OPEN ACCESS

CLINICAL SCIENCE

Achieving remission in psoriatic arthritis by early initiation of TNF inhibition: a double-blind, randomised, placebo-controlled trial of golimumab plus methotrexate versus placebo plus methotrexate

Leonieke J J van Mens,[1,2] Henriëtte M de Jong,[1,2] Inka Fluri,[1,2] Michael T Nurmohamed,[2,3] Marleen G H van de Sande,[1,2] Marc Kok,[4] Arno W R van Kuijk,[2,5] Dominique Baeten[1,2]

Handling editor Josef S Smolen

[1]Clinical Immunology and Rheumatology, Amsterdam UMC, AMC/University of Amsterdam, Amsterdam, The Netherlands
[2]Amsterdam Rheumatology and immunology Center, Amsterdam, The Netherlands
[3]Clinical Immunology and Rheumatology, Amsterdam UMC, VU University, Amsterdam, The Netherlands
[4]Rheumatology, Maasstad Ziekenhuis, Rotterdam, The Netherlands
[5]Rheumatology, Jan van Breemen Research Institute | Reade, Amsterdam, The Netherlands

Correspondence to
Dr Dominique Baeten, Clinical Immunology and Rheumatology, Amsterdam UMC, AMC/University of Amsterdam, Amsterdam 1011 AA, The Netherlands;
d.l.baeten@amc.uva.nl

Received 11 November 2018
Revised 26 January 2019
Accepted 4 February 2019
Published Online First
26 February 2019

ABSTRACT

Objectives Early initiation of effective treatment favours remission in rheumatoid arthritis, but it remains unknown if the same concept applies to psoriatic arthritis (PsA). Therefore, this study investigated whether the combination of golimumab plus methotrexate (MTX) as a first-line treatment is superior to MTX alone in inducing remission in PsA.

Methods This investigator-initiated, multicentre, double-blind, randomised, placebo-controlled trial included 51 MTX and bDMARD-naive patients with PsA fulfilling the CASPAR criteria and with active disease at baseline (≥3 swollen joint count/tender joint count). Patients were randomised to golimumab (50 mg SC monthly)+MTX (n=26) (TNFi arm) or matched placebo+MTX (n=25) (MTX arm). MTX was started 15 mg/week and increased to 25 mg/week over 8 weeks. The primary endpoint was percentage of patients achieving Disease Activity Score (DAS) remission (<1.6) at week 22. Safety was assessed throughout the study.

Results The primary efficacy endpoint was achieved by 81% in the TNFi arm versus 42 % in the MTX arm (p=0.004). This difference in DAS remission was already observed at week 8. A significant difference in favour of the golimumab+MTX arm at week 22 was also observed for other response criteria such as MDA, ACR20/50/70, disease measures and patient-reported outcomes. The occurrence rates of adverse event and treatment-emergent adverse event were similar in both arms.

Conclusions In patients with early PsA, DAS remission at week 22 was almost doubled with golimumab+MTX versus MTX alone. This double-blind, randomised, placebo-controlled study supports the concept that early initiation of TNFi in patients with PsA favours remission.

Trial registration number NCT01871649.

Key messages

What is already known about this subject?

- Data on early intervention in psoratic arthritis (PsA) is sparse, although two studies exploring the concept in PsA (Baranauskaite, an open-label study) and peripheral SpA (Carron, randomised controlled study) suggested the contribution of early intervention in PsA.

What does this study add?

- The major finding of this study was that early initiation of the combination therapy with golimumab plus methotrexate doubled the number of patients achieving a Disease Activity Score remission when compared with methotrexate alone.
- This was confirmed by additional outcome measures, as well as by larger improvement in clinical disease activity measures and patient-reported outcomes but not function or quality of life.
- Our results extend the findings of the open-label RESPOND study that early intervention in PsA contributes to achieve remission in PsA. Future follow-up will explore if these responses are maintained up to week 50 on methotrexate monotherapy.

How might this impact on clinical practice or future developments?

- Taken together, the superior clinical efficacy and good tolerability/absence of novel safety signals, these results—in line with the results the previously published studies of Baranauskaite *et al* and Carron *et al*—suggest the value of early intervention in PsA rather than the classical step-up approach.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis affecting the joints and connective tissue and is associated with psoriasis of skin and nails. Treatment options for PsA have tremendously increased over the last two decades. The initial treatment in most patients consists of conventional synthetic disease-modifying antirheumatic drugs (csDMARDS). Patients with PsA with persistent moderate to high disease activity are eligible for tumour necrosis factor inhibitors (TNFi). In rheumatoid arthritis (RA), there is ample evidence for strategies aiming to reach and maintain remission of inflammation (ie, treat to target).[1–4] Also, the early start of treatment improved outcomes, as the earlier the start of treatment, the higher the remission rates seen.[5 6]

To cite: van Mens LJJ, de Jong HM, Fluri I, *et al*. *Ann Rheum Dis* 2019;**78**:610–616.

