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Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised, controlled trial

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Study design and execution

The study was conceived by Drs Helliwell, Coates, Emery and Conaghan. The study was designed by Drs Helliwell and Coates. Study data and co-ordination were by Leeds Institute of Clinical Trials Research.

Analysis and Writing

The data was analysed by LM, SB, J OD and DM. PH and LC had access to the full data. PH takes responsibility for the data and analysis. All authors approved the final version of the paper.

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Abstract

Background—Early intervention and tight control of inflammation optimise outcomes in rheumatoid arthritis but these concepts have not been evaluated in psoriatic arthritis (PsA). We aimed to assess the effect of tight control on early PsA using a treat-to-target approach.

Methods—Patients with early, DMARD naïve, PsA were randomised 1:1 to receive either tight control (4 weekly review with escalation of therapy if criteria not met) or standard care (12 weekly review) for a period of 48 weeks. Clinical outcomes were recorded by a blinded assessor every 12 weeks. The primary outcome was the proportion of patients achieving an ACR20 response at 48 weeks. The primary analysis was by intention-to-treat (ITT) with multiple imputation for missing ACR components. Cost-effectiveness was also evaluated.

Findings—206 patients were randomised to receive tight control (TC) (n=101) or standard care (StdC) (n=105). In the ITT patient population, odds of achieving an ACR20 response at 48 weeks were higher in the TC arm compared to the StdC arm (odds ratio (OR): 1.91, 95% CI: 1.03, 3.55, p=0.0392). The odds of achieving ACR50 (OR: 2.36, 95% CI: 1.25, 4.47, p=0.0081); and ACR70 (OR: 2.64, 95% CI: 1.32, 5.26, p=0.0058); and PASI75 (OR: 2.92, 95%CI: 1.51, 5.65, p=0.0015) at 48 weeks were also higher in the TC arm.

A greater improvement was observed for patient reported outcomes including BASDAI, BASFI, PsAQoL, HAQ score and ASAS 20/40 in the TC arm. There was no difference in the change of radiographic scores between the treatment arms at week 48 (p=0.9779). The mean incremental cost-effectiveness ratio (ICER) was £50,723 per QALY.

Serious adverse events (SAEs) (25 TC, 8 StdC) were reported from 20 (9.7%) patients (14 (13.9%) TC, 6 (5.7%) StdC) during the course of the study. There were no unexpected SAEs or deaths.

Interpretation—Tight control of PsA disease activity using a treat-to-target approach significantly improves joint and skin outcomes for newly diagnosed PsA patients with no unexpected SAEs observed.

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Trial Registration—ISCRCTN30147736 and NCT01106079

Keywords

psoriatic arthritis; treatment; adverse events; cost-effectiveness; treat-to-target; minimal disease activity

Introduction

Psoriasis affects 2-3% of the population and psoriatic arthritis (PsA) can occur in up to 30% of people with psoriasis (1). The majority of patients with PsA suffer progressive joint damage, increasing disability and reduced life expectancy (2) which is associated with a significant reduction in functional ability and quality of life (3). Observational studies in PsA have shown that the number of active swollen joints is a predictor of clinical (4) and radiological progression (5) but addressing the concept of tight control of inflammation to improve outcome in PsA has never been attempted.

In contrast, in rheumatoid arthritis (RA), the pivotal TIght COntrol in Rheumatoid Arthritis (TICORA) study was the first study to demonstrate that tight control of disease utilising predefined activity levels to guide therapeutic changes resulted in significantly better clinical and radiographic outcomes compared to routine care (6). Following this, a treat-to-target approach has been utilised in many studies in RA and consequently management guidelines for RA from the UK National Institute for Health and Clinical Excellence (NICE) have advised monthly assessments of disease activity aiming for a predefined target (7).

Treatment strategy trials have not been carried out in PsA largely because of disease heterogeneity and the lack of a suitable disease specific treatment target. A potential target for therapy in PsA has now been developed, the minimal disease activity (MDA) criteria. The MDA criteria for PsA assess multiple domains of the disease, including patient reported outcomes, to give a measure of low disease state (8) and have now been validated in multiple cohorts (9, 10).

Observational studies have suggested that control of disease inflammation in PsA leads to improved long term outcomes (11), and more recent data suggested better outcomes in people referred and treated earlier (12). This evidence, together with the availability of a therapeutic target, was the impetus to study the impact of tight control of early PsA in a randomised-controlled trial using a treat-to-target approach, the TICOPA trial (TIght COntrol of Psoriatic Arthritis).

Methods

Study design and patient accrual

For this randomised, controlled, parallel group, open label, UK multi-centre clinical trial we recruited patients with early (less than 2 years), treatment naive PsA. Patients were recruited at eight UK secondary care rheumatology centres between May 2008 and March 2012. Eligibility criteria were adults (18 years or over) with recent onset (<24 months symptom duration), PsA (diagnosed by a consultant rheumatologist) and naïve to disease modifying anti-rheumatic drug (DMARD). Full details of the trial protocol can be found in the paper detailing the protocol (13).

The primary objective of the trial was to compare tight control (TC) with standard care (StdC), in terms of the proportion of patients achieving an American College of Rheumatology (ACR) 20% response at 48 weeks post-randomisation. ACR20 requires at

least a 20% improvement in tender and swollen joint counts with a 20% improvement in 3 out of 5 of the following outcomes: health assessment questionnaire (HAQ) (14), patient global disease activity visual analogue scale (VAS), patient pain VAS, physician global disease activity VAS, and erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). Key secondary outcomes included ACR 50% and 70%, Psoriasis Area Severity Index (PASI) 75% improvement (15) and modified Sharp van der Heijde (mvdH-S) X-ray score at 48 weeks post-randomisation(16). Other physician assessments included the modified Nail Psoriasis and Severity Index (mNAPSI) (17), a 19 point assessment of tenderness at entheses (comprising the Maastricht ankylosing spondylitis enthesitis index (18) and the Leeds Enthesitis Index (19) and including the plantar fascia), dactylitis (assessed by the Leeds Dactylitis Index (20)), and a 66 swollen (SJC) and 68 tender joint count (TJC). Patient completed outcomes included VAS scores noted above, the HAQ, Bath ankylosing spondylitis functional questionnaire (BASFI) (21), Bath ankylosing spondylitis disease activity index (BASDAI) (22), PsA quality of life index (PsAQoL) (23) and EQ-5D. In addition, information on clinic visits, investigations and employment status was gathered in order to perform economic analyses.

