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CLINICAL SCIENCE

GO-DACT: a phase 3b randomised, double-blind, placebo-controlled trial of GOlimumab plus methotrexate (MTX) versus placebo plus MTX in improving DACTylitis in MTX-naive patients with psoriatic arthritis

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ABSTRACT

Objectives To assess the efficacy of golimumab in combination with methotrexate (MTX) versus MTX monotherapy in psoriatic arthritis (PsA) dactylitis.

Methods Multicentre, investigator-initiated, randomised, double-blind, placebo-controlled, parallel-design phase 3b trial in 11 Portuguese rheumatology centres. Patients with PsA along with active dactylitis and naive to MTX and biologic disease-modifying antirheumatic drugs (bDMARDs) were randomly assigned to golimumab or placebo, both in combination with MTX. The primary endpoint was Dactylitis Severity Score (DSS) change from baseline to week 24. Key secondary endpoints included DSS and Leeds Dactylitis Index (LDI) response, and changes from baseline in the LDI and MRI dactylitis score. Analysis was by intention-to-treat for the primary endpoint.

Results Twenty-one patients received golimumab plus MTX and 23 MTX monotherapy for 24 weeks. One patient from each arm discontinued. Patient inclusion was halted at 50% planned recruitment due to a favourable interim analysis. Median baseline DSS was 6 in both arms. By week 24, patients treated with golimumab plus MTX exhibited significantly greater improvements in DSS relative to MTX monotherapy (median change of 5 vs 2 points, respectively; p=0.026). In the golimumab plus MTX arm, significantly higher proportions of patients achieved at least 50% or 70% improvement in DSS and 20%, 50% or 70% improvement in LDI in comparison to MTX monotherapy.

Conclusions The combination of golimumab and MTX as first-line bDMARD therapy is superior to MTX monotherapy for the treatment of PsA dactylitis.

Trial registration number NCT02065713

Key messages

What is already known about this subject?

- Psoriatic dactylitis is associated with higher psoriatic arthritis disease activity and articular erosions.
- Treatment algorithms are controversial due to the absence of randomised controlled trials assessing dactylitis as a primary endpoint, especially in the context of methotrexate (MTX) versus tumour necrosis factor inhibitors /MTX combination.

What does this study add?

- The GO-DACT trial showed that the combination of golimumab plus MTX is associated with significantly greater clinical improvements in dactylitis in comparison with MTX monotherapy.

How might this impact on clinical practice or future developments?

- GO-DACT provides evidence that combining golimumab plus MTX is more efficacious than MTX monotherapy in improving psoriatic arthritis (PsA) dactylitis.
- GO-DACT showed that application of the innovative Dactylitis Severity Score (DSS) and Leeds Dactylitis Index (LDI) response indices (DSS20, 50 and 70 and LDI20, 50 and 70) allowed discrimination between treatment arms, which could be useful for future PsA trials.
- The GO-DACT trial provides data in an area of previously limited evidence to inform the creation of clinically useful treatment algorithms, aiming at the optimal care of patients with PsA.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory disease of substantial phenotypic heterogeneity. Such heterogeneity poses challenges in

management, particularly in deriving a sufficient evidence base to address clinical subtypes. Dactylitis is a hallmark of PsA[1] for which therapeutic strategies remain empirical.[2] Commonly, non-steroidal anti-inflammatory drugs (NSAIDs) and local corticosteroid injections are employed.[3] Patients with PsA with dactylitis have higher disease activity and increased erosion risk.[4–6] Guidelines by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis recommend conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate (MTX), as a first-line on NSAIDs failure, but allow for expedited biologic disease-modifying antirheumatic drugs (bDMARDs) based on individual decisions.[7] European League Against Rheumatism recommends the use of tumour necrosis factor inhibitors (TNFi) or biologics targeting interleukin (IL)-12/IL-23 or IL-17 pathways in patients with dactylitis that impacts function and quality of life.[8]

Across randomised controlled trials (RCTs) of bDMARDs efficacy in peripheral PsA, dactylitis has never been studied as a primary endpoint; current practice arises from the analysis of dactylitis as a secondary outcome.[3 9 10] Golimumab, a human monoclonal antibody TNFi, has been approved for the treatment of active PsA.[11] In GO-DACT, a phase 3b trial, we assessed the efficacy of golimumab in combination with MTX versus MTX monotherapy for improving psoriatic dactylitis as a primary endpoint.

METHODS

Study design

GO-DACT was a multicentre, investigator-initiated, randomised, double-blind, placebo-controlled, phase 3b trial of golimumab plus MTX versus placebo plus MTX, in MTX-naive and bDMARDs-naive patients with PsA and active dactylitis. The study was conducted between August 2014 and June 2017 in 11 rheumatology centres in Portugal. The protocol was previously published.[12]

Patients were centrally randomised in blocks of 4 (2:2) by computer-generated random sequence to receive subcutaneous injections of 50 mg golimumab or placebo, administrated every 4 weeks for 24 weeks, both in combination with MTX. Patients and investigators were blind to treatment by providing identical prefilled syringes (MSD Pharmaceutics). MTX was started orally, 15 mg/week and increased 5 mg every 4 weeks until a maximum dose of 25 mg/week, as tolerated. For gastrointestinal intolerance, patients could be switched to a subcutaneous formulation. After the last golimumab injection, each subject was monitored for safety for 60 days (online supplementary figure 1). A planned interim efficacy analysis was performed when 50% of the estimated recruitment had completed 24 weeks follow-up.

