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Original article

The number of risk factors for persistent disease determines the clinical course of early arthritis

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Abstract

Objectives. Management of early arthritis is based upon early recognition of individuals at high risk of developing persistent arthritis. Therefore, this study investigates whether the number of risk factors for persistent disease or treatment determines the clinical course of early arthritis by comparing the chance at (sustained) DMARD-free remission ((S)DFR) after 2 years follow-up.

Methods. Data from the tREACH trial, a stratified single-blinded multicentre strategy trial with a treat-to-target approach were used. We selected all patients with ≥1 swollen joint who did not fulfil 1987 and/or 2010 criteria for RA. The number of risk factors present; autoantibody-positivity, polyarthritis (>4), erosive disease and elevated acute phase reactants, determined risk group stratification. Multivariate logistic regression analyses were performed with (S)DFR as dependent variables and baseline disease activity score (DAS), treatment, symptom duration and number of risk factors present as independent variables.

Results. In total, 130 early arthritis patients were included and respectively 31, 66 and 33 had 0, 1 and ≥2 risk factors present. DFR rates were respectively 74%, 48% and 45% for early arthritis patients with 0, 1 and ≥2 risk factors present. In accordance SDFR rates were 61%, 32% and 30%. In our logistic model (S)DFR was not influenced by the initial treatment strategies when stratified for risk groups.

Conclusion. The chance at (S)DFR in early arthritis diminishes when more risk factors are present, which is irrespective of the given initial treatment. Our data point out to a stratified management approach in early arthritis based on their risk profile, but validation is needed.

Trial registration. ISRCTN registry: ISRCTN26791028 (http://www.isrctn.com/ISRCTN26791028).

Key words: early arthritis, DMARD-free remission, risk factors, treatment

CLINICAL SCIENCE

Rheumatology key messages

- Early arthritis management is based upon early recognition of individuals at high risk of developing persistent arthritis.
- Early arthritis patients with fewer risk factors for persistent arthritis have higher (S)DFR rates.
- Treatment of early arthritis patients might be stratified on the number of risk factors present, but validation is needed.

Introduction

In the management of early arthritis it is important to identify individuals at high risk of progressing to persistent (rheumatoid) arthritis at an early stage [1]. Recognizing the underlying disease can be challenging, especially in an early phase [2]. Early arthritis may be self-limiting, it can remain an undifferentiated arthritis (UA) or it can develop into RA [2, 3].

Although it is difficult to distinguish between these clinical courses, there are some risk factors specified in the EULAR recommendations for early arthritis that may increase the risk at persistent or erosive disease [2, 4]. These risk factors for developing persistent arthritis are

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[1]: the number of swollen joints [2], the presence of acute-phase reactants [3], the presence of autoantibodies and [4] the presence of erosions [2, 4]. It is known that the chance at persistent arthritis increases when more risk factors are present and subsequently the chance at (sustained) DMARD-free remission ((S)DFR) decreases [4–9]. In early arthritis patients, the chance at (S)DFR is expected to be even higher than (S)DFR rates in RA, as more patients may have a self-limiting disease. However, to our knowledge, no studies have investigated this concept in early arthritis.

Moreover, the EULAR recommendations for early arthritis recommend to start MTX with or without glucocorticoids (GCs) in patients who are at risk of persistent arthritis. Persistent arthritis is defined as having $\geq$1 arthritis and $\geq$1 risk factor present [2, 4]. The choice for MTX as first line therapy in early arthritis is based upon data from trials in early DMARD-naïve or established RA patients, because trials in early arthritis are sparse. However, aforementioned trials compared MTX monotherapy to more intensive treatment strategies and not to other conventional synthetic (cs)DMARDs or GCs [4]. We recently showed that initial HCQ and MTX showed similar (early) treatment responses in autoantibody-negative RA patients, which is in accordance with current beliefs [10–13]. Hence, if stratified treatment is considerable for RA, it might also be in early arthritis.

Therefore, our aim was to investigate whether the disease course of early arthritis depends on the number of risk factors present, for persistent arthritis, by comparing the (sustained) DMARD-free remission ((S)DFR) rates between risk groups after 2 years of follow-up. We also explored if (S)DFR is influenced by treatment when stratified for risk group.

Methods

Patients

For this study, data were used from the treatment in the Rotterdam Early Arthritis Cohort (tREACH) trial. The tREACH trial was a multicentre, stratified single-blinded trial [14]. At each participating center, medical ethics committees approved the tREACH study protocol, and all patients gave written informed consent before inclusion (MEC-2006–252). For more details we would like to refer to the publications of Claessen *et al.* [15] and Visser *et al.* [16].