Randomisation and Blinding

Patients were randomised on a 1:1 basis to receive either tight control or standard care. Randomisation was performed using minimisation incorporating a random element, via a central 24-hour automated telephone system based at the Leeds Clinical Trials Research Unit. Minimisation was employed to ensure that treatment arms were balanced for randomising centre and pattern of arthritis (oligoarticular vs polyarticular).

Study physicians and patients were aware of the allocated treatment arm. Follow up assessments involving a full clinical assessment every 12 weeks were performed by a research nurse blind to the allocated treatment arm.

Procedures

Patients received either TC or StdC for a period of 48 weeks, with follow-up of safety up to 52 weeks. Patients randomised to the TC arm were seen every 4 weeks by the study physician and treated according to a predefined treatment protocol (see Figure 1). At each visit, the MDA criteria were assessed. These criteria include assessment of the following: (i) a full 68 tender and (ii) 66 swollen joint count, (iii) the PASI, (iv) enthesitis count, (v) patient global disease activity (VAS), (vi) patient pain (VAS), and (vii) the HAQ. Treatment with DMARDs was escalated to the maximum dose according to the protocol in Figure 1 if patients had not achieved the MDA criteria. Any patient who could not tolerate the maximum dose specified in the protocol due to toxicity or intolerance, was permitted to continue on the highest tolerable dose and then progress to the next step in the protocol if required. Patients achieving the MDA criteria continued on their current therapy. Intra-articular and intra-muscular steroids, administered after disease assessments, were also used in disease control. Patients were offered local joint injections to active joints and/or intramuscular steroid by the physicians if considered appropriate.

Patients randomised to the StdC arm were treated in a general rheumatology outpatient clinic supervised by a consultant rheumatologist. These patients were generally reviewed every 12 weeks but were seen more often if clinically indicated, with no formal measures of disease activity used in clinical decision making. There was no requirement or restriction on prescribing within this arm of the study. All patients were required to meet the NICE criteria for the use of biologics in PsA prior to use (>3 tender/swollen joints, failed 2 standard DMARDs). At each study site, different physicians treated the patients in the TC and StdC arms.

Radiographs of the hands and feet were performed at baseline and 48 weeks. They were scored using the modified van der Heijde-Sharp scoring method for PsA assessing both erosion and joint space narrowing (24). Scoring was done by two readers (PH and LC) by consensus. All films were scored paired but blinded to treatment arm and time sequence.

Sample Size

The trial was powered for the pre-specified primary outcome, ACR20 at 48 weeks post-randomisation. Based on previous data (20) we assumed a 50% response rate in the StdC arm at 48 weeks. A sample size of 93 evaluable patients per arm (total sample size 186) provided the trial with 80% power to detect an increase in ACR20 rates of 20% between the two treatment arms at 48 weeks, based on a chi-squared test without continuity correction at the 2-sided 5% significant level. To allow for a 10% dropout, a total of 206 patients were recruited.

Statistical Analysis

All statistical analyses were carried out in SAS version 9.2 and Stata V12.0.

The analysis of primacy for the primary endpoint was based on the intention-to-treat (ITT) population. Multiple imputation (MI) was used (25) to impute missing ACR component data (e.g. tender joint count) at baseline, 12, 24, 36 and 48 weeks post-randomisation. This approach creates multiple complete datasets by using the distribution of the observed data to estimate a set of plausible values for the missing data. Each dataset is then analysed separately to obtain a set of parameter estimates, which are then combined using Rubin's rules (26) to obtain an overall estimate of the treatment effect.

In TICOPA, each of the imputed datasets (n=20) were analysed separately using a multivariable logistic regression model to assess the effect of treatment on the odds of patients achieving ACR20 at 48 weeks post-randomisation, adjusting for the minimisation factors, arthritis classification (oligoarticular vs polyarticular) and randomising centre. In addition, a univariable analysis was performed on those patients with an evaluable ACR20 response at 48 weeks (evaluable patient population). The difference in the proportion of patients achieving an ACR20 response between the treatment arms was compared using a chi-squared test. Sensitivity analyses were performed to assess the robustness of the primary analysis using multiple imputation and the assumptions regarding the missing data. These included a complete case analysis, last observation carried forward imputation, non-responder imputation, and direct imputation of the ACR20 response using MI. The results of the sensitivity analyses will be presented separately.

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A multivariable logistic regression analysis adjusting for the minimisation factors was used to assess the effect of treatment on the key secondary outcomes, ACR50/70 (ITT population) and PASI75 (evaluable patient population) at 48 weeks post-randomisation. The difference in the proportion of patients achieving each outcome between the treatment arms was compared using a chi-squared test (evaluable patient population).

To determine the pattern of the treatment effect on ACR20 over time on the evaluable patient population, a repeated measures analysis was conducted on ACR20 response across all follow-up time points, using generalised estimating equations to adjust for the correlated outcome data. The analysis adjusted for the minimisation factors, time since baseline and treatment group; the treatment-by-time interaction was also assessed.

The difference in the median change in modified Sharp van der Heijde (mvdH-S) X-ray score (baseline – week 48) was compared between the treatment arms using the Wilcoxon Rank-Sum test.

A prospective economic evaluation was conducted to assess the cost-effectiveness of TC compared to StdC over 48 weeks. Health service costs were combined with EQ-5D derived quality-adjusted life years (QALY) outcomes. Resource use was captured using patient-completed forms and nurse records of medications and hospital visits. Costs were attached to individuals employing NHS Reference costs, Personal Social Services Research Unit reports and the British National Formulary. Analyses were conducted from the perspective of the healthcare provider. Where appropriate incremental cost-effectiveness ratios (ICER) were calculated using the willingness to pay threshold of £20,000 per QALY gain. The probability of cost-effectiveness was determined by bootstrapping analysis and constructing cost-effectiveness acceptability curves (27) using a range of willingness to pay thresholds for QALY gains. Multiple imputation was employed to account for missing cost and EQ-5D data.

Additional secondary outcomes (measures of disease activity and patient reported outcomes) are summarised by treatment arm and overall in terms of the median improvement from baseline to week 48, for those patients with non-missing data, No formal comparisons between the arms were performed. Measures of disease activity including PASI, enthesitis, dactylitis and mNAPSI, are summarised for those patients with corresponding disease at baseline.