Patient population

Patients over 18 years of age with a diagnosis of PsA according to Classification for Psoriatic Arthritis criteria[1] ≥1 digit with tender dactylitis and ≥1 other site of active inflammation (joints, enthesis, spine, skin or nails), naive to MTX and bDMARDs therapy and refractory to at least two NSAIDs at optimal dosage for 3 months were eligible for inclusion. Informed consent was obtained from all subjects before trial activity. The trial was conducted in accordance with the ethical principles of the Declaration of Helsinki, good clinical practice and approved by Portuguese Ethics Committee for Clinical Research, National Authority of Medicines and Health Products and National Data Protection Committee.

Key exclusion criteria were contraindications for the use of any TNFi or MTX, and factors that could interfere with trial evaluations or patient safety. A maximum of two previous local corticosteroids injections were allowed, administrated at least 4 weeks prior to screening. NSAIDs dose had to be stable throughout the trial. Cessation of other csDMARDs and corticosteroids, according to their recommended washout periods, was required.[12]

Trial procedures and endpoints

The primary endpoint was the change from baseline in Dactylitis Severity Score (DSS) at 24 weeks. Each digit with dactylitis was evaluated in a scale of 0–3 (0=no dactylitis, 1=mild dactylitis, 2=moderate dactylitis, 3=severe dactylitis), where scores greater than 0 indicate the presence of dactylitis and the total score was calculated as the sum of scores for all 20 digits (0–60).[13]

Key secondary endpoints included the change from baseline in Leeds Dactylitis Index (LDI), based on the ratio of the circumference of the affected digit and of the contralateral correspondent digit, multiplied by a tenderness score (graded 0–3 on a Ritchie Index) for each digit with dactylitis[14]; and the number of patients with tender and non-tender dactylitis and with dactylitis remission (DSS=0). New dactylitis response indices, defined as the percentage of patients achieving at least 20%, 50% or 70% of improvement in the DSS (DSS20, 50 or 70); and as at least 20%, 50% or 70% of improvement in the LDI (LDI20, 50 or 70) from baseline, were assessed in this trial. Enthesitis was evaluated resorting to the Leeds Enthesitis Index (LEI)[15] and the Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis score.[16] Enthesitis remission was defined as the absence of tender enthesis, according to LEI.

Additional key secondary endpoints comprised: 68 tender and 66 swollen joint counts,[17] patient-reported outcomes for global assessments of disease activity and pain and psoriasis evaluation using the Psoriasis Area Severity Index (PASI), Body Surface Area (BSA) score and Nail Psoriasis Severity Index (NAPSI) for the target nail. Other efficacy endpoints included physical function and health-related quality of life (psoriasis and global health), composite disease activity and response indices of PsA, as previously described.[12] All clinical efficacy outcomes were collected at every trial visit by a trained rheumatologist blind to treatment.

High-resolution magnetic resonance imaging (MRI), providing better spatial resolution and anatomical definition, was performed for the most affected digit and conventional MRI of the corresponding hand or foot, at baseline and week 24.[12] Images were read by an experienced musculoskeletal radiologist, blind to treatment and chronologic sequence of images. High-resolution dactylitis images were scored according to the presence (0) or absence (1) of eight imaging features (synovitis, bone oedema, subcutaneous oedema, flexor tenosynovitis, extensor tenosynovitis, plantar/volar plate enhancement, collateral ligament enhancement and erosions), at the metacarpal/metatarsophalangeal (MCP/MTP), proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints. The dactylitis total MRI score was calculated as the sum of the partial scores at each location, as previously described.[18] The psoriatic arthritis MRI score (PSAMRIS), was used to assess the overall MRI changes in the hand (PSAMRIS-H)[19] and foot (PSAMRIS-F).[20] A total of 37 patients performed paired MRIs of the hands (16 patients) or feet (21 patients), and 36 patients paired high-resolution dactylitis images, according to the most active dactylitis location. Seven patients did not undergo hand/foot MRI and one other additionally high-resolution dactylitis protocol, due