Whether initiation of potent targeted therapies in an early disease phase favours remission in other types of inflammatory arthritis, including PsA, remains unknown. The current treatment paradigm in PsA still consists of a step-up approach with non-steroidal anti-inflammatory drugs (NSAIDs) and/or non-biological DMARDs, mostly methotrexate (MTX) or leflunomide, as a first-line treatment.[7 8] MTX is most commonly used as first-line treatment despite the fact that its potential efficacy is not supported by randomised, placebo-controlled studies.[9] TNFi, which have demonstrated strong efficacy in multiple randomised, placebo-controlled studies in PsA,[10–13] are merely recommended as second-line therapy for patients with PsA failing to respond to first-line therapy.[7 8] More recently, other targeted therapies such as interleukine(IL)-12/ /IL-23 p40 inhibition, IL-17A inhibition and Janus kinase (JAK) inhibition have become available as second-line or third-line options.[14–17]

A couple of studies have started to explore if early initiation TNFi favours remission in PsA. Baranauskaite *et al* investigated the use of early MTX with or without infliximab in an open-label study in patients with early PsA. They showed high response in both arms, with a significantly greater improvement in the MTX plus infliximab arm compared with the MTX alone arm American College of Rheumatology response criteria (ACR20): 86.3% vs 66.7%). Larger differences were seen between the treatment arms with more stringent outcome measures such as ACR50, ACR70 and Minimal Disease Activity (MDA).[18] However, the important limitation of this study was the open-label design and these data have not yet been confirmed in a placebo-controlled setting in PsA. Exploring the same concept in a slightly different population, Carron *et al* investigated the early initiation of TNFi treatment in a placebo-controlled study in a mixed population of patients with early peripheral spondyloarthritis, of which 40% had concomitant nail or skin psoriasis.[19] Patients achieved clinical remission (defined as absence of arthritis, enthesitis and dactylitis) in 75% in the TNFi-treated arm versus 20% in the placebo arm.

Based on this circumstantial evidence that early treatment with TNFi could favour high remission rates in PsA, the current double-blind placebo-controlled randomised study was initiated to investigate whether the combination of golimumab plus MTX as a first-line treatment is superior in achieving remission compared with treatment with MTX alone in patients with PsA who are naive to MTX and TNFi.

METHODS

Study design

This investigator-initiated, randomised, placebo-controlled, double-blind study was conducted at three centres in the Netherlands between September 2013 and September 2017. Patients were randomly assigned in a 1:1 ratio to receive either five injections with golimumab (50 mg subcutaneous monthly) or matched placebo. In both arms, MTX was started at 15 mg/week orally and increased to 25 mg/week over 8 weeks. Statistical minimisation was applied for centre, number of swollen joints and disease duration using a software program ALEA, a validated randomisation tool (NKI, Amsterdam, the Netherlands). The primary endpoint of the study was measured at the end of the 22-week blinded treatment period.

Patients

Patients aged 18–70 years were eligible if they had PsA according to the Classification Criteria for Psoriatic Arthritis (CASPAR) and current active disease, defined as the presence of at least three swollen and three tender joints at baseline.[20] Patients previously treated with MTX or any biological DMARD were excluded. Allowed co-medication included NSAIDs and/or systemic steroids <10 mg/daily at stable dosages from 2 weeks prior to baseline. Local corticosteroids were not allowed within 4 weeks prior to baseline. Three patients used concomitant fumaric acid and one patient used concomitant sulphasalazine (table 1). Key exclusion criteria were the presence of latent or active tuberculosis, malignancy in the past 5 years (other than basal cell

Table 1 Baseline demographics and clinical characteristics of the study patients by treatment arm

	Golimumab+MTX (N=26)	Placebo+MTX (N=25)
Age, years	47.5 (11.8)	45.8 (11.0)
Gender (male:female)	18:8	20:5
Disease duration arthritis, years	0.5 (0.5–1.8)	0.5 (0.4–3.0)
Disease duration skin, years	6.0 (1–20)	11 (4–19)
Prior use of csDMARD (leflunomide)	1	0
Concomitant use of topical psoriasis treatment	6	13
Concomitant use of fumaric acid (N)	1	2
Concomitant use of sulfasalazine (N)	0	1
Concomitant NSAID use at baseline (N)	16	17
Concomitant corticosteroid use at baseline (N)	0	0
DAS CRP	2.3 (1.03)	2.46 (0.87)
Swollen joint count (median (IQR))	7 (4–8.25)	5 (4–9.5)
Tender joint count (median (IQR))	9.5 (4–15.25)	10 (5.5–17)
PASI score (median (IQR))	1.6 (0.32–3.3)	2.3 (0.3–6.8)
No of patients with baseline PASI >2.5	10	10
No of patients with enthesitis	4	7
No of patients with dactylitis	9	8
No of patients reporting inflammatory axial symptoms at baseline	4	2
ESR (mm/h)	20.5 (6.5–33.3)	15.0 (5.0–29)
No of patients with raised ESR (>20 mm/h)	13	14
CRP (mg/dL)	4.5 (1.23–13.3)	7.0 (2–15.9)
No of patients with raised CRP (>5 mg/dL)	14	9
VAS patient global (mm)	44.7 (24.7)	39.3 (23.4)
VAS patient pain (mm)	43.5 (24.2)	41.3 (28.4)
VAS physician (mm)	44.5 (14.5)	47 (19.7)
Morning stiffness (min)	44 (32.5)	42.3 (33.3)
BASDAI	41.0 (18.6)	41.3 (23.3)

Values are mean (SD), N or median (p25, p75).
BASDAI, Bath ankylosing spondylitis disease activity index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MTX, Methotrexate; NSAID, non steroidal anti inflammatory drug; PASI, psoriasis activity and severity index; VAS, visual analogue scale on a 0-100mm scale.

carcinoma of the skin), recent severe infections or other severe diseases that may affect patient's participation to the study in the opinion of the investigator.