Role of the funding source

Arthritis Research UK and Pfizer who provided funding for this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

A total of 344 patients were screened for eligibility and, of these, 206 (59·9%) patients were randomly assigned to either the TC (n=101, 49·0%) or StdC (n=105, 51·0%) arm (Figure 2).

In TC, 89·1% (n=90) of patients completed treatment and follow-up to week 48 with a similar proportion in StdC (n=92, 87·6%). No patients were found to be ineligible for the trial post-randomisation. A slightly higher number of patients withdrew from treatment alone, or treatment and follow-up in the StdC arm compared to the TC arm (n=4 TC, n=7 StdC); a similar number of patients were lost to follow-up in both treatment arms (n=6 TC, n=5 StdC). One TC patient was withdrawn by the treating clinician as they were 'unable to tolerate treatment' and a further StdC patient was unable to attend the week 48 follow-up visit within the required timelines.

Baseline characteristics were similar across treatment arms, although an increased proportion of patients in the TC arm presented with current enthesitis and dactylitis whilst a decreased proportion presented with distal inter-phalangeal (DIP) joint disease and current psoriasis compared with the StdC arm (Table 1). The vast majority of patients (91·3%, n=188) fulfilled the ClASsification of Psoriatic ARthritis (CASPAR) criteria for PsA (i.e. score ≥3), with 98·1% (n=202) patients scoring at least 2 of the required 3 points. The majority of patients (n=146, 70·9%) presented with polyarticular disease (≥5 joints involved) at baseline in keeping with other PsA cohorts, and had psoriasis currently (84·5%, n=174) although in patients with psoriasis at baseline, activity was low with a median PASI score of 2·6 (IQR: 1·2, 4·8).

Analysis populations

Of the 206 patients randomised, 33 (16.0%) had some or all of the component data missing required for the derivation of the ACR20, a greater proportion in the StdC arm (n=21, 20·0%) compared to the TC arm (n=12, 11·9%) (Figure 2). This included 22 patients who withdrew, were withdrawn by the physician, were lost to follow-up or were unable to attend the week 48 visit, and 11 patients who attended the week 48 visit but failed to have all of the required assessments performed for deriving ACR20. The ITT population consisted of all 206 patients randomised. The evaluable patient population for the univariable analysis of the primary endpoint consisted of patients with an ACR20 response at 48 weeks, prior to any imputation, and included 173 patients (84 (80·0%) StdC, 89 (88·1%) TC). The evaluable patient population for the secondary endpoint analyses included all patients with complete data at baseline and week 48. The safety patient population consisted of all 206 patients randomised.

Primary endpoint

In the ITT population, the odds of achieving an ACR20 response at 48 weeks were higher in the TC arm compared to the StdC arm after adjusting for centre and arthritis classification (odds ratio (OR) 1·91, 95% CI 1·03, 3·55, p=0·0392) (Table 2). In the evaluable patient population (n=173), a higher proportion of TC patients (55/89 (61·8%)) achieved an ACR20 response at 48 weeks compared to StdC patients (37/84 (44·0%))(TC-StdC: 17.8% (95% CI: 3·1%, 32·4%), p=0·0194) (Table 3).

Secondary endpoints

In the ITT population, the odds of achieving ACR50 (OR: 2·36, 95% CI: 1·25, 4·47, p=0·0081) and ACR70 (OR: 2·64, 95% CI: 1·32, 5·26, p=0·0058) at 48 weeks were higher in

the TC arm compared to the StdC arm. Furthermore, in the evaluable patient population (n=156), the odds of achieving PASI75 response at 48 weeks were significantly higher in the TC arm (PASI75 OR: 2·92, 95% CI: 1·51, 5·65, p=0·0015) compared to the StdC arm. The difference in the proportion of patients achieving each response status (ACR50/70 and PASI75) for the evaluable patient populations are presented in Table 3.

For the assessment of the pattern of the treatment effect over time in the evaluable patient population, the odds of achieving an ACR20 response over the whole study duration were higher in the TC arm compared to the StdC arm (OR 1·69 (95% CI: 1·10, 2·60, p=0·0158)). However there was no evidence that the treatment effect varied over time (treatment-by-time interaction, p=0·7255).

Radiographs were available for 195 (94·7%) patients at baseline and 176 (85·4%) at week 48. At baseline, 25·1% of patients had some erosive disease and 84·6% joint space narrowing (JSN) with a slightly higher proportion in the TC arm (Table 5). The total mvdH-S scores (erosions + JSN) at baseline were low with an overall median score of 8·0 (IQR: 2·0, 16·0), predominantly due to joint space narrowing (Table 5); median scores were similar across the treatment arms (9·0 TC vs 8·0 StdC). By week 48, a slight increase was observed in the proportion of patients with erosive disease for both treatment arms (30·7%); JSN remained similar to that observed at baseline (85·8%). The median total mvdH-S scores at week 48 remained similar across the treatment arms (8·0 TC vs 6·0 StdC). There was no evidence of a difference in the change in mvdH-S scores between the treatment arms at week 48 (p=0·9779), with median change of zero in both arms.

The observed improvements from baseline to week 48 for the additional secondary outcomes (measures of disease activity and patient reported outcomes)are presented in Table 6. A higher proportion of patients in the TC arm achieved PASI20 (77·3% TC vs 59·3% StdC) and PASI90 (42·7% TC vs 23·5% StdC) compared to StdC. For the remaining measures of disease activity a similar median improvement at week 48 was observed between the treatment arms with the exception of dactylitis where a greater median improvement was observed in the StdC arm (38·0 TC vs 58·5 StdC), although the number of patients with disease at baseline were small and scores were highly variable.

For the patient reported outcomes, patients with axial disease at baseline reported a greater median improvement in BASDAI (3·9 TC vs 0·9 StdC) and BASFI score (2·0 TC vs -0·1 StdC) in the TC arm compared to StdC. A higher proportion of patients in the TC arm met the minimum clinically important difference (MCID) threshold (28) for both the BASDAI (70·4% TC vs 55·7% StdC) and BASFI (60·5% TC vs 40·0% StdC) compared to the StdC arm. Patients in the TC arm also reported a greater median improvement in PsAQoL score (3·0 TC vs. 0·5 StdC). A greater proportion of patients in the TC arm met the MCID threshold (29) for the change in HAQ score from baseline to week 48 (58·2% TC vs 41·1% StdC) compared with StdC patients (Table 6).

