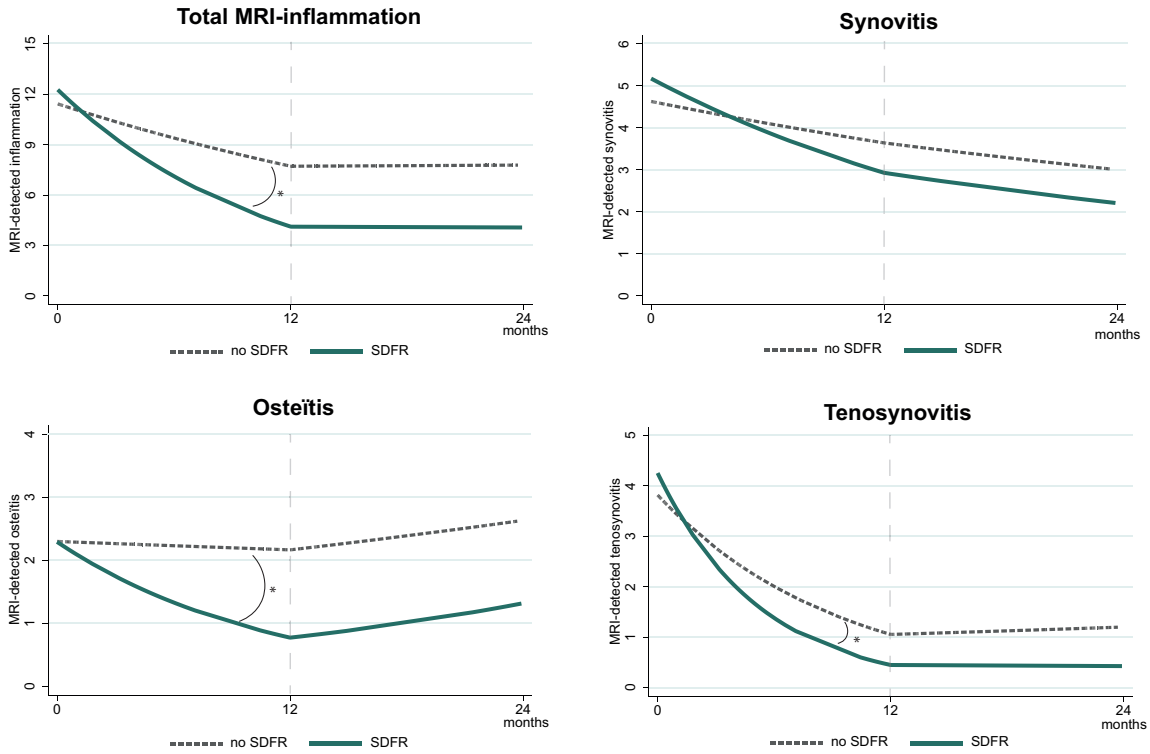
Baseline characteristics of the ACPA-negative and the ACPA-positive study population, and the ACPA-positive validationpopulation, stratified for SDFR development. [a]Significant difference between SDFR and non-SDFR group. [b]In general, symptom duration was less than 2 years in the AVERT-1. Exact symptom duration was not available. DAS28CRP: DAS based on 28-joint counts CRP and VAS; HAQ-DI: HAQ disability index; med: median; SJC: swollen joint count; TJC: tender joint count; VAS: visual analogue scale.

positive RA population ($n = 104$), 12% achieved SDFR, after median 4.7 years of follow-up (IQR 3.9–6.3 years). After SDFR development, ACPA-negative RA patients were followed for a subsequent median 4.5 years (IQR 3.0–5.6 years) and ACPA-positive RA patients for 2.8 years (IQR 1.0–3.8 years), during which no flare occurred, confirming the sustainability of this outcome. Baseline characteristics of RA patients who did and did not achieve SDFR, stratified for ACPA status, are presented in Table 1.