For this analysis, we selected all patients with $\geq$1 swollen joint who did not fulfil 1987 and 2010 criteria for RA and can, therefore, be classified as early arthritis [15, 17]. A total of 130 early arthritis patients were included for this analysis (Fig. 1). Included early arthritis patients were stratified on the number of risk factors present, for persistent disease, namely autoantibody-positivity (rheumatoid factor and/or anti-citrullinated protein antibody), polyarthritis (>4 swollen joints), erosive disease and elevated acute phase reactants [2, 4]. None of the patients had all risk factors present and there was only one with three risk factors present. Therefore, the following risk groups were made: no risk factors present ($n = 31$), one risk factor present ($n = 66$) and $\geq$2 risk factors present ($n = 33$) (Fig. 1).

Treatment

Within the original tREACH trial, the initial treatment depended on the probability stratum and its randomization. However, to explore whether induction therapy with MTX is beneficial over other treatment regimens on achieving (S)DFR, we reallocated the original randomly assigned treatment into the following groups: (1) initial MTX+(iMTX+, $n = 30$), all treatment strategies with MTX, including combination therapies, with or without glucocorticoid bridging therapy; (2) initial HCQ (iHCQ, $n = 40$); and (3) no initial csDMARDs (no iDMARDs, $n = 60$), which included induction therapies comprising of NSAIDs or glucocorticoids (GCs) without any csDMARD.

Medication dosages were: MTX 25 mg/week orally (dosage reached after 3 weeks), sulfasalazine 2 g/day, HCQ 400 mg daily, naproxen 1000 mg daily and GCs either given once intramuscularly (methylprednisolone 120 mg or triamcinolone 80 mg) or in a 10-week oral tapering scheme with starting dose 15 mg daily without any csDMARDs. Folic acid (10 mg per week) was given to patients using MTX. During the first 3 months, osteoporosis prophylaxis (risedronate 35 mg/week and calcium/vitamin D combination 500/400 mg/IU/day) was given to all treatments with an oral GC tapering scheme.

The tREACH trial had a treat-to-target approach aiming for low disease activity [disease activity score (DAS) <2.4] [18]. Every 3 months treatment alterations could occur and in case of very active disease, based on the rheumatologists' insight, an earlier visit could be planned. In case of still active disease (DAS $\geq$ 2.4) treatment was intensified in the following order: (1) triple DMARD therapy, consisting of MTX, sulfasalazine (2000 mg daily) and HCQ; (2) MTX + etanercept (50 mg/week, subcutaneously); (3) MTX + adalimumab (40 mg/2 weeks, subcutaneously) and (4) MTX + abatacept (500–1000mg/4 weeks, intravenously, weight dependent).

Medication was tapered if DAS was <1.6 at two consecutive visits. Tapering occurred in the following steps: (1) biological agent, (2) sulfasalazine, (3) MTX and (4) HCQ. All medication was gradually discontinued, except for HCQ and naproxen, which were stopped immediately. Patients treated with iGCs who had a low disease activity after 10 weeks were in drug-free remission (DFR) from that moment. A flare (DAS $\geq$ 2.4) during tapering, resulted in restarting full treatment, according to the stage in the protocol.

Assessments

Visits occurred every 3 months and at each visit the DAS, medication use and self-reported questionnaires were collected, except for hand/foot radiographs, which were examined at baseline, at six months and yearly thereafter.

FIG. 1 Flowchart of early arthritis patients stratified for risk group

Results are shown as number of patients. Reasons for dropout are: (1) for no risk factors present: 1, emigrated; 2, no time; 1, other diagnosis; 2, refused participation; 6, unknown; (2) for 1 risk factor present: 1, adverse events; 1, emigrated; 2, other health problems; 4, refused participation (of which one patient specifically refused GCs); 1, transfer to other hospital; 7, unknown, 1, wrong randomization; and (3) for ≥2 risk factors present: 1, other health problems; 5, refused participation; 4, unknown. LTFU, loss to follow-up.

Outcomes

Our primary outcome was the proportional difference in DMARD-free remission (DFR) after 2 years of follow-up between our prespecified risk groups for persistent arthritis. Secondary outcomes were: (1) the proportional difference in sustained DFR between risk groups; (2) medication use after 2 years of follow-up; (3) the proportional difference in DFR between treatment groups (iMTX+ *vs* iHCQ *vs* no iDMARDs) stratified for risk group; (4) DAS (over time); (5) HAQ (over time) and (6) difference in radiographic progression.