Treatments

MTX monotherapy was used in 26·7% (n=27) of TC patients throughout the duration of the trial compared to 60·0% (n=63) in the StdC arm. A higher proportion of TC patients were

treated with combination DMARDs (73·3% (n=74) TC, 28·6% (n=30) StdC) and biologic therapies (38·6% (n=39) TC, 6·7% (n=7) StdC) during the course of the trial compared to StdC. All patients in the TC arm (n=101) reached a MTX dose level of at least 15mg/week by their 12 week visit compared to 66·7% (n=70) of StdC patients. A higher proportion of TC patients reached an MTX dose level of at least 20 mg/week (90·1% (n=91) TC vs. 29·5% (n=31) StdC) and of at least 25mg/week (82·2% (n=83) TC, 7·6% (n=8) StdC) by their 12 week assessment compared to the StdC arm. At 12 weeks, the majority of patients in both treatment arms were reported to be on MTX monotherapy (56·4% (n=57) TC, 68·6% (n=72) StdC), with more patients in the TC arm moving onto combination DMARD therapy (36·6% (n=37) TC, 3·8% (n=4) StdC). By week 48, just under half (48.6%, n=51) of the patients in the StdC arm were reported to still be on MTX monotherapy but in the TC arm only 25·7% (n=26) continued on MTX monotherapy with more patients on combination DMARDs alone (23·8% (n=24) TC, 10·5% (n=11) StdC) or any biologics (36·6% (n=37) TC, 6·7% (n=7) StdC). Over the duration of the trial, patients in the TC arm received more steroid treatment in the form of intra-articular or intra-muscular injections compared to those in the StdC arm (median (IQR): 120mg (0mg, 260mg) per patient over 48 weeks (TC), 80mg (0mg, 160mg) (StdC)) but doses overall were relatively low.

Minimal Disease Activity and compliance with the protocol in the TC arm

At the 12 week assessment, 82·2% (n=83) of the patients reached 25mg/wk of MTX with 32·7% (n=33) patients following the exact MTX escalation schedule as per the TC protocol (see Figure 1). A total of 23·8% (n=24) of patients had reached MDA by week 12; of the 75 patients who did not reach MDA, treatment was escalated in 70·7% (n=53) of patients. Between weeks 12 to 48, 72·3% (n=73) of patients reached MDA at least once with 56·4% (n=57) of patients reaching MDA on at least two consecutive visits. Furthermore, on average, patients reached MDA at 40·7% of assessments attended and of those assessments where treatment was required to be escalated, treatment was escalated on average 37·2% of the time. Reasons for non-escalation of treatment, as allowed within the protocol, included: on current DMARD therapy for less than 12 weeks; concurrent disease; on maximum therapy already; recent missed treatment; unable to tolerate escalated dose.

Adverse events

Serious adverse events (SAEs) were reported in 20 (9·7%) of 206 patients and were more common in the TC arm with 25 SAEs observed in 14 patients (13·9%) compared to eight SAEs observed in six patients (5·7%) in the StdC arm. In patients experiencing an event, a similar median number of SAEs were reported between the treatment arms (1·0 (range: 1·0, 6·0) TC, 1·0 (1·0, 2·0) StdC). Ten SAEs were suspected to be related to drug therapy, with eight in the TC arm (cellulitis (n=2), pneumonia (n=2), MSK chest pain (n=1), raised LFTs (n=1), collapse and pancytopenia (n=1), anaphylaxis (n=1)) and two in the StdC arm (migraine, septic arthritis), all of which required hospitalisation, but none were deemed to be life-threatening. There were no unexpected serious adverse events or deaths.

Adverse events (AEs) were reported in 179 (86·9%) of 206 patients and were more commonly reported by patients in the TC arm (97·0%, n=98) compared to the StdC arm (77·1%, n=81). In patients experiencing an event, a higher median number of AEs were

reported in the TC arm (6·0 (range: 1·0, 20·0)) compared to the StdC arm (3·0 (range: 1·0, 10·0)). Of all AEs reported (n=866), the most commonly reported AEs were nausea (10·6% of AEs), liver abnormalities (8·8% of AEs), and infections (common cold) (6·9% of AEs) (Table 7). Nausea, fatigue, the common cold, headache/migraines, musculoskeletal pain and gastrointestinal upset were reported more frequently in the TC arm although abnormalities in liver function tests were seen equally in each treatment arm. A similar proportion of AEs were suspected to be related to drug therapy in both arms (68·2% TC, 72·8% StdC).

Economic analysis

Costs and mean QALY values by trial arm at 12, 24 and 48 weeks are included in Table 4. The mean cost per patient in the TC arm was £4,198 compared to £2,000 for the StdC arm. Mean QALYs were 0·602 and 0·561 for TC and StdC, respectively. These yielded a deterministic ICER of £53,948 per QALY. Bootstrapped uncertainty analysis produced a mean simulation ICER of £50,723 and suggested that TC had a 0·07 probability of being cost-effective at a £20,000 threshold. Scenario analyses, which reduced total costs in both arms by 25% and reduced consultations for TC patients achieving MDA on two consecutive occasions (assumed reduction to 3 monthly follow-up visits), yielded an ICER of £30,632.

Discussion

This study is the first to show that a treat to target approach can improve clinical outcomes for patients with early PsA. Treat to target using a tight control strategy significantly improved the primary composite clinical outcome (ACR20) , with the greatest benefits seen with more stringent outcome measures such as ACR70 and PASI75. Benefits were demonstrated across both articular and skin outcomes and for a range of patient reported outcomes. There was no difference seen in radiographic progression between the two arms although radiological damage at baseline, and the progression of damage at 48 weeks, were low overall. Adverse and serious adverse events were reported more often in the tight control arm.

Physicians may be reluctant to treat to target, or even treat at all, as evidenced by the high proportion of people without any or only topical treament for psoriasis and psoriatic arthritis in the US (30). This may perhaps due to a lingering perception that psoriatic arthritis is not a progressive disabling disease, despite evidence demonstating an equivalent impact to rheumatoid arthritis after similar disease duration (3). It is acknowledged that treating to a low disease activity target in RA leads to better outcomes, both clinical and radiographic (31). The target in RA is usually a composite which largely reflects articular inflammation. The target used in the current study is also a composite index and includes joints, skin, enthesitis, function and patient completed visual analogue scores for pain and general disease activity. In interventional trials in PsA, achieving these criteria (MDA) leads to better radiographic outcomes (9). However, to achieve this state consistently across a patient group, patients need to be reviewed regularly and treated by an aggressive algorithm, as outlined in this study. It is also important to note that the patient should be involved in the decision to treat to target and that each patient may have their own preference for both target and the means to achieve it, and this should be respected.