MRI-detected inflammation in relation to SDFR development in ACPA-negative RA

At diagnosis, MRI-detected inflammation scores were similar between ACPA-negative RA patients achieving SDFR and those who did not (Fig. 1; Supplementary Table S2, available at *Rheumatology* online). However, in the first year after DMARD start, total inflammation scores became significantly lower in ACPA-negative RA patients who achieved SDFR compared with ACPA-negative RA patients who did

Fig. 1 Trajectories of MRI-detected joint inflammation in ACPA-negative RA patients achieving SDFR compared with those who did not



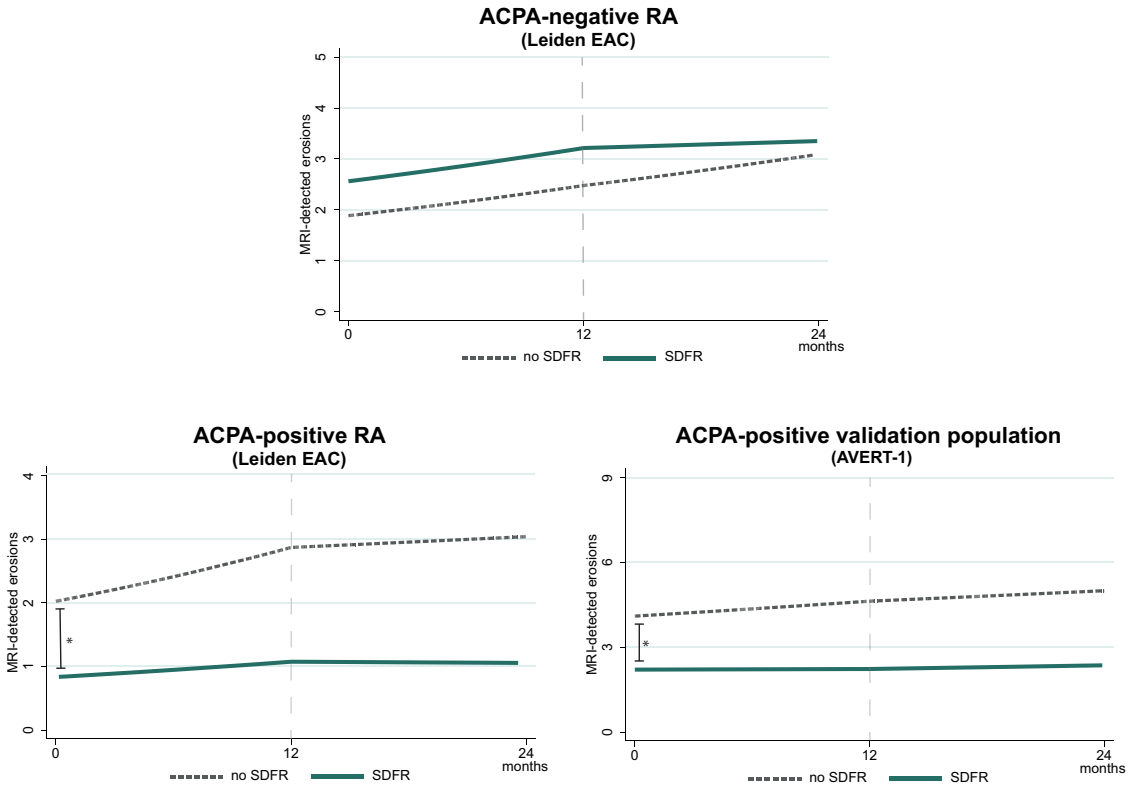
Trajectories of MRI-detected inflammation during follow-up in ACPA-negative RA patients achieving SDFR compared to those who did not. Despite similar baseline levels of MRI inflammation, the decline in these levels in the first year of DMARD treatment was significantly stronger in ACPA-negative RA patients achieving SDFR. This effect was seen in all individual inflammatory features, but predominantly in osteitis and tenosynovitis. Patterns were visualized based on estimated marginal means resulting from the Poisson mixed models. *$P<0.05$. SDFR: sustained DMARD-free remission.

not; IRR 0.50 (95% CI : 0.32, 0.77/$P<0.01$); i.e. within the first year of DMARD treatment, MRI inflammation levels declined two times stronger (95% CI : 1.3, 3.1 times) in ACPA-negative RA patients achieving SDFR. This relatively stronger decline was seen in all individual MRI features (Fig. 1; Supplementary Table S2, available at *Rheumatology* online); however, especially tenosynovitis and osteitis became significantly lower in ACPA-negative RA patients achieving SDFR; IRR 0.38 (95% CI : 0.15, 0.96/$P=0.04$) and 0.36 (95% CI : 0.19, 0.66/$P<0.01$) respectively. In the second year of follow-up, the course of MRI inflammation, and its individual features, did not significantly differ between the SDFR and non-SDFR patients. Erosion scores over time did not differ between the SDFR and non-SDFR patients (Fig. 2, Supplementary Table S2, available at *Rheumatology* online).