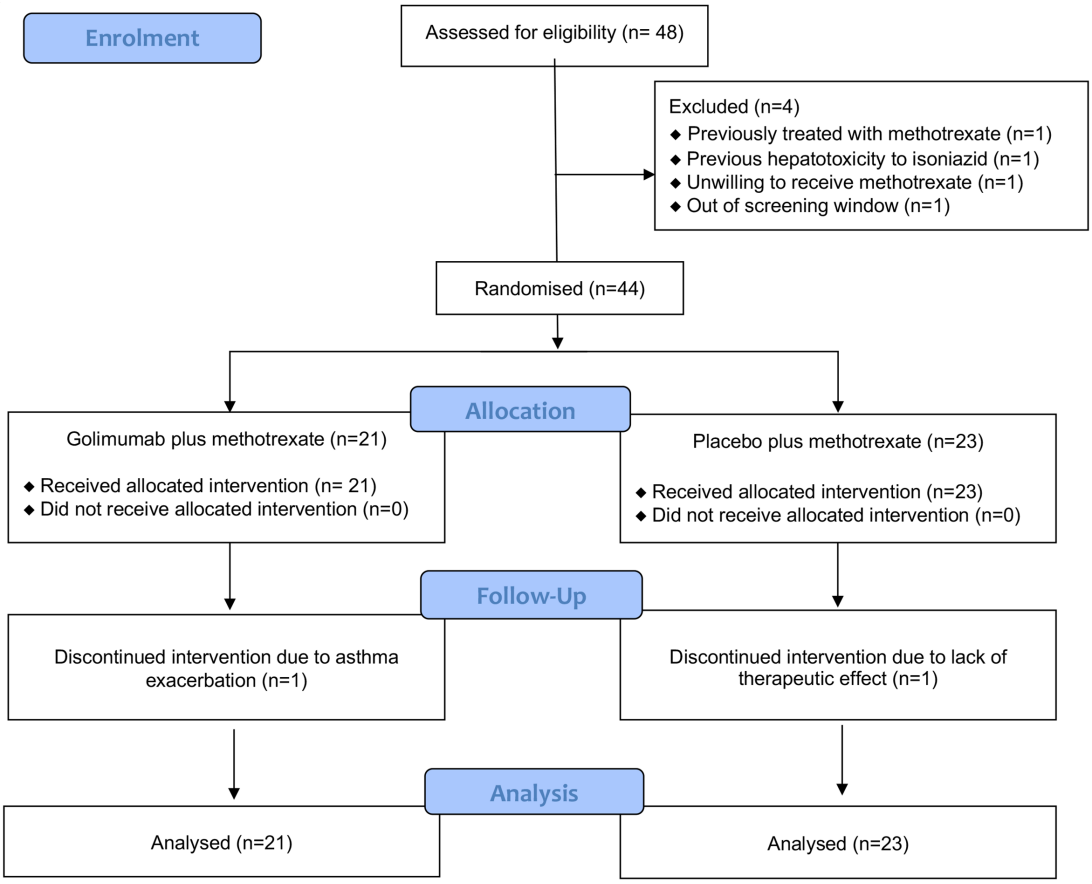

Figure 1 GO-DACT trial consort flow diagram.

to MRI equipment failure/unavailability, inability to tolerate or trial discontinuation.

Safety and tolerability were evaluated and recorded throughout.

Statistical analysis

We estimated that a sample size of 90 patients was required to detect a difference in DSS of 2.52 between groups (absolute change from GO-REVEAL trial), assuming a SD of 4.01, with a 0.05 significance level, 80% power and accounting for a dropout rate of 10%.[11 21] An interim analysis was planned when 50% of this sample size was included; when conducted, this detected favourable results for the primary endpoint. Based on these findings, patient inclusion was halted at this milestone. Efficacy endpoints were assessed as changes from baseline or as the proportion of patients achieving responses at 12 and 24 weeks. An intention-to-treat analysis was performed for the primary endpoint, applying the last observation carried forward method and including all randomly assigned patients who received at least one dose of study medication. For the remaining clinical endpoints, a per-protocol analysis was conducted, taking into consideration that only two patients (one in each treatment arm) were lost to follow-up. For safety analysis, all patients receiving at least one dose of study medication were included. All statistical analyses were done by a statistician blind to treatment. Continuous variables were summarised by median and interquartile range (IQR), and comparisons were performed using the non-parametric Wilcoxon rank-sum test. Categorical variables were summarised by frequency and percentage, and significance of difference between the two arms analysed with Fisher's exact test (including a generalised version for variables with more than two categories). All analyses were conducted using R V.3.5.0 software (https://www.R-project.org).

RESULTS

Patients disposition and baseline characteristics

A total of 44 patients with PsA enroled at 11 trial centres were randomised. Forty-two completed the study, with one patient on golimumab/MTX discontinuing due to an adverse event (asthma exacerbation), and another patient on placebo/MTX discontinuing due to an insufficient therapeutic effect (figure 1). The mean MTX dose of golimumab/MTX group was 16.3 mg/week (range: 10–25 mg) and 19.2 mg/week (range: 15–25 mg) in MTX monotherapy group. Baseline demographics and disease activity were well matched; all patients had active dactylitis at baseline, with a median baseline DSS of 6 in both arms (table 1, online supplementary table 1).

Musculoskeletal efficacy

The primary efficacy endpoint was met, whereby patients treated with golimumab/MTX exhibited significantly greater improvements by DSS at week 24 (median change of 5) relative to the placebo/MTX group (median change of 2) (p=0.026), and as early as 12 weeks (p=0.004; figure 2A). Key secondary analyses followed a similar pattern. The proportion of DSS50 and DSS70 responders at week 24 were significantly higher for patients treated with golimumab/MTX (DSS50: p=0.005, DSS70: p=0.010; figure 2B). Greater improvements from baseline and in the proportion of LDI responders were observed in the golimumab/MTX group at 24 weeks (figure 2C). The number of patients achieving dactylitis remission (DSS=0) was low in both treatment groups (6/20, 30% vs 4/22, 18.2%; table 2) and was not significantly different. A