Which aspect of the care received in the TC arm led to better outcomes? It is difficult to tease out the individual impact of the different aspects of T2T. Certainly patients appreciated the more intense visit schedule mandated by the TC arm, even when they were in stable MDA and, theoretically, not needing to visit the hospital every month. This will be an aspect of the T2T approach to be examined in future studies. The end result is that outcomes improved as a result of the monthly visits, the targeted approach, and the aggressive treatment algorithm. Clearly the greater use of biologics in the TC arm will increase the chance of achieving an ACR20 response but the data indicate that more patients in the TC arm reached an ACR20 at weeks 12 and 24, before biologics would have been introduced. As with T2T in rheumatoid arthritis, improved outcome is achieved by regular and timely review of the patient and the combination of having a target and the means to reach it.

Similarly, assessing the gains made by this approach is complex. Although a 20% improvement in the ACR response criteria (the primary outcome) is equivalent to only modest benefit, a 50% and 70% improvement is very noticeable by the patient. These gains are also reflected by the increased proportion of patients achieving the minimal clinical important difference in several patient reported outcomes and the improvements made in the skin disease. Offset against these improvements are adverse effects from the treatment regime but, overall, improvement was seen in quality of life, albeit modestly.

In the UK and elsewhere (32), methotrexate is commonly the first drug to be used in PsA, unless the patient has only axial disease. However, the methotrexate in PsA (MIPA) study has recently reported that methotrexate is ineffective in PsA (33). The most important aspect of the MIPA study was the 15mg weekly target dose of methotrexate used. Although the investigators had the option to further escalate the dose of methotrexate, at 5 months this had only occurred in 11% of cases; with another 11% of cases on doses less than 15mg, presumably because of intolerance. We accept that treatment approaches evolve and that, at the time the MIPA trial was started, lower doses of methotrexate were used, but current doses are higher (34). In the current study, for example, methotrexate target dose was 25mg and 82% of patients in the TC arm reached this dose by 12 weeks. Further, throughout the study, methotrexate monotherapy was used in just over a quarter of the TC arm with these patients consistently achieving MDA. Future analysis of this cohort plans to examine the relative efficacy of methotrexate monotherapy in both oligoarthritis and polyarthritis.

Methotrexate has been shown to be effective in psoriasis, so it was not surprising to find greater improvement in the skin in the TC arm. It is perhaps more surprising to find that other secondary outcomes did not show more improvement in the TC arm, including dactylitis and enthesitis, although baseline scores for dactylitis were higher in the StdC arm and scores were highly variable. Dactylitis involves inflammation in several tissues of the digit, including the joint and the outcome measure used in this study has been shown to be sensitive to change in other studies. However, it must be remembered that both groups in this study were treated and therefore cardinal features of this disease, such as dactylitis and enthesitis, were likely targeted by physicians in the StdC arm.

There was no difference seen in radiographic progression between the two arms. The lack of a difference is perhaps unsurprising when considering that these patients were very early in

the course of their disease, had a variable clinical phenotype with around 30% with oligoarticular disease and both study arms were given active treatment. Previous work has shown that a quarter of patients are erosive at first presentation increasing to 43% at two years, despite treatment, but numbers of erosions per patient were low (35). In the current study 25% had at least one erosion at baseline with this figure increasing to 31% at 48 weeks. The method employed for radiographic evauation utilised blinded time order, which, although reducing assessment bias, may have reduced the sensitivity to demonstrate change. However the infrequent erosions at baseline, and the relative lack of deterioration over 48 weeks, implies that longer intervals, or alternative imaging such as MRI, are required to demonstrate structural damage progression in PsA using modern treatment paradigms.

The economic evaluation suggests that TC is unlikely to be considered cost-effective using willingness to pay thresholds of £20,000 to £30,000 per QALY. TC conferred a small incremental quality of life benefit (0.041 QALYs), at an additional (particularly drug and consultation) cost. It is likely that in a ‘real life’ situation patients would not be reviewed as often as the protocol demanded, particularly once they had achieved low disease activity. The sensitivity analyses, including reduced consultations for TC patients achieving MDA after two consecutive visits, yielded an ICER which approached a level of acceptable cost–effectiveness. It is also likely that drug costs will ultimately be less, given the imminence of biosimilars, but it is not possible to determine at this time the impact of those changes on the incremental cost of a tight control strategy. At the moment it has to be accepted that, using the current treatment algorithm, the costs for TC remain higher than the current standard of care. Further sub-group and sensitivity analyses are required.

Adverse events were reported more frequently in the TC arm: the largest difference was seen in frequency of ‘colds’. Interestingly, and because of the larger doses of methotrexate used in the TC arm, liver enzyme abnormalities were reported in similar numbers in both arms. In contrast, symptoms such as nausea, fatigue and gastrointestinal upset were more frequently reported in the TC arm. The higher frequency of reporting of AEs is considered to be related to the more intensive treatment schedule including rapid escalation of DMARD therapy, particularly methotrexate. Recall bias could be another factor, with TC patients having more opportunity to recall events over a four week period compared to those seen every 12 weeks in the StdC arm The more intensive treatment schedule is considered to be the main reason for the higher reporting of AEs in the TC arm. . Serious adverse events including those suspected to be related to trial medications were also reported more frequently in the TC arm. Half of these were infections, as might be expected with the treatment regime used. All required hospitalisation but none were deemed to be life-threatening or resulted in death, and no serious unexpected adverse events were observed.

The open label design of this trial may have caused unintentional bias in favour of the tight control arm: to avoid this a blinded assessor was used. However, we were unable to test the efficacy of this blinding. The StdC arm were more likely to experience resentful disillusionment, and therefore be more likely to discontinue the study early. Early discontinuation occurred in only 13 patients in the StdC are compared to 11 in TC. A blunting of the efficacy of TC might also have occurred because the StdC patients were all treated by consultant rheumatologists working in teaching hospitals and might therefore

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already be following a more aggressive approach in their treatment of this disease, particularly as they would have been aware of the study. The intended treatment effect might also have been diluted by deviations from the treatment escalation protocol, as indicated in the Results. Despite this, almost 83% of patients in the TC arm achieved a 25mg dose of methotrexate by week 12. Finally, it could be argued that the primary outcome measure was inappropriate for assessing response to therapy in this disease, as the ACR response criteria were originally designed for rheumatoid arthritis. Although most of the intervention trials with biologic drugs in psoriatic arthritis use the ACR20 as the primary outcome, a composite outcome which reflects the whole spectrum of disease manifestations would be more appropriate (36), and such measures have been shown to have more power (37). However, these composite measures were not available when this study commenced.