MRI-detected inflammation in relation to SDFR development in ACPA-positive RA

ACPA-positive RA patients achieving SDFR had significantly lower MRI inflammation levels at diagnosis compared with ACPA-positive RA patients who did not achieve SDFR (Fig. 3, Supplementary Table S2, available at *Rheumatology* online) which remained significantly lower during follow-up; IRR 0.45 (95% CI: 0.24, 0.86/$P=0.02$). That is, total MRI inflammation levels at baseline and during follow-up were 2.2 times lower (95% CI: 1.2, 4.2 times) in ACPA-positive RA patients achieving SDFR. When studying the inflamed tissues separately, especially synovitis was lower at baseline and during follow-up in ACPA-positive RA patients achieving SDFR: IRR 0.35 (95% CI: 0.16, 0.78/$P=0.01$). A similar effect was seen in osteitis scores, but this was borderline significant (IRR 0.40, 95% CI: 0.15, 1.09/$P=0.07$). Tenosynovitis levels at baseline, nor during follow-up, did not significantly differ between the SDFR and non-SDFR group ($P=0.13$). Erosion scores were also significantly lower at baseline and during the subsequent follow-up the SDFR group compared with the non-SDFR group: IRR 0.38 (95% CI: 0.15, 0.96/$P=0.04$) (Fig. 2, Supplementary Table S2, available at *Rheumatology* online).

FIG. 2 Trajectories of MRI-detected erosion scores in RA patients achieving SDFR compared with those who did not



Trajectories of MRI-detected erosions during follow-up in RA patients achieving SDFR, compared to those who did not in the ACPA-negative population, the ACPA-positive population and the ACPA-positive validation population. In both ACPA-positive RA populations, erosion scores were significantly lower at baseline and remained lower for the entire follow-up thereafter. In the ACPA-negative population, no difference in levels or change over time was observed. Patterns were visualized based on estimated marginal means resulting from the Poisson mixed models. *$P<0.05$. SDFR: sustained DMARD-free remission.

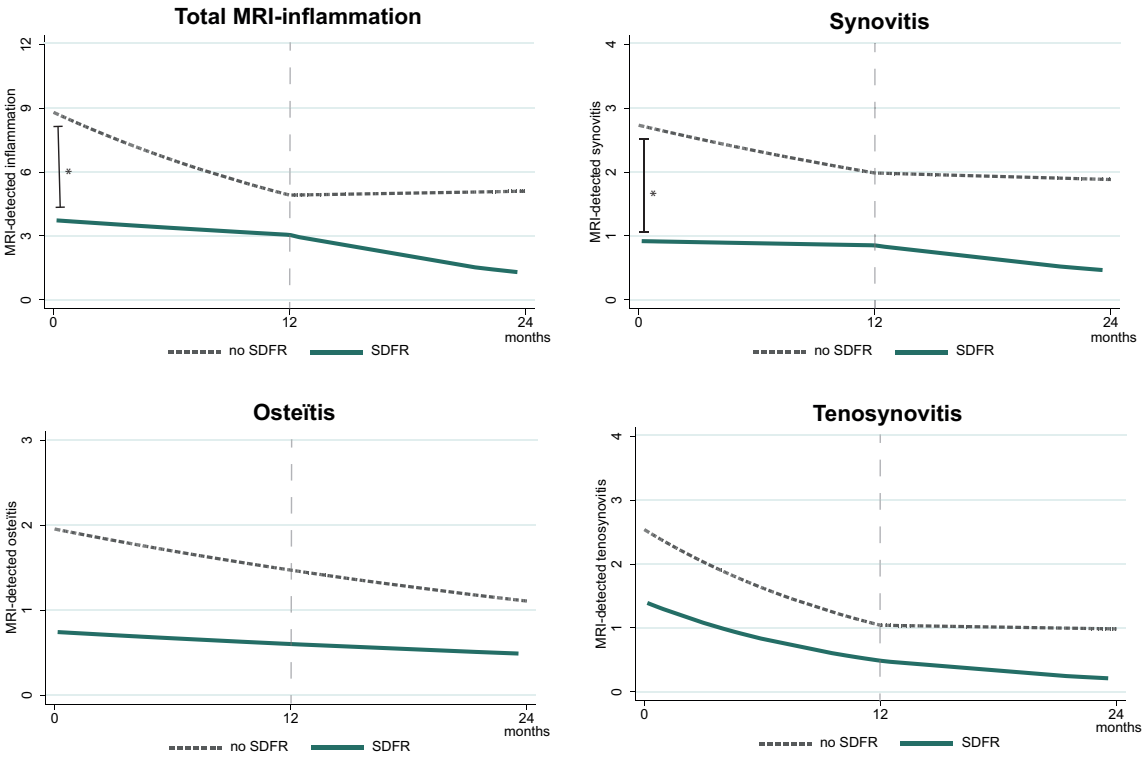
MRI trajectories in ACPA-negative and ACPA-positive RA patients achieving SDFR are different