The study was conducted in compliance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki.

Assessments

The primary efficacy endpoint of this study was the proportion of patients achieving a status of Disease Activity Score (DAS) remission at week 22, defined by a DAS C reactive protein (CRP) score <1.6 (0.54×SQRT(Ritchie Articular Index)+0.065× swollen joint count (SJC)44+0.17×ln(CRP+1)+0.0072×Visual Analogue Scale (VAS) global health+0.45).[21] Secondary endpoints included additional response criteria such as MDA,[22] DAS score low disease activity (LDA) (<2.4), DAPSA LDA and ACR20/50/70 responses. Disease activity measures included 66/68 tender and swollen joint count (TJC/SJC), dactylitis count, Leeds Enthesitis Index including the plantar fascii,[23] Psoriasis acitivity and severity index (PASI) and PASI 75 (≥75% improvement in the PASI score) for subjects with baseline PASI ≥2.5, CRP, ESR and VAS physician. Patient-reported outcomes (PROs) were patient pain and patient global score on a VAS from 0 to 100 mm, morning stiffness duration, and Bath Ankylosing Spondylitis Index (BASDAI). Function and quality of life were assessed using the Short Form 36 (SF36), Health Assessment Questionnaire (HAQ) and Dermatology Life Quality Index (DLQI) scores. All efficacy endpoints were evaluated at week 22 as well as at week 8.

Safety endpoints included adverse events (AEs) and serious AEs (SAEs), and discontinuation or interruption of study treatments because of AEs. Routine laboratory investigations, vital signs and physical examination findings were recorded at screening and at every visit (baseline, weeks 4, 8, 14 and 22).