In conclusion, adopting a tight control strategy in psoriatic arthritis leads to better outcomes but with more adverse events and higher costs. Although an impact of tight control on structural damage was not demonstrated, longer follow up or alternative imaging may be more appropriate in future studies in this disease.

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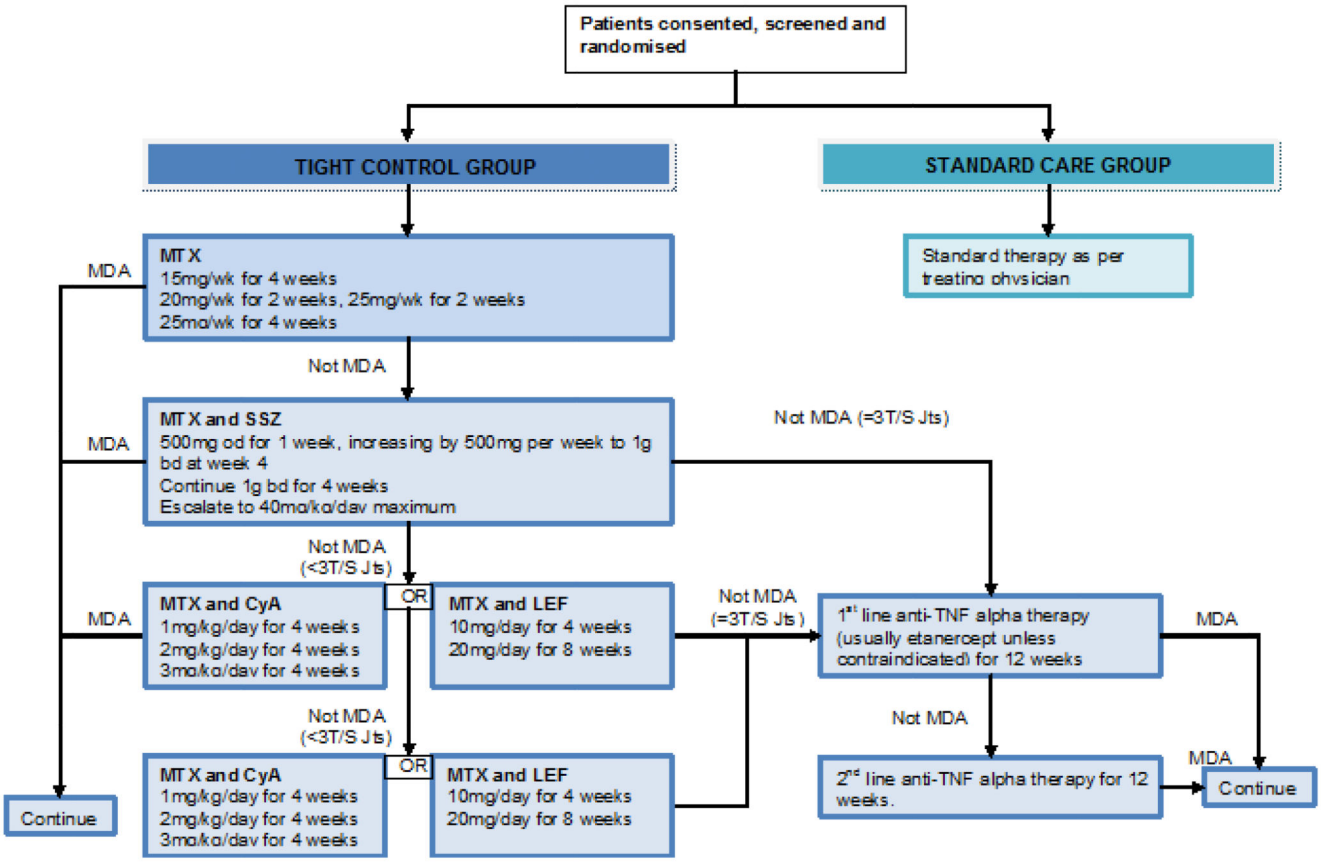

Figure 1.

Treatment protocol for the TICOPA study

MDA, minimal disease activity; MTX, methotrexate; SSZ, sulfasalazine; Cya, cyclosporin; LEF, leflunomide; TNF, tumour necrosis factor; Jts, joints.