Table 1 Baseline demographic and disease characteristics of the study population

Characteristics	Study population n=44	GLM+MTX n=21	PLB+MTX n=23
Male gender, n (%)	37 (84.0%)	17 (81.0%)	20 (87.0%)
Age at randomisation, years, median (IQR)	45.7 (19.6)	46.2 (15.5)	44.1 (24.6)
Disease duration, median (IQR)	3.9 (6.9)	3.8 (6.7)	4.2 (6.1)
Body mass index (kg/m^2), median (IQR)	26.6 (6.1)	29.0 (4.5)	25.9 (5.4)
Clinical subtype, n (%)			
Symmetric polyarthritis	9 (20.5)	5 (23.8)	4 (17.4)
Predominant arthritis of the distal interphalangeal joints	3 (6.8)	2 (9.5)	1 (4.3)
Asymmetric oligoarthritis	31 (70.5)	13 (61.9)	18 (78.3)
Arthritis mutilans	0 (0)	0 (0)	0 (0)
Predominant axial	1 (2.3)	1 (4.8)	0 (0)
Dactylitis			
DSS, median (IQR)	6 (4)	6 (5)	6 (3.5)
LDI, median (IQR)	64.7 (81.7)	69.4 (73.8)	64.0 (100)
Enthesitis			
Enthesitis, median (IQR)	1 (2)	1 (2)	1 (2)
Enthesitis ≥1 n (%)	23/44 (52.3%)	11/21 (52.4%)	12/23 (52.2%)
LEI, median (IQR)	0 (1)	0 (1)	0 (1)
LEI≥1, n (%)	16/44 (36.4%)	7/21 (33,3%)	9/23 (39,1%)
SPARCC, median (IQR)	1 (2)	1 (2)	1 (2)
SPARCC≥1, n (%)	23/44 (52.3%)	11/23 (47.8%)	12/23 (52.2%)
Peripheral joints			
Tender joints (68), median (IQR)	7.5 (9.25)	8 (9)	6 (8)
Swollen joints (66), median (IQR)	6.5 (6.5)	7 (10)	6 (5)
Psoriasis			
PASI, median (IQR)	3.05 (4.3)	4 (4)	2.4 (2.65)
BSA, median (IQR)	9.75 (21.6)	13 (29.5)	8.2 (15.3)
Target NAPSI, median (IQR)	4 (8)	4 (10)	4 (5)
Physical function			
HAQ-DI, median (IQR)	0.875 (IQR)	0.875 (0.625)	0.875 (1.25)
Health-related quality of life			
DLQI, median (IQR)	3 (4.25)	4 (4)	1 (4)
Composite indices of disease activity			
DAS28 4v, median (IQR)	4.01 (1.68)	3.71 (0.96)	4.14 (1.99)
DAPSA, median (IQR)	24.41 (21.31)	24.3 (20.84)	24.5 (20.20)
PASDAS, median (IQR)	6.13 (2.35)	6.1 (1.83)	6.2 (2.58)
CPDAI, median (IQR)	11 (I3.5)	11.0 (3.5)	11.5 (2.5)

BSA, body surface area; CPDAI, Composite Psoriatic Disease Activity Index; DAPSA, disease activity in psoriatic arthritis; DAS28 4v, Disease Activity Score 4 variablesDLQI, Dermatology Life Quality Index; DSS, Dactylitis Severity Score; GLM, golimumab; HAQ-DI, Health Assessment Questionnaire Disability Index; LDI, Leeds Dactylitis Index; LEI, Leeds Enthesitis Index; MTX, methotrexate; NAPSI, Nail Psoriasis Severity Index; PASDAS, Psoriatic Arthritis Disease Activity Score; PASI, Psoriasis Area and Severity Index; PLB, placebo; SPARCC, Spondyloarthritis Research Consortium of Canada Enthesitis Index.

total of 66.7% (14/21) patients treated with golimumab/MTX and 21.7% (5/23) treated with MTX monotherapy had absence of tenderness (LDI tenderness=0) at 24 weeks, in the digits previously affected with dactylitis.

The median baseline dactylitis MRI score was balanced between arms: 8.5 (IQR 7) in the golimumab/MTX and 8.0 (IQR 10) in placebo/MTX. At week 24, we observed significantly lower scores in patients treated with golimumab/MTX than in those treated with placebo/MTX (p=0.017). The median change of dactylitis MRI score from baseline was numerically larger for golimumab/MTX (5.5) in comparison with MTX monotherapy (3.5; p=0.273; table 3). Both golimumab/MTX and MTX monotherapy arms reduced bone oedema, subcutaneous oedema, volar and palmar/plantar and collateral enhancement scores at the MCP/MTPs and PIPs, between baseline and week 24. These changes were numerically more prevalent in golimumab/MTX group, but only significantly different between treatment arms for synovitis and bone oedema at PIPs. No change in mean erosion score at the dactylitis digits was observed during the 24 weeks of treatment (table 3). At 24 weeks, the absence of dactylitis associated-inflammatory lesions was observed in 31.0% (9/29) of all patients, 53.8% (7/13) of those receiving golimumab/MTX and 12.5% (2/16) of those receiving placebo/MTX.

GO-DACT patients had a median of 6.5/66 swollen and 7.5/68 tender joints, and moderate Disease Activity Score four variables (DAS28 4v) or high Disease Activity in Psoriatic Arthritis (DAPSA) peripheral disease activity at baseline, despite the absence of inclusion criteria regarding the number of active peripheral joints. DAS28 4v, DAPSA and Psoriatic Arthritis Disease Activity Score (PASDAS) demonstrated improvements of disease activity in the golimumab/MTX in both week 12 (p=0.004; p=0.012; p=0.0007) and week 24 (p=0.013, p=0.039; p=0.008; table 2, figure 2E) that were significantly greater than with placebo/MTX.