DFR was defined as being in remission (DAS < 1.6) without any DMARDs for at least 6 months, while patients in SDFR are in DFR for longer than 1 year [14, 19]. DAS and its thresholds were used to determine disease states (moderate to high disease activity: DAS ≥ 2.4; low disease activity: 1.6≥ DAS <2.4; and remission: DAS <1.6) [18]. Boolean remission criteria are

defined as having a tender joint count, swollen joint count, C-reactive protein (in mg/dl) and patient global assessment (0–10 scale) of ≤1 [20]. Functional ability was measured with the HAQ and higher scores reflect poorer function [21]. Radiographic progression was measured with the modified Total Sharp Score (mTSS) [22]. Radiographs were read chronically by two out of three qualified assessors, who were blinded to the patients' treatment allocation [23]. Weighted kappa for the total mTSS between assessors was 0.67 with 99% agreement. The proportion of patients with radiographic progression was defined as a change in mTSS >0.5 and >0.9 (the smallest detectable change) over 2 years of follow-up, which is in agreement with guidelines for presentation of radiological results in clinical trials [24].

Statistical analysis

A χ^2 test was used to measure the proportional difference in (S)DFR between risk groups. Early arthritis patients who are in (S)DFR are more prone for lost to follow-up and, therefore, we used the last observation carried forward to handle missing data. The drop-out ratios for no, 1 and ≥2 risk factors present were, respectively, 42% (13/31), 26% (17/66) and 30% (10/33) (Fig. 1). Sensitivity analyses using only complete cases were performed due to the skewed drop-out ratio to ensure our findings are valid. We hypothesized that patients with no risk factors were more likely to drop out due to inactive disease.

A logistic model was used to evaluate whether different initial treatment strategies have an additional effect on reaching (S)DFR besides the number of risk factors presents. Within this model, (S)DFR is the dependent variable and treatment, risk group, symptom duration and baseline DAS were the independent variables.

For the DAS and HAQ over time, we used a linear mixed model (LMM) with an unstructured covariance matrix in which time, risk groups and baseline DAS and HAQ were, respectively, the covariates.

All other statistical comparisons, i.e. between baseline characteristics and outcomes after 24 months, were made by student's *t test*, χ^2 test or Wilcoxon rank-sum test, when appropriate. For normally distributed data, means were presented and for non-normally distributed data, medians. Data was analysed using STATA V.15.1 and a *P*-value <0.05 was considered statistically significant.

Results

Patients

The baseline characteristics of our early arthritis population are given in Table 1 and are stratified for risk group, which is based upon the number of risk factors present for persistent disease. Patients were mostly female (68%) with a median symptom duration of 136 days (interquartile range, IQR: 77–223). Although no differences in initial treatment strategy were seen between risk groups, DAS and its components(except for general health and tender joint count) were significantly higher when more risk factors are present (Table 1). Logically, the prevalence for each risk factor separately increases when the number of risk factors present increases. Elevated acute phase reactants ($n = 92$, 71%) was most common, followed by polyarthritis ($n = 30$, 23%) and autoantibody-positivity ($n = 11$, 8%). No erosions were seen.

Sustained DMARD-free remission ((S)DFR)

After 2 years of follow-up, DFR was seen in 74% ($n = 23$, 95% CI: 58%, 90%), 48% ($n = 32$, 95% CI: 36%, 61%) and 45% ($n = 15$, 95% CI: 28%, 63%) of early arthritis patients with respectively no, 1 and ≥2 risk factors present (Fig. 2B, $P < 0.05$). The cumulative DFR rates after 2 years were 74% ($n = 23$), 53% ($n = 35$) and 45% ($n = 15$) of early arthritis patients with, respectively, no, 1 and ≥2 risk factors present (Fig. 2A). Three early arthritis patients with one risk factor present had a flare after reaching DFR and were, therefore, not in DFR after 2 years of follow-up. SDFR, defined as DFR for ≥1 year, also occurred more often in early arthritis patients without risk factors (61%, 95% CI: 44%, 79%) compared with the other two risk groups, respectively, 1 (32%, 95% CI: 20%, 43%, $P < 0.01$) and ≥2 (30%, 95% CI: 14%, 46%, $P < 0.05$) risk factors present (Fig. 2B).

In our logistic model, the chance at SDFR was lower for patients who did not start with csDMARDs compared with iMTX+ [odds ratio 4.28 (95% CI: 1.34, 13.72), $P < 0.05$]. DFR rates on the other hand did not differ between patients treated with MTX+ or no iDMARDs [odds ratio 2.22 (95% CI: 0.82, 6.01), $P = 0.117$]. Also, no difference was seen between patients who started with iHCQ compared with iMTX+ [odds ratio 1.25 (95% CI: 0.43, 3.63), $P = 0.677$ & 1.64 (95% CI: 0.47, 5.69), $P = 0.435$ for, respectively, DFR and SDFR]. However, we did find that patients with a symptom duration <6 months had a significantly higher chance at (S)DFR compared with those with a longer symptom duration [odds ratio 3.30 (95% CI: 1.58, 6.91), $P < 0.005$ & 3.37 (95% CI: 1.52, 7.51), $P < 0.005$ for, respectively, DFR and SDFR]. On the other hand, presence of autoantibodies and their corresponding levels were not associated with (S)DFR.