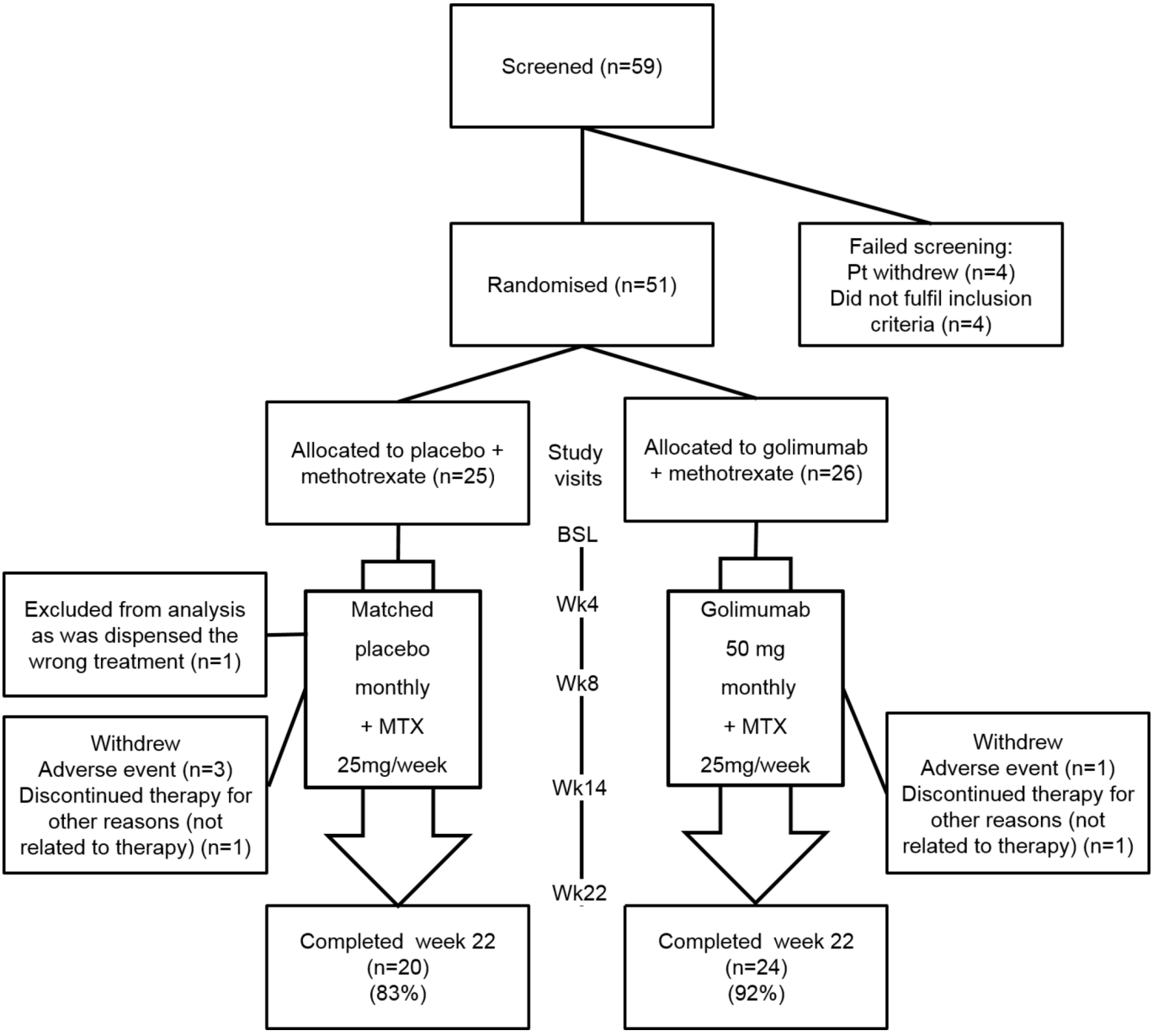

Figure 1 Overview of patient disposition and study design. Patients were randomly assigned in a 1:1 ratio to receive either five injections with golimumab (50 mg SC monthly) or matched placebo. In both arms, methotrexate (MTX) was started at 15 mg/week orally and increased to 25 mg/week over 8 weeks.

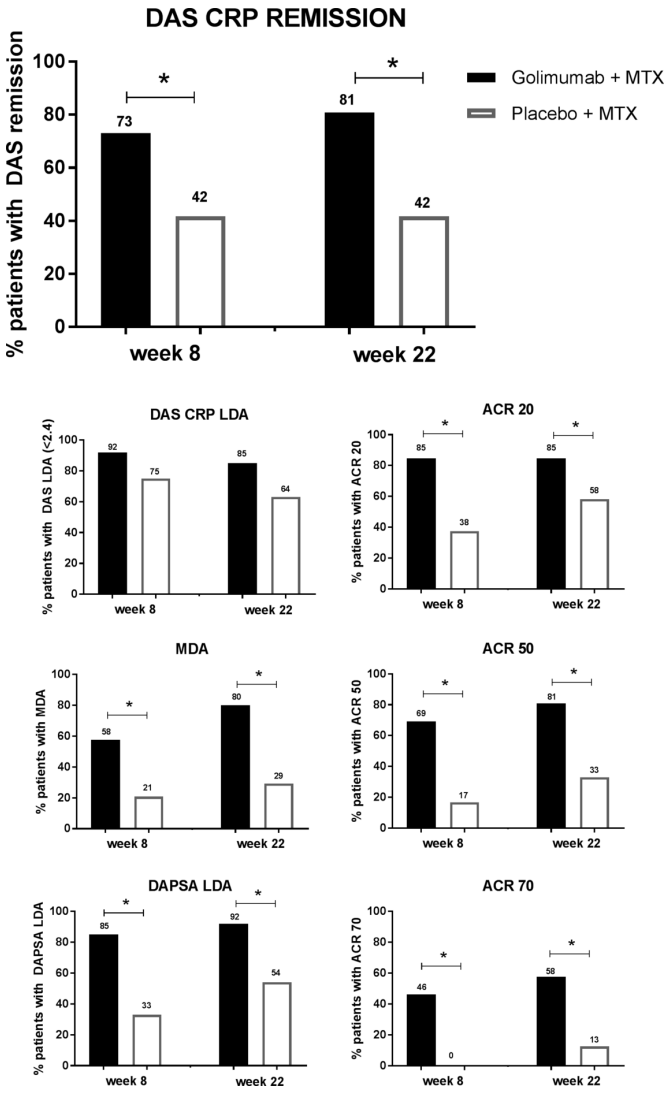

Figure 2 Primary and secondary response measures: upper panel: percentage of patients in DAS CRP remission after 8 and 22 weeks in the golimumab+MTX and the placebo+MTX arm, respectively. Other panels: percentage of patients reaching DAS CRP LDA, MDA, DAPSA LDA and ACR20/50 and 70 responses.

Statistical analysis

The sample size was calculated based on the results of the RESPOND study. This open-label study of Baranauskaite *et al*[18] showed a DAS remission rate of 68.6% in the TNFi+MTX arm versus 29.2% in the MTX arm. Therefore, we estimated an expected 40% difference in response rate between both treatment arms. Considering a two-sided significance level of 0.05 and a power of 80%, the power analysis indicated 24 patients each arm.

Baseline characteristics and safety analyses included all randomised patients who received at least one dose of trial medication (51 patients). For efficacy analyses, one individual with wrong administration of golimumab versus placebo due to protocol violation was excluded from the MTX arm. Therefore, the intention-to-treat population for efficacy included 50 patients. Missing data were handled using non-responder imputation for the primary endpoint as well as all other binary endpoints and using last observation carried forward for continuous variables. Values are reported as mean (SD) or median (IQR) as applicable. At each time point, differences between placebo and golimumab were tested using a χ^2 test for the categorical variables, and an ANCOVA with the baseline variable as covariate for continuous variables. All statistical tests were two sided and p values of <0.05 were considered statistically significant.

RESULTS

Study population and patient disposition

A total of 59 patients were screened at three rheumatology clinics in The Netherlands between September 2013 and September 2017 (figure 1). Fifty-one patients were randomised to receive either golimumab+MTX (n=26) (TNFi arm) or placebo+MTX (n=25) (MTX arm). The baseline characteristics were similar in the two treatment arms(table 1).