Subsequently, trajectories of MRI inflammation of ACPA-negative and ACPA-positive RA patients were compared in relation to SDFR to test our hypothesis that these trajectories are different in ACPA-negative and ACPA-positive RA patients achieving SDFR. At baseline, levels of MRI inflammation were significantly lower in ACPA-positive RA patients achieving SDFR compared with ACPA-negative RA patients achieving SDFR (IRR 0.29 (95% CI: 0.17, 0.51)/$P<0.001$) (Fig. 4). In contrast, ACPA-negative RA patients achieving SDFR MRI inflammation levels declined 2.6 times (95% CI: 1.02, 6.45 times) stronger in the first year of DMARD treatment compared with ACPA-positive RA patients achieving SDFR (IRR 0.39 (95% CI: 0.15, 0.98)/$P=0.046$). Comparing ACPA-negative and ACPA-positive RA patients who did not achieve SDFR, no differences in baseline MRI levels ($P=0.20$) or subsequent trajectories were found ($P=0.50$) (Fig. 4).

Validation in external ACPA-positive RA population

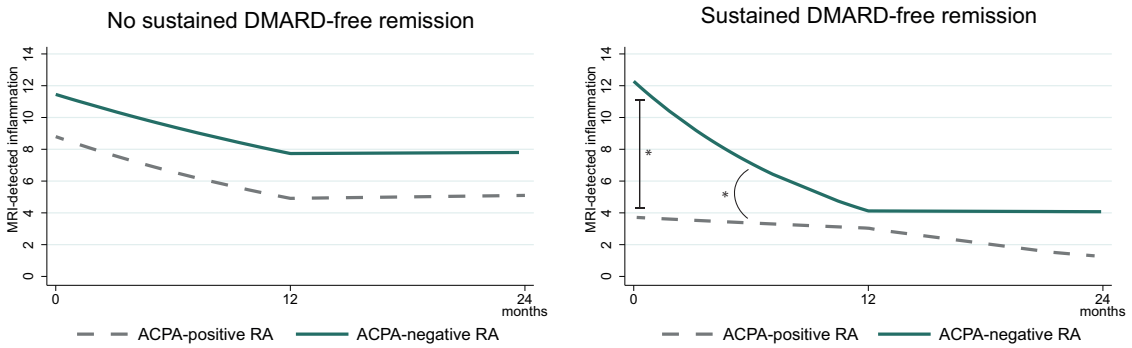
A total of 174 ACPA-positive RA patients included in the AVERT-1 were studied: mean age was 46 years, 78% were female and symptom duration was <2 years in all patients (Table 1). Median follow-up was 1.4 years (IQR 1.3–1.6 years). In total, 14 RA patients (8%) achieved SDFR. Baseline characteristics of RA patients who did and did not achieve SDFR are presented in Table 1. Also in this ACPA-positive RA population, MRI inflammation scores at disease presentation and in the subsequent follow-up were significantly lower in patients achieving SDFR compared with patients who did not achieve SDFR; IRR 0.23 (95% CI: 0.10, 0.54/$P<0.01$) (Fig. 5). Both synovitis and osteitis scores were lower in ACPA-positive RA patients achieving SDFR: IRR 0.32 (95% CI: 0.16, 0.64/$P<0.01$) and IRR 0.15 (95% CI:0.04, 0.57/$P\leq0.01$) respectively. Again, also erosion scores were significantly lower at baseline and remained significantly lower during follow-up: IRR 0.49 (95% CI: 0.26, 0.94/$P=0.03$) (Fig. 2, Supplementary Table S2, available at *Rheumatology* online).