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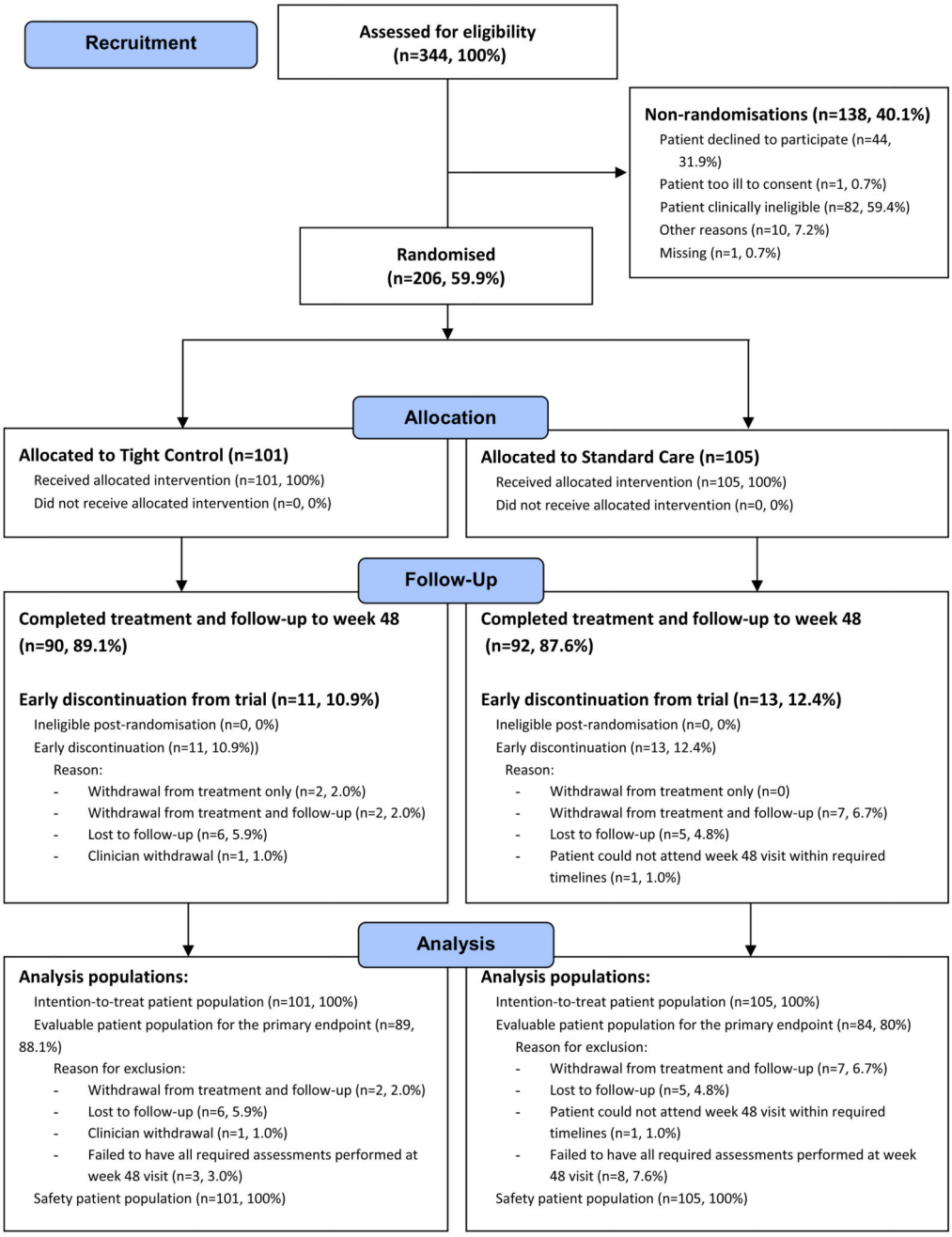

Figure 2.
TICOPA CONSORT Diagram

Table 1

Baseline characteristics of the study population

Parameter	Tight control (n=101)	Standard care (n=105)	Total (n=206)
Male sex, n (%)	53 (52·5)	55 (52·4)	108 (52·4%)
Age (years), median (IQR)	46 (38, 55)	45 (36, 51)	45 (38, 53)
Ethnicity: Caucasian, n (%)	92 (91·1)	96 (91·4)	188 (91·3)
Disease duration at randomisation (months)	0·9 (0·5, 2·1)	0·7 (0·4, 1·8)	0·8 (0·4, 2·0)
Number of swollen joints (0-66), median (IQR)	6.0 (3·0, 10·0)	4.0 (2·0, 8·0)	5·0 (2·0, 9·0)
Number of tender joints (0-68), median (IQR)	9.0 (3·0, 19·0)	9.0 (4·0, 17·0)	9·0 (4·0, 18·0)
CRP(mg/dl), median (IQR)	7.5 (5·0, 24·0)	6.3 (5·0, 15·5)	6·7 (5·0, 18·2)
Rheumatoid factor negative, n (%)	94 (93·1)	101 (96·2)	195 (94·7)
CCP negative, n (%)	87 (86·1)	85 (81·0)	172 (83·5)
Early morning stiffness (EMS), n (%)	88 (87·1)	96 (91·4)	184 (89·3%)
EMS duration (hours), median (IQR) (patients with EMS)	1·0 (0·5, 2·0)	1·0 (0·5, 2·0)	1·0 (0·5, 2·0)
Arthritis pattern, n (%) of patients			
Polyarthritis (≥5 joints)	72 (71·3)	74 (70·5)	146 (70·9)
Oligoarthritis (<5 joints)	29 (28·7)	31 (29.5)	60 (29·1)
DIP disease	18 (17·8)	27 (25·7)	45 (21·8)
Axial involvement	20 (19·8)	23 (21·9)	43 (20·9)
Arthritis mutilans	0 (0·0)	0 (0·0)	0 (0·0)
CASPAR criteria met (score ≥3), n (%)	90 (89·1)	98 (93·3)	188 (91·3)
CASPAR score ≥2, n (%)	99 (98·1)	103 (98·1)	202 (98·1)
Current psoriasis, n (%)	81 (80·2)	93 (88·6)	174 (84·5)
PASI score (all patients), median (IQR)	1·7 (0·4, 4·2)	2·1 (0·8, 4·2)	1·9 (0·6, 4·2)
PASI score (condition at baseline), median (IQR)	2·6 (1·2, 4·8)	2·5 (1·2, 4·7)	2·6 (1·2, 4·8)
Current enthesitis, n (%)	82 (81·2)	80 (76·2)	162 (78·6)
Enthesitis score (all patients), median (IQR)	3·0 (1·0, 6·0)	2·0 (1·0, 6·0)	2·0 (1·0, 6·0)
Enthesitis score (condition at baseline), median (IQR)	4.0 (2·0, 7·0)	4.0 (2·0, 7·0)	4.0 (2·0, 7·0)
Current dactylitis, n (%)	35 (34·7)	27 (25·7)	62 (30·1)
Dactylitis score (all patients), median (IQR)	0·0 (0·0, 22·0)	0·0 (0·0, 0·0)	0·0 (0·0, 13·0)
Dactylitis score (condition at baseline), median (IQR)	36·0 (20·0, 67·0)	41·0 (16·0, 112·0)	37·0 (19·0, 96·0)
Current nail disease, n (%)	62 (61·4)	62 (59·0)	124 (60·2)
mNAPSI score (all patients), median (IQR)	2·0 (0·0, 10·0)	1·5 (0·0, 11·5)	2·0 (0·0, 10·0)
mNAPSI score (condition at baseline), median (IQR)	8·5 (3·0, 15·0)	8·0 (2·0, 23·0)	8·0 (2·0, 19·0)

CRP, C-reactive protein; CCP, cyclic citrullinated peptide antibody; CASPAR, ClASsification of Psoriatic Arthritis; PASI, Psoriasis Area Severity Index; mNAPSI, Modified Nail Psoriasis Severity Index.