Median time since diagnosis was 0.5 (0.5–2) years, most patients (35/50) presented with a polyarticular disease pattern, and the median SJC was 5 (4–8) and TJC 10.[5–15] Twenty patients had a PASI score ≥2.5 at baseline, and enthesitis was present in 11 patients and dactylitis in 17 patients.

Prior to unblinding, one patient from the MTX arm was excluded from all efficacy analyses due to an error at the pharmacy causing the wrong treatment to be administered. The efficacy analyses are therefore based on data of 50 patients: golimumab+MTX (n=26) and placebo+MTX (n=24).

During the 22-week period, in total six patients did not complete the study period as scheduled; reasons reported for drop out were two patients were lost to follow-up due to adverse events (one in the TNFi arm and one in the MTX arm both at week 14 of the study) and four patients withdrew their informed consent (one in the TNFi arm and three in the MTX arm).

All patients completing the 22-week study period received the full 5/5 of assigned study injections. The overall mean dosage of MTX during the full 22-week period was mean (SD) of 19.2 (4.5) mg/week in the TNFi arm and 21.2 (2.4) mg/week in the MTX arm.

Efficacy

The study met the primary efficacy endpoint with DAS remission at week 22 achieved by a greater number of patients in the TNFi arm (21/26;81%) versus the MTX arm (10/24;42%) (p=0.004) (figure 2). This difference in favour of the golimumab+MTX arm was confirmed by other composite response criteria at week 22 (figure 2): TNFi-treated patients reached an MDA in 21/26 (81%) versus 7/24 (29%) in the MTX arm (p<0.001). Although not reaching statistical significance, a similar trend was seen for DAS CRP LDA (85% vs 64%, p=0.072), and a DAPSA LDA was achieved in 92% versus 54% (p=0.001). An ACR 20/50/70 response was achieved by respectively 85%, 81% and 58% in the TNFi arm versus 58%, 33% and 13% in the MTX arm (p=0.039, p=0.001 and p=0.001, respectively). With exception of DAS CRP LDA, statistically significant differences were already seen by week 8 for all these response measures (figure 2).

Disease activity measures, PROs, and measures of physical function and quality of life are listed in table 2.

Significant differences in response on PROs included VAS patient pain, VAS patient global, morning stiffness duration and BASDAI. This effect was already seen at week 8 for VAS global. No significant differences were seen in physical functioning and in health-related quality of life between both arms at week 22. No significant differences were seen in the achievement of PASI75 and DLQI scores.

Safety and AEs

One serious AE occurred in a patient in the MTX arm (cervical spine stenosis, requiring surgery), which was considered not

Table 2 Disease activity and patient-reported outcomes at baseline, week 8 and week 22

	Baseline		Week 8			Week 22		
Efficacy measures	Golimumab+MTX	Placebo+MTX	Golimumab+MTX	Placebo+MTX	P value for group difference	Golimumab+MTX	Placebo+MTX	P value for group difference
DAS CRP	2.1 (1.7–2.7)	2.4 (1.9–2.9)	1.12 (0.7–1.61)	1.8 (1.31–2.34)	0.002	0.91 (0.68–1.36)	1.8 (1.18–2.19)	0.000
Swollen joint count	7 (4–8.3)	5 (4–10.3)	1 (0–3)	4 (1.5–8)	0.003	0 (0–1.25)	2 (0–4)	0.042
Tender joint count	9.5 (4–15.3)	10 (5.3–15.5)	1 (0–4)	5 (3–9.8)	0.019	0 (0–4)	3 (1–5)	0.019
PASI (in group with BSL PASI >2.5)	5.75 (4.0–7.55)	4.95 (3.5–8.45)	0.65 (0–3.05)	2.7 (0.75–4.25)	0.210	0.55 (0–1.9)	0.5 (0–1.95)	0.924
No of patients with enthesitis	4	7	4	3	0.594	2	4	0.209
No of patients with dactylitis	9	8	5	5	0.836	0	1	0.313
ESR (mm/h)	20.5 (6.5–33.3)	15.5 (5–30.5)	2 (2–5)	8 (5–19)	0.003	2 (2–18)	8 (2–13)	0.566
CRP (mg/dL)	4.5 (1.2–13)	7.1 (2.2–16.6)	0.75 (0.3–2.95)	2.9 (1.25–7.75)	0.079	1.1 (1.48–2.85)	3.6 (1.2–7.0)	0.144
VAS patient global (mm)	48(26–59)	36 (25–54)	21 (6–36)	31 (16–46)	0.184	9 (4–32)	31 (14–57)	0.038
VAS patient pain (mm)	44 (29–64)	34 (17–7)	11 (3–24)	30 (16–38)	0.003	6 (2–18)	34 (6–58)	0.001
VAS physician (mm)	48 (37–53)	46 (37–64)	10 (6–25)	33 (19–50)	0.000	4 (1–20)	18 (9–33)	0.047
BASDAI	40.5 (29.9–56.3)	47.1 (19.1–56.9)	36.5 (16.3–59.6)	41.6 (22.5–61.0)	0.287	18.1 (4.9–23)	24.6 (11.7–49.5)	0.022
HAQ	0.38 (0.19–1.0)	0.63 (0.19–1.47)	0 (0–0.3)	0.43 (0.03–0.84)	0.003	0 (0–0.125)	0.25 (0–0.5)	0.403
SF36 PCS	41.1 (35.8–48.1)	43.6 (36.1–48.5)	47.0 (40.9–55.1)	48.8 (45.3–53.0)	0.056	50.1 (43.7–52.2)	50.7 (44.5–52.1)	0.543
SF36MCS	47.9 (40.7–55.4)	51.6 (47.4–56.6)	51.7 (40.7–56.8)	50.3 (44.2–56.5)	0.041	50.7 (40.0–55.5)	50.9 (37.8–52.7)	0.125
DLQI	2 (0–7)	2 (0–5.75)	1 (0–3.5)	1 (0–5)	0.891	1 (0–3)	0 (0–3.5)	0.272