Fig. 3 Trajectories of MRI-detected joint inflammation in ACPA-positive RA patients achieving SDFR compared with those who did not



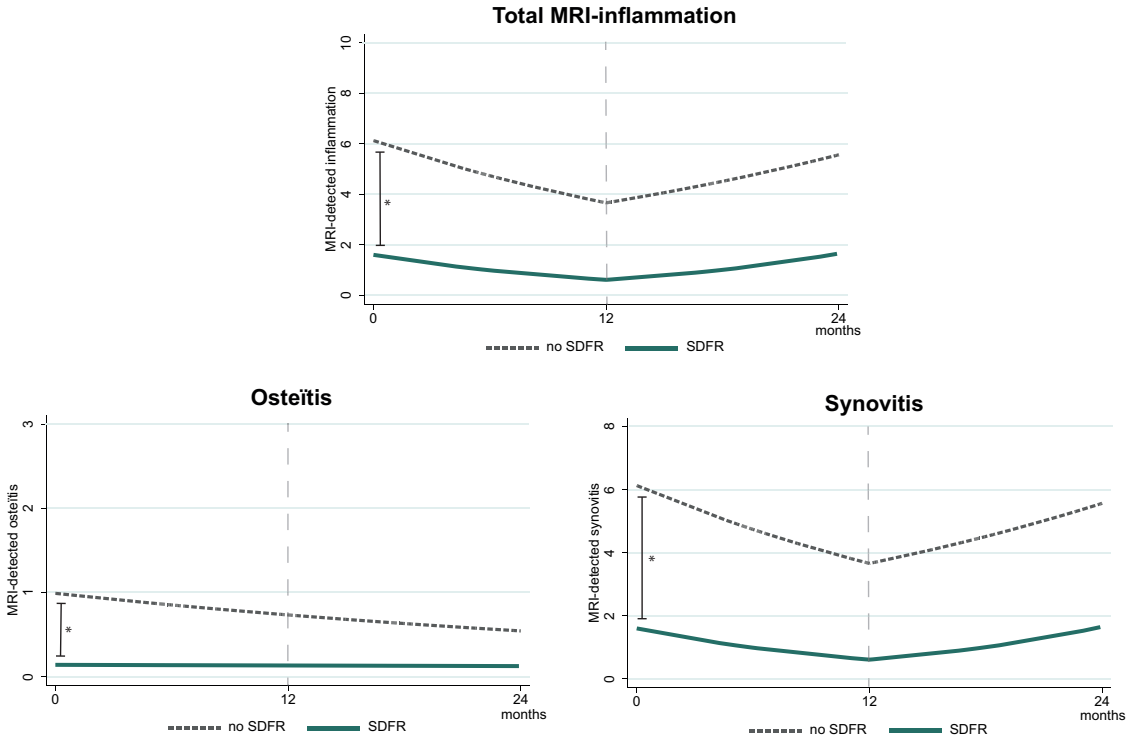
In ACPA-positive RA patients achieving SDFR, significantly lower baseline MRI inflammation was observed, which remained significantly lower during follow-up. This effect was predominantly seen in synovitis. Patterns were visualized based on estimated marginal means resulting from the Poisson mixed models. *$P < 0.05$. SDFR: sustained DMARD-free remission.

Fig. 4 Trajectories of MRI-detected joint inflammation of ACPA-negative ACPA-positive RA patients, in relation to SDFR



Comparison of trajectories of MRI-detected joint inflammation of ACPA-negative RA patients and ACPA-positive RA patients in relation to SDFR development. MRI trajectories in ACPA-negative and ACPA-positive RA patients who do not achieve SDFR were not statistically different. ACPA-negative RA patients achieving SDFR demonstrate a significantly stronger decline in MRI inflammation in the first year of DMARD treatment compared to ACPA-positive RA patients achieving SDFR ($P = 0.046$). In contrast, ACPA-positive RA patients achieving SDFR have already lower MRI-detected inflammation levels from diagnosis onwards ($P < 0.01$).

FIG. 5 Trajectories of MRI-detected joint inflammation in ACPA-positive RA patients achieving SDFR compared with those who did not in the ACPA-positive validation population



Trajectories of MRI-detected inflammation in ACPA-positive RA patients from the validation population who achieved SDFR compared to those who did not. In ACPA-positive RA patients achieving SDFR, significantly lower baseline MRI inflammation was observed, which remained significantly lower during follow-up. This effect was seen in both osteitis and synovitis. Patterns were visualized based on estimated marginal means resulting from the Poisson mixed models. *$P < 0.05$. SDFR: sustained DMARD-free remission.