Treatment

In accordance with our results on (S)DFR, we saw that early arthritis patients with less risk factors present were more often able to taper their medication and also had a lower risk at flares (Fig. 2B). Of the early arthritis patients with no, 1 and ≥2 risk factors present, respectively, 28 (90%), 53 (80%) and 23 (70%) were able to taper medication. Flare rates after tapering were 0% (0/28), 11% (6/53) and 17% (4/23) (Fig. 2B).

Treatment intensifications on the other hand occurred more often in early arthritis patients who had more risk factors present [odds ratio 2.68 (95% CI: 1.09, 6.57), $P < 0.05$ for no *vs* 1 and 2.20 (95% CI: 1.30, 3.73)

Table 1 Baseline characteristics for all early arthritis patients stratified for risk group

Characteristics	No risk factors present ($n = 31$)	1 risk factor present ($n = 66$)	≥2 risk factors present ($n = 33$)	*P*
Demographic				
Age (years), mean (S.D.)	48 (13)	48 (15)	55 (13)	<0.05 for no and 1 *vs* ≥2 risk factors
Sex, female, *n* (%)	21 (68)	41 (62)	26 (79)	
Disease characteristics				
Symptom duration (days), median (IQR)	154 (91–238)	145 (72–221)	106 (69–204)	
DAS, mean (S.D.)	2.09 (0.57)	2.33 (0.59)	2.57 (0.83)	<0.01 no *vs* ≥2 risk factors
TJC44, median (IQR)	4 (2–6)	3 (2– 6)	3 (1–6)	
SJC44, median (IQR)	2 (1–3)	2 (2–3)	6 (5–7)	0.000 for no and 1 *vs* ≥2 risk factors
General health, median (IQR)[a]	31 (22–47)	43 (28–54)	40 (27–65)	
ESR in mm/h, median (IQR)	7 (3–11)	14 (9–29)	22 (10–36)	0.000 for no *vs* 1 and 2 risk factors
CRP in mg/l, median (IQR)	1 (1–1)	9 (5–18)	9 (5–18)	0.000 for no *vs* 1 and 2 risk factors
mTSS (0–488), median (IQR)	0 (0–1)	0 (0–0)	0 (0–0.5)	
HAQ, mean (S.D.)	0.49 (0.50)	0.58 (0.49)	0.86 (0.65)	<0.05 for no and 1 *vs* ≥2 risk factors
Treatment strategy				
– iMTX+, *n*(%)	7 (23)	13 (20)	10 (30)	
– iHCQ, *n*(%)	12 (39)	20 (30)	8 (24)	
– no iDMARDs, *n*(%)[b]	12 (39)	33 (50)	15 (45)	
Risk factors				
Polyarthritis (SJC44 > 4), *n*(%)	0 0	4 (6)	26 (79)	0.000 for no and 1 *vs* ≥2 risk factors
Presence of autoantibodies (ACPA or RF), *n* (%)	0 0	3 (5)	8 (24)	<0.005 for no and 1 *vs* ≥2 risk factors
Elevated acute phase reactants, *n* (%)[c]	0 0	59 (89)	33 (100)	0.000 for no *vs* 1 risk factor
Erosive disease, *n* (%)[d]	0 0	0 0	0 0	

[a]General health is measured with a Visual Analogue Scale from 0 to 100 mm. [b]No iDMARDs implies the group of patients who started with glucocorticoids or naproxen. [c]Acute-phase reactants defined as having a CRP ≥ 3 or ESR >22 mm/h for men and >29 mm/h for women. [d]Erosive disease is defined as having an erosion score >1 in three separate joints [34]. DAS, Disease Activity Score; iDMARDs, initial therapies comprising of NSAIDs or glucocorticoids; iHCQ, initial HCQ; iMTX+, all initial MTX treatment strategies including combination therapies with or without glucocorticoid bridging therapy; SJC44, swollen joint count (44 joints); TJC44, tender joint count (44 joints); mTSS, modified Total Sharp Score.

$P < 0.005$ for no *vs* ≥2 risk factors present] (Fig. 2B). This is best reflected by the biological use after 2 years of follow-up. Biological use was higher for early arthritis patients with ≥2 risk factors present (29%, 95% CI: 14%, 46%) compared with patients without risk factors (0%, 95% CI: −2%, 15%, $P < 0.05$). Two patients (6%) without risk factors, 10 (15%) patients with one risk factor and 10 patients (30%) with ≥2 risk factors used a biological after 2 years (Fig. 2B).