Values are median (p25, p75) or No of patients.
BASDAI, Bath ankylosing spondylitis disease activity index; CRP, C-Reactive Protein; DLQI, Dermatology Life Quality Index; ESR, Erythrocyte Sedimentation Rate; HAQ, Health Assessment Questionnaire; PASI, psoriasis activity and severity index; SF36, Short form 36 Physical Component Score; SF36 MCS, Short form 36 Mental Component Score; VAS, Visual Analogue Scale.

to be study related and did not result in early withdrawal. AEs occurring during the study period are described in table 3.

The incidence in adverse events was similar between arms. In total, 43/50 patients experienced at least one AE during the trial period (range, 1–7), all of which were graded mild to moderate. The most frequent AE involved nausea and occurred in similar incidences in both treatment arms and considered to likely to be treatment related. In 18 patients, an AE led to temporary halt and/or lowering of MTX dosage, and four AEs led to early withdrawal from the trial. No deaths occurred.

Table 3 Adverse event types and incidence up to 22 weeks

	Golimumab+MTX (n=26)	Placebo+MTX (n=25)
Subjects with SAE (non study-drug related)	0	1
Subjects with AE/event leading to lower or quit MTX		
Total	8	11
ALAT elevation	2	6
Nausea/vomiting	4	2
Infection	2	3
No of subjects with other treatment-related AE	21	22
Liver toxicity	2	5
Upper airway infections	5	5
Other infections	3	8
Headaches	1	1
Malaise/tiredness around MTX intake	5	5
Nausea/vomiting	17	13
Other	8	8

MTX, methotrexate; SAE, Severe adverse event.

DISCUSSION

The major finding of this randomised, double-blind, placebo-controlled study was that the combination of golimumab plus MTX as a first-line treatment is superior to treatment with MTX alone in patients with early PsA who are naive to MTX.

When interpreting the data of this study, two factors related to study design should be carefully considered. First, the study was specifically designed to compare the combination of a TNFi+MTX with MTX monotherapy and not to study the efficacy of MTX monotherapy itself. Monotherapy with MTX was chosen as the control arm for the sole reason that this is currently the most frequently used first-line therapy in PsA and is recommended by several guidelines.[8 24] Therefore, MTX reflects current standard of care despite the fact that previous trials of MTX in PsA failed to unequivocally establish efficacy.[9 18] As one of the potential reasons for the lack of efficacy in previous trials was the relatively low dosage of MTX (up to 15 mg/week), we used a more aggressive dosing scheme with a start dose of 15 mg/kg, a rapid dose increase to 25 mg/week over 8 weeks, which resulted in a mean dose of around 20 mg/week over the 22-week study period. Whereas this was aimed to reflect the full potential of MTX in early PsA, the absence of a non-treated placebo arm and the powering (aimed for the golimumab+MTX vs MTX alone) precludes meaningful conclusions on the potential efficacy of MTX as standalone treatment.

Also, we used here golimumab as a prototype TNFi; although not formally demonstrated, there is no scientific or clinical evidence suggesting that the concept demonstrated here would not apply to all TNFi. Whether the concept also applies to other biologic targeted therapies used in PsA (anti-IL-17A, anti-p40, anti-p19) remains to be investigated.

Second, the population included in this trial of patients with early, MTX-naïve PsA differs considerably from previous pivotal

large phase III randomised controlled trials. As expected, disease duration was much shorter (0.5 years in our study vs 6–7 years in the large phase III studies) and, in line with the inclusion criterium of a minimum SJC/TJC of 3 at baseline, both SJC (median 5 vs 12) and TJC (10 vs 21) were lower in this trial in early, MTX-naive disease.[10 16 25] Whereas the population we included here is likely more representative of early untreated PsA, the differences in baseline features do not allow to compare the outcomes between this study and previous pivotal phase III trials.

Within this particular framework of study design, the study met its primary endpoint by demonstrating that almost double the number of patients treated with golimumab+MTX achieved DAS remission at week 22 versus MTX alone. Similar or even more pronounced differences were confirmed by other outcome measurements such as DAPSA LDA, MDA, AR50 and ACR70, as well as by several PROs. Moreover, most of these differences were already observed at week 8. The early and consistent improvement in stringent response criteria in favour of the golimumab+MTX arm confirms and extends the results of the open-label RESPOND study[18] that early initiation of TNFi contributes to achieve low disease activity or even remission in PsA.