Discussion

Sustained DMARD-free remission has become an increasingly achievable treatment aim and is currently the best proxy for cure in RA. However, biological mechanisms underlying SDFR development are incompletely understood. In this study, we demonstrated that ACPA-positive RA patients and ACPA-negative RA patients achieving SDFR are characterized by different courses of MRI-detected joint inflammation compared with patients not achieving SDFR. ACPA-positive RA patients achieving SDFR were characterized by lower levels of MRI-detected joint inflammation at diagnosis and during follow-up, whereas ACPA-negative RA patients achieving SDFR were similar in terms of MRI-detected joint inflammation at diagnosis to non-SDFR patients but demonstrated a stronger decline in inflammation after treatment initiation. These differences imply that biological pathways underlying SDFR development are intrinsically different between these two types of RA.

Although multiple studies attempted to find a link between patient or disease characteristics at diagnosis and disease resolution in RA, little associations were found, except for the association with autoantibodies [2, 3]. However, recently, after analysing ACPA-positive and ACPA-negative RA patients separately, and including longitudinal measurements, several associations with SDFR development in ACPA-negative RA were found [5, 17]. A steeper decrease in SJC, in DAS and in serological markers after treatment initiation were observed in ACPA-negative RA patients who, later on, achieved SDFR, compared with ACPA-negative RA patients with persistent disease [5, 6]. Because most of these measures are related to local joint inflammation, we hypothesized that specific joint-level processes might be related to disease resolution in RA. Our finding that MRI-detected joint inflammation, especially tenosynovitis and osteitis, declined stronger in ACPA-negative RA patients achieving SDFR substantiates this idea. If tissue-based research would be considered in order to increase understanding of disease resolution in RA, next to synovium, the tenosynovium might be a target tissue that may also be feasible to take small biopsies from. Moreover, because ACPA-negative RA patients achieving SDFR share distinct patterns of systemic and local inflammation upon DMARD initiation, which are not present in other ACPA-negative RA patients who are treated similarly, this might suggest that these patients represent

a subgroup within ACPA-negative RA with specific favourable characteristics, prone to achieve disease resolution.

Until this study was performed, no associations were found between patient or disease characteristics and SDFR development in ACPA-positive RA. Our finding that ACPA-positive RA patients achieving SDFR were characterized by already less MRI-detected joint inflammation (especially synovitis and osteitis) from the time of diagnosis suggests that the ability of achieving SDFR in these patients might already be determined at disease presentation, before the initiation of DMARDs. Interestingly, in AVERT-1, ACPA-positive RA patients achieving SDFR also had significantly less swollen joints at baseline compared with patients without SDFR (Table 1). In RA patients from the Leiden EAC who were selected based on the period in which longitudinal MRIs were performed, a similar tendency was observed, although this did not reach statistical significance, probably due to the small number of ACPA-positive patients with SDFR. Considering the larger group of ACPA-positive RA patients included in the EAC (irrespective of the period in which repeated MRIs were made, see Supplementary Fig. S1, available at *Rheumatology* online) also a significantly lower number of SJC (–28) was observed in ACPA-positive RA patients achieving SDFR: 3 (IQR 1–5) *vs* 5 (IQR 2–8) swollen joints at diagnosis in ACPA-positive RA patients that did not achieve SDFR ($P < 0.01$). Thus, ACPA-positive patients that develop SDFR have less inflammation from the start of the disease, while the symptom duration was not shorter compared with patients without SDFR. This could suggest that the capability of achieving disease resolution in ACPA-positive RA is determined by patient-specific characteristics instead of disease-phase characteristics. Interestingly, a recent study in ACPA-positive RA who achieved disease resolution demonstrated that also Fab glycosylation of ACPA was already less pronounced at diagnosis and continued to be lower until SDFR was achieved [18]. This also fits with the idea that ACPA-positive RA patients achieving disease resolution might represent a subgroup of patients with favorable patient characteristics.