Other clinical outcomes

Disease activity, functional ability and radiographic progression (over time) in early arthritis patients stratified for risk group are presented in Table 2 and Fig. 3A–E.

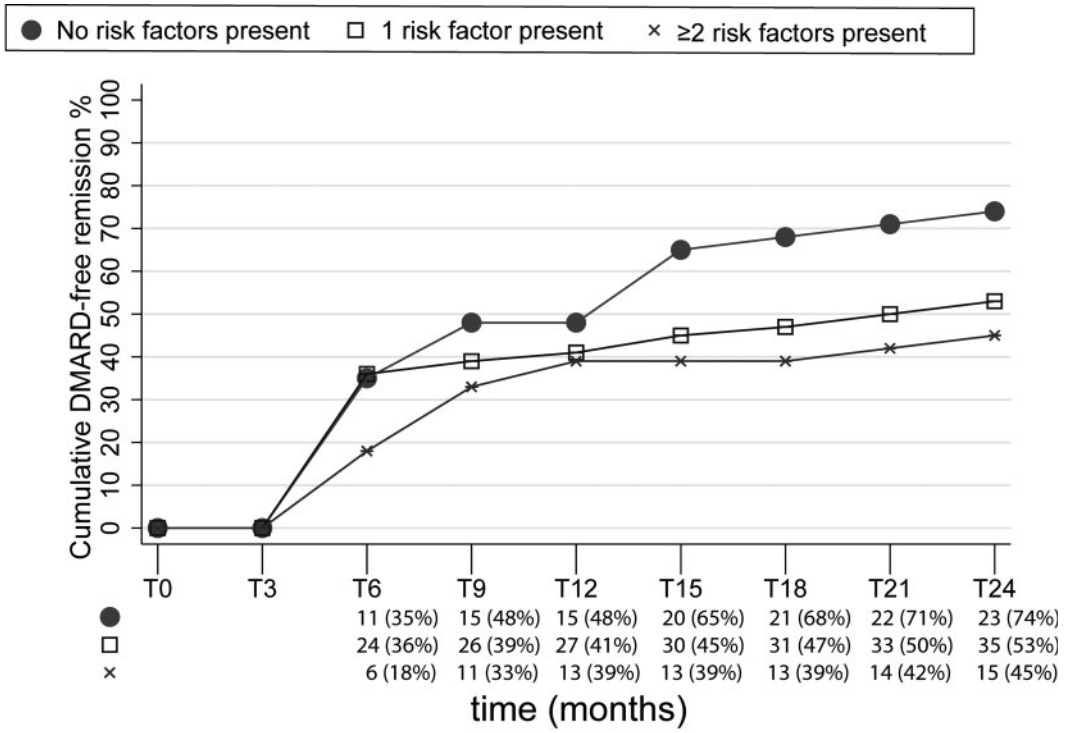
Disease activity after 2 years of treatment was 1.33 (0.68), 1.50 (0.77) and 1.89 (1.02) for patients with, respectively, no, 1 and ≥2 risk factors present (Table 2). Our uncorrected LMM showed that patients with, respectively, 1 and ≥2 risk factors present had a significantly higher DAS over time compared with patients without risk factors ($\beta = 0.27$, 95% CI: 0.02, 0.53 and $\beta = 0.48$, 95% CI: 0.15, 0.81). However, our corrected LMM, for baseline DAS, showed no significant difference in DAS over time.

Functional ability after 2 years of treatment was 0.30 (0.49), 0.49 (0.53) and 0.66 (0.66) for patients with, respectively, no, 1 and ≥2 risk factors present (Table 2). Our uncorrected LMM showed that patients with ≥2 risk factors present had a significantly higher HAQ over time compared with patients without risk factors ($\beta = 0.28$, 95% CI: 0.04, 0.52). However, after correction for baseline HAQ, the aforementioned significant difference disappeared, while the difference in HAQ over time between patients with one risk factor present compared with patients without risk factors became significant ($\beta = 0.14$, 95% CI: 0.01, 0.28).