The DAS remission was chosen as the primary endpoint as this measure a 'depth of response' instead of a decrease of disease activity as measured by ACR response. We included several secondary endpoints, including the traditional response measures, showing similar results.

Our data raise a number of additional questions. First, clear effects were already seen at week 8, but most outcomes were even more pronounced at week 22. It remains unknown if the responses—in particular the stringent responses such as remission—have already plateaued at week 22 or could even further increase over time. Similarly, it remains to be determined if the combination of TNFi and MTX is only needed for the induction of remission or is also needed to maintain this state of remission over time. To this purpose, golimumab (or placebo) was stopped at week 22 in those patients achieving DAS CRP remission and an extension of the present study will explore if responses are maintained up to week 50 on MTX monotherapy.

Second, the improvement in outcome measurements was paralleled by significant improvement of single disease parameters such as SJC and TJC, but not enthesitis, dactylitis and PASI. This could of course be due to the fact that only a fraction of the patients included in this PoC study had these disease manifestations (table 1) and, accordingly, that the study was underpowered to detect potential differences. Alternatively, MTX could be more effective for these disease manifestations than for pure articular disease, as suggested for skin by the proven efficacy of MTX in psoriasis.[26]

Third, HAQ showed a significantly larger improvement in golimumab+MTX versus placebo+MTX at week 8 but that was not maintained at week 22, with a gradual improvement in HAQ also observed in the MTX alone arm. More intriguingly, there was no difference at all in SF36 and DLQI scores between both treatment arms. Obviously, the study was not powered to this purpose, but the total absence of numerical trends suggest that the improvements in disease outcome measures are not reflected in function and QoL in this population with early disease. Further research is needed to fully explore this disconnect.

Fourth, in this study we did not include MRI or ultrasound to evaluate the presence or absence of active synovitis or enthesitis or their resolution over time. Arthritis and enthesitis was scored by joint and enthesitis counts. These types of assessments would have required a much larger study population. An interesting follow-up question would be if the observed clinical remission in peripheral PsA truly represents a resolution of inflammation without any signs of subclinical inflammation on imaging, and second, if the differences in achieved remission rates also protect from development of structural damage.

Finally, the potential benefit of early initiation of TNFi should be balanced against potential risks. In this study, treatment with either golimumab+MTX or placebo+MTX was well tolerated, only a small number of patients withdrew from the study due to AEs and no treatment-related severe AEs occurred during the study period. The AEs in this study were similar in both treatment arms and were consistent with previous studies with TNFi and MTX (mostly in longer standing disease),[10 13 27 28] without any novel safety signal. However, the study size and duration limits the interpretation of safety and tolerability.

In conclusion, initiation of combination therapy with golimumab+MTX in patients with early, MTX-naive PsA doubled the number of patients achieving DAS remission when compared with placebo+MTX. This was confirmed by additional outcome measures, as well as by larger improvement in clinical disease activity measures and PROs but not function or QoL. Taken together with the good tolerability and absence of novel safety signals, these results—in line with the results of an open-label study in PsA[9] and a randomised controlled trial in pSpA[19]—suggest the value of early intervention in PsA rather than the classical step-up approach.

Correction notice This article has been corrected since it first published online. The open access licence type has been amended.

Acknowledgements We like to thank the referring physicians, study personnel and patients for their contribution to this study. DB was supported by a VICI grant from the Netherlands Organization for Scientific Research (NWO) and a Consolidator grant from the European Research Council (ERC).

Contributors All authors were involved in drafting the article or revising it critically, and all authors approved the final version of the manuscript to be published. LJJvM, MTN, AWRvK and DB were involved in the study conception and design. LJJvM, HMdJ, IF, MGHvdS, MK and AWRvK were involved in the acquisition of study data. LJJvM, IF, HMdJ, MGHvdS, MK, AWRvK and CB were involved in the analysis and interpretation of the study data.

Funding This investigator-initiated study was supported by supply of study medication and an unrestricted grant from MSD.

Competing interests DB is currently an employee of UCB Pharma. LJJvM, IF and HMdJ have nothing to disclose. MGHvdS has been an advisor for Abbvie and Novartis, and received research grants from Janssen, Eli Lily and Novartis. The department of MK is supported by Novartis, Abbvie, Pfizer, Roche, Lilly and BMS, and MK has been an advisor for Novartis and Abbvie. MTN received research grants, consultation and/or speaking fees from Abbvie, BMS, Celgene, Eli Lilly, Janssen, MSD, Mundipharma, Novartis, Pfizer, Roche, Sanofi and UCB Pharma. AWRvK received speaker fees from Celgene, Novartis, Eli Lilly and Janssen, and received research support from MSD and Janssen.

Patient consent for publication Obtained.

Ethics approval The study was approved by the medical ethics committee of the Academic Medical Centre in Amsterdam.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Moura CS, Abrahamowicz M, Beauchamp M-E, *et al*. Early medication use in new-onset rheumatoid arthritis may delay joint replacement: results of a large population-based study. *Arthritis Res Ther* 2015;17:1–9.
2 Nell VPK, Machold KP, Eberl G, *et al*. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. *Rheumatology* 2004;43:906–14.