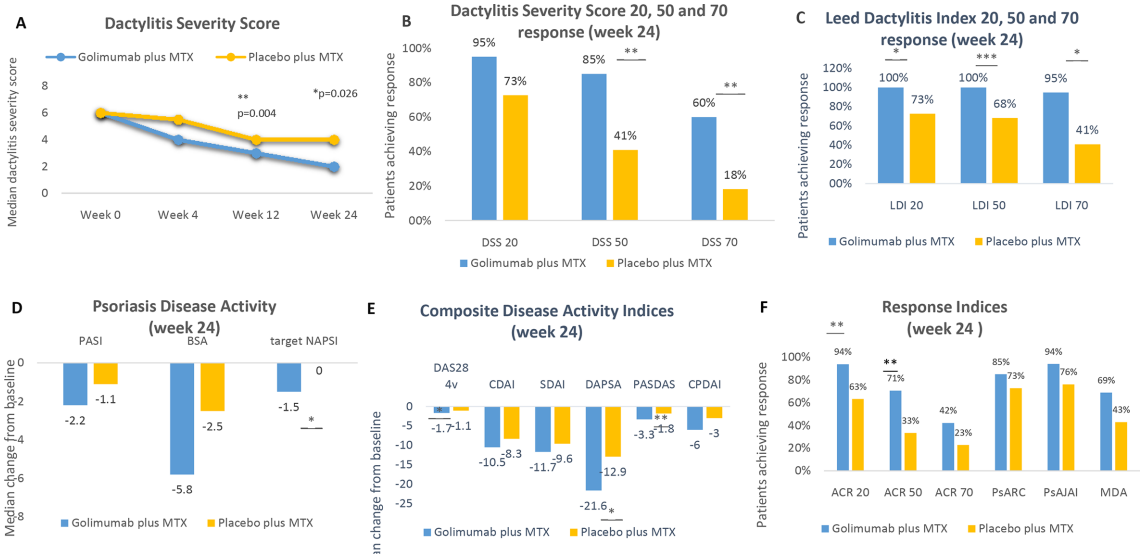

Figure 2 Changes from baseline to week 24 in DSS (A), psoriasis disease activity (D) and composite disease activity indices (E). Proportion of responders at week 24 of DSS 20, 50 and 70 (B), LDI 20, 50 and 70 (C) and response indices (F). ACR, American College of Rheumatology response index; BSA, body surface area; CDAI, clinical disease activity index; CPDAI, composite psoriatic disease activity index; DSS, Dactylitis Severity Score; DAPSA, disease activity in psoriatic arthritis; DAS28 4v, Disease Activity Score four variables; LDI, Leeds Dactylitis Index; MDA, minimal disease activity; MTX, methotrexate; NAPSI, Nail Psoriasis Severity Index; PASDAS: Psoriatic Arthritis Disease Activity Score; PASI: Psoriasis Area and Severity Index; PsAJAI, Psoriatic Arthritis Joint Activity Index; PsARC, Psoriatic Arthritis Response Criteria; SDAI, simplified disease activity index. *p<0.05; **p<0.005; ***p<0.001.

Overall, 36.4% (16/44) and 52.3% (23/44) of the patients had baseline enthesitis according to LEI and SPARCC, respectively. Median changes from baseline for both LEI and SPARCC and the percentage of patients with enthesitis remission at week 24 were not significantly different between groups (table 2).

Cutaneous efficacy

PASI and BSA and skin-related quality of life (Dermatology Life Quality Index) improved in both groups at week 24. Patients in the golimumab/MTX arm demonstrated numerically but not significantly greater responses than placebo/MTX. Golimumab/MTX was also associated with improvements in the target NAPSI, whereas no changes from baseline to week 12 or 24, were detected in placebo/MTX recipients (figure 2D).

Response indices of disease activity

At week 24, patients' improvement was numerically greater in the golimumab/MTX than placebo/MTX group for Minimal Disease Activity (MDA), Psoriatic Arthritis Response Criteria (PsARC) and Psoriatic Arthritis Joint Activity Index (PsAJAI). Statistically significant improvement was noted for American College of Rheumatology (ACR) 20 and ACR50 responses (figure 2F).

Imaging outcomes

MRI changes were described according to PSAMRIS-H and PSAMRIS-F. DIP readings were applicable only to the hands, and MCP/MTP and PIP readings were grouped together for hands and feet. Osteoproliferation at MTPs/PIPs and periarticular inflammation at PIPs of the feet were excluded due to low image resolution. Golimumab/MTX delivered greater reduction in PSAMRIS inflammatory lesion scores between baseline and week 24, but these differences were only significant in comparison with placebo/MTX for changes in PIP synovitis. Bone erosion and proliferation did not differ significantly between timepoints, regardless of location or treatment (table 4, online supplementary table 3). At 24 weeks, resolution of inflammation, defined as a PSAMRIS of 0 (excluding erosions and bone proliferation), was achieved by 12 patients; 50% (7/14) of patients in golimumab/MTX and 29.4% (5/17) in MTX monotherapy.

Safety

One hundred and two adverse events were reported during the GO-DACT study period, mostly of mild to moderate severity, overall with similar incidence between treatment arms. There were no new safety issues during this trial.

DISCUSSION

Herein we show that the combination of golimumab plus MTX is associated with significantly greater clinical improvements in dactylitis activity than MTX monotherapy. GO-DACT also demonstrated that the application of innovative DSS and LDI response indices (DSS20/50/70 and LDI20/50/70) discriminated between treatment arms, as early as 12 weeks, despite the small trial size. DSS and LDI response indices might be useful instruments for future trials assessing dactylitis. We also observed a trajectory for DSS and LDI response from week 12 to 24 commensurate with a slower achievement of maximal dactylitis response. This has been observed in RCTs with longer follow-up periods[11] ; evaluation of complete resolution of dactylitis in future trials may require follow-up longer than 24 weeks. The follow-up of these patients, according to clinical practice, might bring additional information on the long-term dactylitis remission rates.