The median increase (IQR) in mTSS was 0 (0–1), 0 (0–0) and 0 (0–1) for patients with, respectively, no, 1 and ≥2

FIG. 2 (S)DFR and medication use in early arthritis patients stratified for risk group

A



B

	No risk factors present (n=31)	1 risk factor present (n=66)	≥2 risk factors present (n=33)
Medication after 2 years			
No medication	23 (74)	32 (48)	15 (45)
Initial therapy	3 (10)	10 (15)	1 (3)
Triple DMARD therapy	3 (10)	14 (21)	7 (21)
Biological use	2 (6) +	10 (15)	10 (30)
Medication switches, median (IQR)	0 (0-1) #	1 (0-1)	1 (0-2)
Tapered treatment [a]	28 (90)	53 (80)	23 (70)
Flare after tapering [b]	0/28 (0)	6/53 (11)	4/23 (17)
DMARD-free remission [c]	23 (74) *	32 (48)	15 (45)
Sustained DMARD-free remission [d]	19 (61)^	21 (32)	10 (30)

Results are shown as number (%) unless stated otherwise. (**A**) shows the cumulative probability plot of DMARD-free remission over time for each risk group separately. (**B**) shows a table with medication use (over time). [a]Treatment could be tapered after 6 months of follow-up. [b]A flare is defined as a Disease Activity Score $\geq$2.4. The proportion is calculated by dividing the number of flares by the total patients who tapered. [c]DMARD-free remission (DFR), defined as having a DAS<1.6 without DMARD therapy for 6 months. [d]Sustained DMARD-free remission, defined as having DFR for $\geq$1 year. ^{+}P <0.05 for no *vs* $\geq$2 risk factors present group. $^{\#}P$<0.05 for the no *vs* 1 risk factor and P<0.005 for no *vs* $\geq$2 risk factors present group. $^{*}P$<0.05 for the no *vs* 1 risk factor present and P<0.05 for no *vs* $\geq$2 risk factors present group. ^P<0.01 for the no *vs* 1 risk factor present and P<0.05 for no *vs* $\geq$2 risk factors present group.

TABLE 2 Clinical response in early arthritis after 2 years of follow-up stratified for risk group

Clinical response	No risk factors Present ($n = 31$)	1 risk factor present ($n = 66$)	≥2 risk factors present ($n = 33$)
Disease activity			
DAS, mean (S.D.)	1.33 (0.68)	1.50 (0.77)	1.89 (1.02)
TJC44, median (IQR)	0 (0–1)	0 (0–2)	0 (0–4)
SJC44, median (IQR)	0 (0–0)	0 (0–0)	0 (0–1)
General health, median (IQR)[a]	13 (5–27)	24 (8–37)	23 (12–39)
ESR in mm/h, median (IQR)	6 (4–10)	8 (4–13)	11 (5–22)
CRP in mg/l, median (IQR)	1 (1–2)	4 (2–10)	5 (2–11)
ΔDAS (T24–T0), mean (S.D.)	−0.76 (0.81)	−0.83 (0.88)	−0.69 (0.93)
Disease state according to DAS, *n* (%)			
Moderate to high disease activity (DAS ≥ 2.4)	2 (6)	7 (11)	11 (33)
Low disease activity (1.6≥ DAS <2.4)	8 (26)	19 (29)	7 (21)
Remission			
• DAS <1.6	21 (68)	40 (61)	15 (45)
• DAS <1.6 & SJC44 = 0	20 (65)	34 (52)	12 (36)
• Boolean	18 (58)	18 (27)	6 (18)
Radiographs (hand/foot)			
mTSS (0–488), median (IQR)	0 (0–1)	0 (0–0)	0 (0–0)
Erosion score (0–280), median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)
JSN score (0–168), median (IQR)	0 (0–1)	0 (0–0)	0 (0–0)
ΔmTSS (T24–T0), median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)
Patients with progression >0.5, *n* (%)	1 (3)	1 (2)	3 (9)
Patients with progression >0.9, *n* (%)	1 (3)	1 (2)	3 (9)
Erosive disease, *n* (%) [b]	1 (3)	0 0	1 (3)
Functional ability			
HAQ, mean (S.D.)	0.30 (0.49)	0.49 (0.53)	0.66 (0.66)
ΔHAQ (T24–T0), mean (S.D.)	−0.26 (0.41)	−0.13 (0.51)	−0.23 (0.66)

[a]General health is measured with a Visual Analogue Scale from 0 to 100 mm. [b]Erosive disease is defined as having an erosion score >1 in three separate joints [34]. DAS, Disease Activity Score; JSN, joint space narrowing; mTSS, modified Total Sharp Score; SJC44, swollen joint count (44 joints); TJC44, tender joint count (44 joints).

risk factors present. Respectively, 3%, 2% and 9% of patients with no, 1 and ≥2 risk factors present had radiological progression, defined as an increase in mTSS of >0.9 (Table 2). There was no significant difference in radiographic progression between risk groups. The cumulative probability plots were also superimposable (Fig. 3E).