3 Machold KP, Landewé R, Smolen JS, *et al*. The stop arthritis very early (save) trial, an international multicentre, randomised, double-blind, placebo-controlled trial on glucocorticoids in very early arthritis. *Ann Rheum Dis* 2010;69:495–502.
4 Verstappen SMM, McCoy MJ, Roberts C, *et al*. Beneficial effects of a 3-week course of intramuscular glucocorticoid injections in patients with very early inflammatory polyarthritis: results of the STIVEA trial. *Ann Rheum Dis* 2010;69:503–9.
5 Bijlsma JWJ, Welsing PMJ, Woodworth TG, *et al*. Early rheumatoid arthritis treated with tocilizumab, methotrexate, or their combination (U-Act-Early): a multicentre, randomised, double-blind, double-dummy, strategy trial. *The Lancet* 2016;388:343–55.
6 Rantalaiho V, Korpela M, Laasonen L, *et al*. Early combination disease-modifying antirheumatic drug therapy and tight disease control improve long-term radiologic outcome in patients with early rheumatoid arthritis: the 11-year results of the Finnish rheumatoid arthritis combination therapy trial. *Arthritis Res Ther* 2010;12.
7 Gossec L, Smolen JS, Ramiro S, *et al*. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. *Ann Rheum Dis* 2015.
8 Coates LC, Kavanaugh A, Mease PJ, *et al*. Group for research and assessment of psoriasis and psoriatic arthritis: treatment recommendations for psoriatic arthritis 2015. *Arthritis Rheumatol* 2016;67.
9 Kingsley GH, Kowalczyk A, Taylor H, *et al*. A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. *Rheumatology* 2012;51:1368–77.
10 Antoni C, Krueger GG, de Vlam K, *et al*. Infliximab improves signs and symptoms of psoriatic arthritis: results of the impact 2 trial. *Ann Rheum Dis* 2005;64:1150–7.
11 Kavanaugh A, McInnes I, Mease P, *et al*. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum* 2009;60:976–86.
12 Mease PJ, Fleischmann R, Deodhar AA, *et al*. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). *Ann Rheum Dis* 2014;73:48–55.
13 Mease PJ, Gladman DD, Ritchlin CT, *et al*. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005;52:3279–89.
14 Kavanaugh A, Ritchlin C, Rahman P, *et al*. Ustekinumab, an anti-IL-12/23 p40 monoclonal antibody, inhibits radiographic progression in patients with active psoriatic arthritis: results of an integrated analysis of radiographic data from the phase 3, multicentre, randomised, double-blind, placebo-controlled PSUMMIT-1 and PSUMMIT-2 trials. *Ann Rheum Dis* 2014;73:1000–6.
15 Mease PJ, McInnes IB, Kirkham B, *et al*. Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. *N Engl J Med* 2015;373:1329–39.
16 McInnes IB, Sieper J, Braun J, *et al*. Efficacy and safety of secukinumab, a fully human anti-interleukin-17A monoclonal antibody, in patients with moderate-to-severe psoriatic arthritis: a 24-week, randomised, double-blind, placebo-controlled, phase II proof-of-concept trial. *Ann Rheum Dis* 2014;73:349–56.
17 Gladman D, Rigby W, Azevedo VF, *et al*. Tofacitinib for psoriatic arthritis in patients with an inadequate response to TNF inhibitors. *N Engl J Med* 2017;377:1525–36.
18 Baranauskaite A, Raffayová H, Kungurov NV, Kungurov NV, *et al*. Infliximab plus methotrexate is superior to methotrexate alone in the treatment of psoriatic arthritis in methotrexate-naive patients: the respond study. *Ann Rheum Dis* 2012;71:541–8.
19 Carron P, Varkas G, Cypers H, *et al*. Anti-TNF-induced remission in very early peripheral spondyloarthritis: the CRESPA study. *Ann Rheum Dis* 2017;76:1389–95.
20 Taylor W, Gladman D, Helliwell P, *et al*. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006;54:2665–73.
21 van Gestel AM, Prevoo ML, van 't Hof MA, *et al*. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism criteria. *Arthritis Rheum* 1996;39:34–40.
22 Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. *Ann Rheum Dis* 2010;69:48–53.
23 Healy PJ, Helliwell PS. Measuring clinical enthesitis in psoriatic arthritis: assessment of existing measures and development of an instrument specific to psoriatic arthritis. *Arthritis Rheum* 2008;59:686–91.
24 Gossec L, Smolen JS, Ramiro S, *et al*. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. *Ann Rheum Dis* 2016;75:499–510.
25 Keystone EC, Genovese MC, Klareskog L, *et al*. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. *Ann Rheum Dis* 2009;68:789–96.
26 Schmitt J, Rosumeck S, Thomaschewski G, *et al*. Efficacy and safety of systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. *Br J Dermatol* 2014;170:274–303.
27 Mease PJ, Kivitz AJ, Burch FX, *et al*. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. *Arthritis Rheum* 2004;50:2264–72.
28 Kavanaugh A, van der Heijde D, McInnes IB, *et al*. Golimumab in psoriatic arthritis: one-year clinical efficacy, radiographic, and safety results from a phase III, randomized, placebo-controlled trial. *Arthritis Rheum* 2012;64:2504–17.