Improvements favouring the golimumab plus MTX group occurred across other than dactylitis PsA domains including peripheral arthritis, nail psoriasis and composite measures of disease activity (DAS28 4v, DAPSA and PASDAS). PASDAS showed the ability to discriminate between treatment arms

Table 2 Efficacy outcomes change from baseline to week 12 and 24, for both treatment arms

	12 Weeks			24 Weeks		
Efficacy outcomes	**Median change GLM+MTX**	**Median change PLB+MTX**	**P value**	**Median change GLM+MTX**	**Median change PLB+MTX**	**P value**
Dactylitis						
DSS	-3.5	-1	0.004	-5	-2	0.026
DSS response						
DSS 20, n (%)	19/20 (95)	12/23 (52.2)	0.002	19/20 (95.0)	16/22 (72.7)	0.096
DSS 50, n (%)	17/20 (85)	7/23 (30.4)	0.001	17/20 (85.0)	09/22 (40.9)	0.005
DSS 70, n (%)	7/20 (35)	5/23 (21.7)	0.497	12/20 (60.0)	4/22 (18.2)	0.010
Dactylitis remission (DSS=0), n (%)	2/20 (10)	4/23 (17.4)	0.67	6/20 (30.0)	4/22 (18.1)	0.477
LDI	-58.6	-34.6	0.169	-69.4	-31.1	0.042
LDI response						
LDI 20, n (%)	19/19 (100.0)	18/23 (78.3)	0.053	19/19 (100.0)	16/22 (72.7)	0.023
LDI 50, n (%)	17/19 (89.5)	13/23 (56.5)	0.037	19/19 (100.0)	15/22 (68.2)	0.001
LDI 70, n (%)	16/19 (84.1)	9/23 (39.1)	0.004	18/19 (94.7)	9/22 (40.9)	0.011
Enthesitis						
Enthesitis	-0.5	0	0.512	-1	0	0.224
LEI	0	0	0.752	0	0	0.953
SPARCC	-0.5	0	0.589	-1	0	0.216
Enthesitis remission (LEI=0), n (%)	9/11 (81.8)	10/12 (83.3)		11/11 (100.0)	9/11 (90.0)	0.476
Peripheral joints						
Tender joints (68)	-5.5	-2	0.026	-7.5	-5	0.077
Swollen joints (66)	-6.5	-2	0.006	-7	-4	0.060
Psoriasis						
PASI	-2.4	-0.6	0.027	-2.2	-1.1	0.130
BSA	-7	-0.5	0.097	-5.8	-2.5	0.337
Target NAPSI	-2	0	0.044	-1.5	0	0.027
Patient-reported and physician-reported outcomes						
PGA for arthritis activity (0–100 mm)	-20	-12.5	0.874	-34	-16.5	0.190
PGA for psoriasis activity (0–100 mm)	-30	-10	0.846	-10	-9	0.860
Physical function						
HAQ-DI	-0.5	-0.125	0.163	-0.375	-0.188	0.414
Health-related quality of life						
DLQI	-2	-0.5	0.101	-2.5	-1	0.161
Composite indices of disease activity						
DAS28 4v	-1.67	-0.83	0.004	-1.72	-1.15	0.013
DAPSA	-17.05	-9.32	0.012	-21.62	-12.88	0.039
PASDAS	-2.7	-1.39	0.001	-3.27	-1.76	0.008
CPDAI	-2	-2	0.312	-6	-3	0.292
Response indices						
ACR						
ACR 20, n (%)	17/17 (100.0)	9/19 (47.4)	0.001	15/16 (93.8)	12/19 (63.2)	0.047
ACR 50, n (%)	11/19 (57.9)	5/21 (23.8)	0.052	12/17 (70.6)	7/21 (33.3)	0.049
ACR 70, n (%)	6/20 (30.0)	1/22 (4.5)	0.041	8/19 (42.1)	5/22 (22.7)	0.313
MDA, n (%)	10/18 (55.6)	3/23 (13.0)	0.006	11/16 (68.8)	9/21 (42.9)	0.185
PsARC, n (%)	16/20 (80.0)	13/23 (56.5)	0.119	17/20 (85.0)	16/22 (72.7)	0.460
PsAJAI, n (%)	16/18 (88.9)	14/22 (63.6)	0.082	16/17 (94.1)	16/21 (76.2)	0.197
PASI						
PASI 50, n (%)	16/20 (80.0)	10/22 (45.5)	0.029	17/20 (85.0)	12/20 (60.0)	0.155
PASI 70, n (%)	10/20 (50.0)	8/22 (36.4)	0.534	12/20 (60.0)	9/20 (45.0)	0.527
PASI 90, n (%)	5/20 (25.0)	4/22 (18.2)	0.714	5/20 (25.0)	8/20 (40.0)	0.501

ACR, American College of Rheumatology; BSA, body surface area; CPDAI, Composite Psoriatic Disease Activity Index; DAPSA, Disease Activity in Psoriatic Arthritis; DAS28 v4, Disease Activity Score four variables; DLQI, Dermatology Life Quality Index; DSS, Dactylitis Severity Score; GLM, golimumab; HAQ-DI, Health Assessment Questionnaire Disability Index; LDI, Leeds Dactylitis Index; LEI, Leeds Enthesitis Index; MDA, minimal disease activity; MTX, methotrexate; NAPSI, Nail Psoriasis Severity Index; PASDAS, Psoriatic Arthritis Disease Activity Score; PASI, Psoriasis Area and Severity Index; PGA, patient global assessment; PhGA, physician global assessment; PLB, placebo; PsAJAI, Psoriatic Arthritis Joint Activity Index; PsARC, Psoriatic Arthritis Response Criteria; SPARCC, Spondyloarthritis Research Consortium of Canada Enthesitis Index.p<0.05.

and performed better than the Clinical Disease Activity Index (CDAI), reinforcing previously published golimumab trials and 'real-world' data, suggestive of larger effect sizes for PASDAS.[22 23] Nail psoriasis has not been frequently studied in PsA RCTs.[24–26] Here, we showed significant benefit from golimumab plus MTX and an absence of improvement of target NAPSI in MTX monotherapy-treated patients, supporting previously reported lack of efficacy of MTX.[27] Others though have described improvement of the nail matrix component with MTX.[28]