The fact that MRIs in the Leiden EAC were scored by a different (single) reader than the MRIs in the AVERT-1, scored by two readers, could be considered a limitation as the readers for the different cohorts were not trained together. In addition, in the Leiden EAC, MRIs were scored with known time order and in AVERT-1 with random time order, the latter is known to be less sensitive to change over time [19]. However, MRIs in the Leiden EAC and in the AVERT-1 were all scored according to the same RAMRIS scoring method, which is a validated and standardized scoring method [14, 15, 20]. Ideally, for optimal validation, MRIs should have been scored by the same reader. Encouragingly, intrareader reliability in the Leiden EAC and inter-reader reliability in the AVERT-1 were excellent (Supplementary Table S2 and Data S2, available at *Rheumatology* online). Importantly, MRI scores were only compared within the cohorts, not between the cohorts, and thus potential inter-reader variability between the readers of the Leiden EAC and the AVERT-1 presumably did not affect the results.

It has been suggested that SDFR development in ACPA-negative patients solely reflects spontaneous resolution of inflammation in patients misclassified as RA [21]. However, to prevent that we studied patients with self-limiting disease, we only analysed patients who had a clinical RA diagnosis after 1 year of follow-up and additionally fulfilled the 1987 and/or 2010 criteria for RA [11, 12]. Patients diagnosed with other conditions than RA (e.g. reactive arthritis/inflammatory osteoarthritis) were excluded. Thus, according to current standards, these patients had RA.

A strength is that a validation set of ACPA-positive RA patients was included, as SDFR is infrequent in this type of RA. Similar findings in the validation cohorts support the robustness of our findings. While tapering was non-protocolized in the EAC, and protocolized in the AVERT trial, similar observations were done. In the Leiden EAC, SDFR was achieved after a median disease duration of 3.5 years (IQR 2.6–4.7 years). Because total median follow-up was 6.1 years (IQR 4.2–7.4 years) most patients had sufficient time to achieve the outcome. Importantly, patients achieving SDFR were followed for an extra median 4.2 years (IQR 2.3–5.2 years) after SDFR development during which no flares occurred, ensuring the sustainability of this outcome. In the AVERT-1, DMARD tapering was protocolized and SDFR could already be achieved after a disease duration of 2 years. However, follow-up after SDFR development was limited and therefore flares after SDFR development might have been missed. The fact that both patients and rheumatologists were blinded for MRI data avoided an influence of MRI results on treatment and tapering decisions.

In conclusion, within ACPA-positive and ACPA-negative RA different patterns of MRI-detected inflammation are present in patients achieving SDFR, suggesting that different biological pathways are involved in disease resolution in these subsets of RA. ACPA-positive RA patients achieving SDFR are distinguished by less MRI-detected inflammation already at diagnosis, whereas negative RA patients achieving SDFR differentiate themselves by a larger decline and subsequent milder course of inflammation over time. ACPA-stratified molecular research seems warranted to further increase understanding of disease resolution, the ultimate treatment aim in RA.

Acknowledgements

We would like to thank Prof. S. le Cessie from the department of Clinical Epidemiology and the department of Medical Statistics and Bioinformatics (Leiden University Medical Center) for her contributions to the development of the statistical analyses.

A.H.M. and M.V. contributed to the conception and study design. M.V. contributed to acquisition of the data and analysed the data. All authors contributed to interpretation of the data and the development of the manuscript. All authors approved the final version of the manuscript.

Funding: The research leading to these results has received funding from the Dutch Arthritis Foundation and the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (starting grant, agreement No. 714312). The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Disclosure statement: T.W.J.H. has received research support/lecture fees/consultancy fees from Merck, UCB, Bristol Myers Squibb, Janssen, Pfizer, Novartis, Sanofi-Aventis, Galapagos, Boeringher and Eli Lilly. S.E.C. is a shareholder and employee of Bristol Myers Squib. M.A.M. is a shareholder and employee of Bristol Myers Squib.

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information.

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Matthijssen XME, Niemantsverdriet E, Huizinga TWJ *et al.* Enhanced treatment strategies and distinct disease outcomes among autoantibody-positive and -negative rheumatoid arthritis patients over 25 years: a longitudinal cohort study in the Netherlands. PLoS Med 2020;17: e1003296.

2 Verstappen M, van Mulligen E, de Jong PHP *et al.* DMARD-free remission as novel treatment target in rheumatoid arthritis: a systematic literature review of achievability and sustainability. RMD Open 2020;6: e001220.

3 Ajeganova S, van Steenbergen HW, van Nies JA *et al.* Disease-modifying antirheumatic drug-free sustained remission in rheumatoid arthritis: an increasingly achievable outcome with subsidence of disease symptoms. Ann Rheum Dis 2016;75:867–73.