Sensitivity analyses

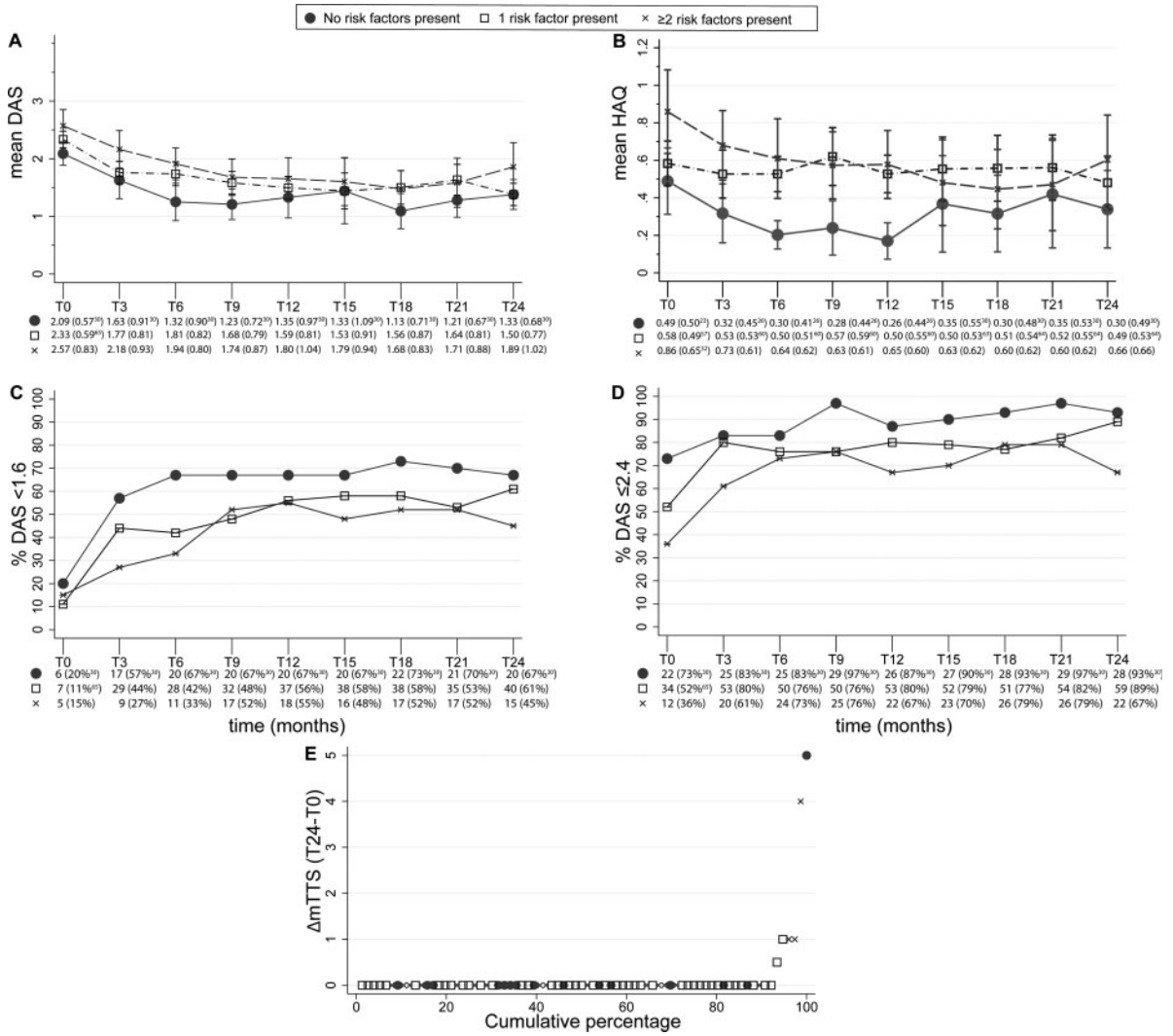
Our sensitivity analyses showed similar results between the complete cases and our imputed data. However, DAS (thresholds), its components and HAQ tended to be more severe for complete cases compared with our imputed dataset, especially for patients without risk factors (see online Supplementary Files, available at *Rheumatology* online).

Discussion

We investigated whether the number of risk factors for persistent disease determines the clinical course of early arthritis by comparing the chance at (sustained) DMARD-free remission. We also explored if (S)DFR is influenced by treatment when stratified for risk group. We found that the chance at (S)DFR in early arthritis diminishes when more risk factors are present and this is irrespective of the given initial csDMARD therapy. iNSAIDs and iGCs are not indicated for this subgroup of patients. Furthermore, patients with a shorter symptom duration had a higher chance at reaching (S)DFR. Therefore, it remains important to initiate csDMARD treatment as soon as possible.