We included an exploratory imaging evaluation. Evidence that either TNFi or MTX can ameliorate hand/feet PsA MRI features is limited. Both golimumab plus MTX and MTX monotherapy

Table 3 Dactylitis MRI total and partial scores

	Baseline				Week 24						
Dactylitis total score	**Population (n=36)**	**GLM+MTX (n=18)**	**PLB+MTX (n=18)**	**P value***	**Population (n=36)**	**GLM+MTX (n=18)**	**PLB+MTX (n=18)**	**P value†**	**Median change GLM+MTX**	**Median change PLB+MTX**	**P value‡**
Median (IQR)	8 (7)	8.5 (7)	8.0 (10)	0.696	3.5 (4)	2 (3)	5.5 (3)	0.017	−5.5 (4.8)	−3.5 (6.5)	0.273
(observed range)	2 to 20	2 to 17	2 to 20		0 to 17	0 to 17	0 to 7		−14 to 0	−13 to 2	

	MCP/MTP				PIP				DIP			
	GLM+MTX		PLB+MTX		GLM+MTX		PLB+MTX		GLM+MTX		PLB+MTX	
Dactylitis partial scores	**Baseline**	**Change**	**Baseline**	**Change**	**Baseline**	**Change**	**Baseline**	**Change**	**Baseline**	**Change**	**Baseline**	**Change**
Synovitis, mean	0.56	−0.28	0.78	−0.17	0.78	−0.61*	0.5	−0.22	0.38	−0.31	0.31	0.12
(observed range)	(0 to 1)	(−1 to 1)	(0 to 1)	(−1 to 0)	(0 to 1)	(−1 to 0)	(0 to 1)	(−1 to 0)	(0 to 1)	(−1 to 0)	(0 to 1)	(0 to 1)
Bone oedema, mean	0.44	−0.28	0.5	−0.39	0.67	−0.56§	0.44	−0.22	0.31	−0.23	0.38	−0.06
(observed range)	(0 to 1)	(−1 to 0)	(0 to 1)	(−1 to 1)	(0 to 1)	(−1 to 0)	(0 to 1)	(−1 to 0)	(0 to 1)	(−1 to 0)	(0 to 1)	(−1 to 0)
Subcutaneous oedema, mean	0.5	−0.44	0.67	−0.39	0.78	−0.61	0.5	−0.33	0.38	−0.31	0.5	−0.12
(observed range)	(0 to 1)	(−1 to 0)	(0 to 1)	(−1 to 0)	(0 to 1)	(−1 to 0)	(0 to 1)	(−1 to 0)	(0 to 1)	(−1 to 0)	(0 to 1)	(-1 to 1)
Flexor tenosynovitis, mean	0.33	−0.22	0.56	−0.17	0.44	−0.22	0.44	−0.17	0.23	−0.08	0.25	−0.19
(observed range)	(0 to 1)	(−1 to 1)	(0 to 1)	(−1 to 1)	(0 to 1)	(−1 to 0)	(0 to 1)	(−1 to 1)	(0 to 1)	(−1 to 0)	(0 to 1)	(−1 to 0)
Extensor paratenonitis, mean	0	0	0.11	−0.11	0	0.06	0.11	−0.11	0.15	−0.08	0.06	−0.06
(observed range)	(0 to 0)	(0 to 0)	(0 to 1)	(−1 to 0)	(0 to 0)	(0 to 1)	(0 to 1)	(−1 to 0)	(0 to 1)	(−1 to 0)	(0 to 1)	(−1 to 0)
Volar and palmar/plantar plate enhancement, mean	0.5	−0.33	0.59	−0.47	0.5	−0.44	0.44	−0.28	0.23	−0.15	0.31	−0.12
(observed range)	(0 to 1)	(−1 to 1)	(0 to 1)	(−1 to 0)	(0 to 1)	(−1 to 0)	(0 to 1)	(−1 to 0)	(0 to 1)	(−1 to 0)	(0 to 1)	(−1 to 1)
Collateral ligament enhancement, mean	0.39	−0.28	0.67	−0.33	0.39	−0.28	0.44	−0.28	0.23	−0.15	0.38	−0.12
(observed range)	(0 to 1)	(−1 to 0)	(0 to 1)	(−1 to 0)	(0 to 1)	(−1 to 0)	(0 to 1)	(−1 to 0)	(0 to 1)	(−1 to 0)	(0 to 1)	(−1 to 0)
Erosions, mean	0.39	0	0.44	0	0.61	−0.06	0.28	0	0.31	0	0.5	0
(observed range)	(0 to 1)	(−1 to 1)	(0 to 1)	(0 to 0)	(0 to 1)	(−1 to 0)	(0 to 1)	(0 to 0)	(0 to 1)	(0 to 0)	(0 to 1)	(0 to 0)

*Differences in the dactylitis total score at baseline, between treatment arms.
†Differences in the dactylitis total score at week 24, between treatment arms.
‡Differences in the median change of the dactylitis total score from baseline to week 24, between treatment arms.
§Differences in the mean change of the dactylitis partial score from baseline to week 24, between treatment arms. p<0.05.
DIP, distal interphalangeal joints; GLM, golimumab; MCP/MTP, metacarpal/metatarsophalangeal joints; MTX, methotrexate; PIP, proximal interphalangeal joints; PLB, placebo.