4 Burgers LE, Boeters DM, Reijnierse M, van der Helm-van Mil AHM. Does the presence of magnetic resonance imaging-detected osteitis at diagnosis with rheumatoid arthritis lower the risk for achieving disease-modifying antirheumatic drug-free sustained remission: results of a longitudinal study. Arthritis Res Ther 2018;20:68.

5 Verstappen M, Niemantsverdriet E, Matthijssen XME *et al.* Early DAS response after DMARD-start increases probability of achieving sustained DMARD-free remission in rheumatoid arthritis. Arthritis Res Ther 2020;22:276.

6 Verstappen M, van Steenbergen HW, de Jong PHP, van der Helm-van Mil AHM. Unraveling heterogeneity within ACPA-negative rheumatoid arthritis: the subgroup of patients with a strong clinical and serological response to initiation of DMARD treatment favor disease resolution. Arthritis Res Ther 2022;24:4.

7 Krabben A, Stomp W, Huizinga TW *et al.* Concordance between inflammation at physical examination and on MRI in patients with early arthritis. Ann Rheum Dis 2015; 74:506–12.

8 Ohrndorf S, Boer AC, Boeters DM *et al.* Do musculoskeletal ultrasound and magnetic resonance imaging identify synovitis and tenosynovitis at the same joints and tendons? A comparative study in early inflammatory arthritis and clinically suspect arthralgia. Arthritis Res Ther 2019;21:59.

9 Matthijssen XME, Niemantsverdriet E, Le Cessie S *et al.* Differing time-orders of inflammation decrease between ACPA subsets in RA patients suggest differences in underlying inflammatory pathways. Rheumatology 2021; 60:2969–75.

10 de Rooy DPC, van der Linden MPM, Knevel R *et al.* Predicting arthritis outcomes—what can be learned from the Leiden Early Arthritis Clinic? Rheumatology 2011;50: 93–100.

11 Aletaha D, Neogi T, Silman AJ *et al.* 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569–81.

12 Arnett FC, Edworthy SM, Bloch DA *et al.* The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.

13 Emery P, Burmester GR, Bykerk VP *et al.* Evaluating drug-free remission with abatacept in early rheumatoid arthritis: results from the phase 3b, multicentre, randomised, active-controlled AVERT study of 24 months, with a 12-month, double-blind treatment period. Ann Rheum Dis 2015;74:19–26.

14 Østergaard M, Peterfy C, Conaghan P *et al.* Core set of MRI acquisitions, joint pathology definitions, and the OMERACT RA-MRI scoring system. J Rheumatol 2003; 30:1385–6.

15 Haavardsholm EA, Østergaard M, Ejbjerg BJ *et al.* Introduction of a novel magnetic resonance imaging tenosynovitis score for rheumatoid arthritis: reliability in a multireader longitudinal study. Ann Rheum Dis 2007;66: 1216–20.

16 Sundin U, Aga AB, Skare Ø *et al.* Conventional versus ultrasound treat to target: no difference in magnetic resonance imaging inflammation or joint damage over 2 years in early rheumatoid arthritis. Rheumatology 2020; 59:2550–5.

17 Verstappen M, van Steenbergen HW, de Jong PHP *et al.* Unraveling heterogeneity within ACPA-negative rheumatoid arthritis: the subgroup of patients with a strong clinical and

serological response to initiation of DMARD treatment favor disease resolution. Arthritis Res Ther 2022;24:4.

18 Kissel T, Hafkenscheid L, Wesemael TJ *et al.* ACPA-IgG variable domain glycosylation increases before the onset of rheumatoid arthritis and stabilizes thereafter; a cross-sectional study encompassing over 1500 samples. bioRxiv 2021;2021.11.05.467407. doi: 10.1101/2021.11.05.467407.

19 van Der Heijde D, Boonen A, Boers M *et al.* Reading radiographs in chronological order, in pairs or as single films has important implications for the discriminative power of rheumatoid arthritis clinical trials. Rheumatology 1999;38:1213–20.

20 Haavardsholm EA, Østergaard M, Ejbjerg BJ *et al.* Reliability and sensitivity to change of the OMERACT rheumatoid arthritis magnetic resonance imaging score in a multireader, longitudinal setting. Arthritis Rheum 2005; 52:3860–7.

21 Zeidler H. Drug-free sustained remission or spontaneous remission by natural history in rheumatoid arthritis? An unsolved question: comment on the article of Ajeganova *et al*. Ann Rheum Dis 2017;76:e16.