This is the first study that shows that early arthritis patients with fewer risk factors for persistent arthritis have higher (S)DFR rates. Our DFR and SDFR rates were, respectively, 54% and 38% after 2 years of follow-up, which is higher compared with other early arthritis studies [5, 6, 9]. The PROMPT study, for example, reported a DFR of 32% after 5 years of follow-up, but some of the included early arthritis patients would nowadays be classified as having RA if the 2010 criteria are applied [9]. DFR rates were even lower in the more recent IMPROVED study, respectively, 12% and

FIG. 3 Disease activity (states), functional ability and radiographic progression over time



Superscript numbers represent the sample size. (**A**) and (**B**), respectively show disease activity and functional ability over time. Error bars indicate respectively 95% CIs and interquartile ranges for given means and medians. (**C**) and (**D**) present the disease activity <1.6 & ≤ 2.4 over time. In (**E**), the cumulative probability plot for radiological progression stratified for risk factors presents in early arthritis is given. Each point on the plot represents the radiological progression in an individual patient (score after 2 year minus score at baseline). DAS, Disease Activity Score; mTSS, modified Total Sharp Score.

26% after 2 and 5 years of follow-up, but only 21% of the included patients had an undifferentiated arthritis [5, 6].

In the future, DFR rates might also be influenced by the ongoing debate on the definition of remission and which criteria should be used when tapering of medication is considered. Current EULAR recommendation recommend to taper medication in patients who are in persistent (Boolean) remission, while none of the current tapering trials used this definition [8, 25, 26]. The Boolean remission criteria are more stringent than the DAS-based criteria (DAS <1.6). Our data, for example, showed that less patients are in Boolean remission (32%) compared with those who are in DAS remission (58%). If tapering is only commenced in patients who are in Boolean remission, than fewer patients are able to taper medication and subsequently reach DFR, but this might also lead to less disease flares during tapering. However, recently, van Mulligen *et al.* [25] showed that flare rates during tapering were similar for patients who were and were not in Boolean remission. On the other hand, the chance at a flare, while in DFR, diminishes with time and when patients are >1 year in DFR, this chance is $<5\%$, which emphasizes the importance of reaching SDFR [27].

Due to the fact that the number of risk factors present determines the clinical course of early arthritis, one

could argue that treatment should also be stratified for the number of risk factors present. Especially, since in our study (S)DFR rates were independent of the initial csDMARD treatment strategy. Also, no differences in radiographic progression were seen. iNSAIDs or iGCs on the other hand are not indicated for early arthritis patients. However, this should be investigated in a randomized controlled trial.

Higher (S)DFR rates were also seen in patients with a shorter symptom duration, which emphasizes the concept of the 'window of opportunity'. Early initiation of DMARDs within this window improves clinical outcomes and increases the chance at remission, which is confirmed in our study [1, 28–33]. On the other hand, the presence of autoantibodies and their corresponding levels were not associated with (S)DFR; however, the number of patients with autoantibodies was low ($n = 11$, 8%) and, therefore, these results should be interpreted cautiously.

Our study had certain limitations. First, within the tREACH trial only 130 patients fulfilled the criteria for UA (undifferentiated arthritis). Although at first sight this seems a small population, the sample size is comparable to previous UA studies [5, 6, 9]. Still, one should be careful with the interpretation of some results due to the low frequencies (i.e. presence of autoantibodies).

Secondly, the drop-out ratio was skewed with more drop-outs in patients without any risk factors. We hypothesized that patients with no risk factors were more likely to drop out due to inactive disease and, therefore, we used the last observation carried forward (LOCF) as imputation method. To ensure our results and hypothesis were valid, we performed sensitivity analyses using only complete cases. Results of the complete cases were similar, but tended to be more severe for all outcomes, which confirms our hypothesis.

Finally, the selection of early arthritis patients from the tREACH trial may have introduced a selection bias. In our analysis, we saw that the baseline DAS ($P < 0.05$) was in favour of the group without risk factors. Therefore, we adjusted for baseline DAS in all our analysis. The crude and adjusted analyses showed similar results for the primary outcomes.

The strength of this study is the consistency within the results. For example, early arthritis patients without risk factors had a higher chance at (S)DFR, used less biologicals and could taper their treatment more often with less chance at a disease flare. No contradictory results were found. However, we had a small number of patients with no risk factors present. Therefore, future research is needed to validate our results.

In conclusion, the chance at drug-free remission in early arthritis diminishes when more risk factors for persistent disease are present and this is irrespective of the given initial csDMARD therapy. Moreover, early initiation of csDMARDs within this group of patients is associated with a better clinical course. Therefore, it is important to start csDMARDs as soon as possible, even if a definite diagnosis is not made, but treatment might be stratified on the number of risk factors present. However, validation is needed.

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Date availability statement

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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