Table 4 PSAMRIS for individual MRI features as assessed by PSAMRIS-H and PSAMRIS-F, for both treatment arms, at baseline and change from baseline to week 24

	MCP/MTP				PIP				DIP			
	GLM+MTX		PLB+MTX		GLM+MTX		PLB+MTX		GLM+MTX		PLB+MTX	
PSAMRIS features	Baseline	Change	Baseline	Change	Baseline	Change	Baseline	Change	Baseline	Change	Baseline	Change
Synovitis, mean	3.8	−2.87	3.44	−1.94	1.93	−1.54*	1.06	0	1	−0.67	1	−0.71
(observed range)	(0 to 12)	(−9 to 0)	(0 to 7)	(−7 to 2)	(0 to 4)	(−4 to 1)	(0 to 3)	(−3 to 3)	(0 to 3)	(−2 to 0)	(0 to 4)	(-2 to 0)
Flexor tenosynovitis, mean	0.56	−0.38	0.47	−0.05	0.56	−0.38	0.47	−0.05	1.4	−1	1	−0.33
(observed range)	(0 to 3)	(−2 to 0)	(0 to 3)	(−2 to 2)	(0 to 3)	(−2 to 0)	(0 to 3)	(−2 to 2)	(0 to 3)	(−2 to 0)	(0 to 3)	(-2 to 2)
Periarticular inflammation, mean	3.14	−1.86	3	−2.41	0.33	0	0.33	0.14	0.6	−0.4	0.5	−0.29
(observed range)	(0 to 24)	(−14 to 0)	(0 to 7)	(−7 to 0)	(0 to 2)	(0 to 0)	(0 to 2)	(0 to 1)	(0 to 2)	(−1 to 0)	(0 to 2)	(-1 to 0)
Bone marrow oedema, mean	4.56	−2.94	3.11	−2.67	4.82	−3.59	3	−0.72	1.33	−1	2	-1
(observed range)	(0 to 23)	(−14 to 0)	(0 to 16)	(−16 to 0)	(0 to 24)	(−22 to 1)	(0 to 16)	(−8 to 4)	(0 to 6)	(−6 to 0)	(0 to 8)	(-4 to 0)
Bone erosion, mean	2.06	0.5	1.47	−0.06	1.47	0	1.53	0.89	6.33	0	2.89	0
(observed range)	(0 to 12)	(−3 to 12)	(0 to 8)	(−2 to 1)	(0 to 13)	(0 to 0)	(0 to 14)	(−1 to 10)	(0 to 14)	(0 to 0)	(0 to 8)	(0 to 0)
Bone proliferation, mean	2.83	0	1.67	0	2.67	0	2.67	0	2.2	−0.8	2	0
(observed range)	(0 to 5)	(0 to 0)	(0 to 5)	(0 to 0)	(0 to 5)	(0 to 0)	(0 to 5)	(0 to 0)	(0 to 4)	(−4 to 0)	(0 to 4)	(0 to 0)

*Difference between treatment groups in the change from baseline to week 24 (p=0.0054); p<0.05.
DIP, distal interphalangeal joints; GLM, golimumab; MCP/MTP, metacarpal/metatarsophalangeal joints; MTX, methotrexate; PIP, proximal interphalangeal joints; PLB, placebo; PSAMRIS, Psoriatic Arthritis MRI Score; PSAMRIS-F, Psoriatic Arthritis MRI Score for the foot.; PSAMRIS-H, Psoriatic Arthritis MRI Score for the hand.

reduced articular and periarticular inflammatory scores either on dactylitis and overall PSAMRIS, while erosions and osteoproliferation scores remained globally unchanged throughout the 24 weeks of the trial. Due to slow progression, erosions or new bone formation changes in PsA are difficult to depict in short-term studies, and MRI complete resolution of inflammation remains a challenging target.[29]

We studied an MTX-naive population to avoid bias from MTX prior non-responders. Although less efficacious alone than in combination with golimumab, we observed small improvements in dactylitis (−2 DSS units from baseline to week 24) and other PsA domains (peripheral arthritis and plaque psoriasis) in MTX monotherapy-treated patients. Furthermore, MTX monotherapy patients consistently attained higher rates of response from week 12 to week 24 for peripheral arthritis and composite indices (ACR, MDA, PsARC, PsAJAI, PASI) of PsA activity, suggesting incremental therapeutic benefits that continued through follow-up. These results are in line with a recently published RCT showing moderate but consistent benefits from MTX.[30]

Global assessment of safety on golimumab plus MTX was as expected.[31]

Considering the high disease burden of dactylitis in patients with PsA, including a lower chance of achieving MDA[6] and the risk of structural damage,[4 5] and advantages of early TNFi intervention,[32] it seems reasonable to argue that patients with PsA active dactylitis could benefit from first-line TNFi plus MTX therapy. We expect that these results will be reproducible with other TNFi combination therapies.[33]

Limitations in our study include the small number of patients enroled, which can increase the risk of type II errors. However, because the primary endpoint showed significant differences between treatment groups, recruitment was halted at half of the planned enrolment. MRI assessment was included as a secondary exploratory endpoint in a limited number of patients with single imaging reading, which implies caution in data interpretation. Although a golimumab monotherapy arm could also have been included, results from GO-REVEAL suggested a 10% additional benefit in dactylitis improvements from combination with MTX. GO-DACT included several variables to capture disease activity in its different domains, increasing the risk of type I error through multiple comparisons. Nevertheless, the population was well-balanced between groups, and results were consistent between the variables and with the published literature. This was potentiated by the lack of consensus, especially regarding composite disease activity scores.

CONCLUSIONS

GO-DACT provides strong evidence that combination of golimumab plus MTX is more efficacious than MTX monotherapy in improving PsA dactylitis. GO-DACT also exemplified that application of the innovative DSS and LDI response indices (DSS20, 50 and 70 and LDI20, 50 and 70) allowed discrimination between treatment arms, which could be useful for future PsA trials.

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