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Table 2

Multivariable logistic regression analysis for the effect of treatment on the primary endpoint, ACR20 at 48 weeks post-randomisation (ITT population with multiple imputation)

Parameter	OR & 95% CI	p-value
Treatment arm: Tight control vs Standard care	1·91 (1·03, 3·55)	0·0392
Arthritis type: Oligoarthritis vs Polyarthritis	0·62 (0·31, 1·24)	0·1733
Centre: Other sites vs Chapel Allerton Hospital	2·33 (0·87, 6·27)	0·0929
Centre: St Luke's Hospital Bradford vs Chapel Allerton Hospital	0·93 (0·41, 2·09)	0·8607
Centre: York District Hospital vs Chapel Allerton Hospital	0·50 (0·17, 1·52)	0·2223

Other sites included: Harrogate District Hospital, Manchester Royal Infirmary, St Bartholomew's Hospital, North Tyneside General Hospital and Royal National Hospital for Rheumatic Diseases. These smaller recruiting sites were combined to prevent model convergence problems.
OR, Odds Ratio; CI, Confidence Interval

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Table 3

Univariable analysis (chi-squared test of independence) for the proportion of patients achieving a response at 48 weeks post-randomisation (evaluable patient population) for the key secondary endpoints

Outcome at 48 weeks	Tight control n (%)	Standard care n (%)	Difference in proportions (%) & 95% CIs (TC-StdC)	p-value
ACR20	55/89 (61·8)	37/84 (44·0)	17·8 (3·1, 32·4)	0·0194
ACR50	44/86 (51·2)	21/84 (25·0)	26·2 (12·1, 40·2)	0·0004
ACR70	33/87 (37·9)	15/86 (17·4)	20·5 (7·5, 33·5)	0·0026
PASI75	44/75 (58·7)	27/81 (33·3)	25·3 (10·2, 40·5)	0·0015

ACR, American College of Rheumatology; PASI, Psoriasis Area Severity Index.

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Table 4

QALYs Gained and Costs by treatment arm

Treatment Arm	Variable	QALYs: Mean	QALYs: Std. Dev.	QALYs: Min per Patient	QALYs: Max per Patient	Cost: Mean	Cost: Std. Dev.	Cost: Min per Patient	Cost: Max per Patient
Tight control	12-week Follow-up	0.131	0.057	-0.042	0.231	663.16	417.15	406.98	3,148.43
	24-week Follow-up	0.151	0.049	-0.004	0.231	696.06	414.95	400.38	2,806.79
	48-week Follow-up	0.320	0.106	-0.045	0.462	2,837.61	2,381.77	800.76	9,858.05
Standard Care	12-week Follow-up	0.132	0.061	-0.048	0.231	459.24	665.65	133.46	4,971.96
	24-week Follow-up	0.144	0.066	-0.048	0.231	425.40	470.20	133.46	3,087.13
	48-week Follow-up	0.285	0.130	-0.097	0.462	1,114.09	1,710.20	266.92	8,590.48

QALYs, Quality-Adjusted Life-Years

Table 5

Total Modified Sharp van der Heijde (mvdH-S) radiographic scores (hands+feet) at baseline and week 48 (evaluable patient population)

	Tight control N (%)	Standard care N (%)	Total N (%)
Erosive disease at baseline?			
Yes	25 (26.6%)	24 (23.8%)	49 (25.1%)
No	69 (73.4%)	77 (76.2%)	146 (74.9%)
Total	94 (100%)	101 (100%)	195 (100%)
Erosive disease at week 48?			
Yes	29 (32.6%)	25 (28.7%)	54 (30.7%)
No	60 (67.4%)	62 (71.3%)	122 (69.3%)
Total	89 (100%)	87 (100%)	176 (100%)
mvdH-S Erosion Score			
Baseline			
Median (IQR)	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)	0.0 (0.0, 1.0)
N	94	101	195
Week 48			
Median (IQR)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)
N	89	87	176
Joint space narrowing (JSN) at baseline?			
Yes	81 (86.2%)	84 (83.2%)	165 (84.6%)
No	13 (13.8%)	17 (16.8%)	30 (15.4%)
Total	94 (100%)	101 (100%)	195 (100%)
Joint space narrowing (JSN) at week 48?			
Yes	78 (87.6%)	73 (83.9%)	151 (85.8%)
No	11 (12.4%)	14 (16.1%)	25 (14.2%)
Total	89 (100%)	87 (100%)	176 (100%)
mvdH-S JSN Score			
Baseline			
Median (IQR)	8.0 (3.0, 16.0)	8.0 (2.0, 13.0)	8.0 (2.0, 15.0)
N	94	101	195
Week 48			
Median (IQR)	8.0 (4.0, 15.0)	6.0 (2.0, 15.0)	8.0 (2.0, 15.0)
N	89	87	176
Total mvdH-S Heidje Score (Erosion + JSN)			
Baseline			
Median (IQR)	9.0 (3.0, 17.0)	8.0 (2.0, 16.0)	8.0 (2.0, 16.0)
N	94	101	195

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	Tight control N (%)	Standard care N (%)	Total N (%)
Week 48			
Median (IQR)	8.0 (4.0, 16.0)	6.0 (2.0, 17.0)	8.0 (3.0, 17.0)
N	89	87	176
Total mvdH-S Heidje Score (Erosion + JSN), median improvement (IQR)	0.0 (-2.0, 0.5)	0.0 (-2.0, 0.0)	0.0 (-2.0, 0.0)
Non-missing N (total N)	84	85	169

Summaries correspond to those patients with non-missing data at baseline and week 48.

Table 6

Additional secondary outcomes – improvement in score from baseline to week 48 (evaluable patient population)

	Tight control	Standard care
Measures of disease activity		
PASI[1], median improvement (IQR)	1·2 (0·5, 3·2)	1·0 (-0·4 , 2·5)
Non-missing N (total N)	75 (81)	81 (93)
PASI20, N (%)	58/75 (77·3)	48/81 (59·3)
PASI90, N (%)	32/75 (42·7)	19/81 (23·5)
Enthesitis[2], median improvement (IQR)	2·0 (0·0, 4·0)	1·0 (-1·0, 4·0)
Non-missing N (total N)	73 (82)	72 (80)
Dactylitis[3], median improvement (IQR)	38.0 (20·0, 72·0)	58.5 (30·0, 112·0)
Non-missing N (total N)	31 (35)	22 (27)
mNAPSI[4], median improvement (IQR)	3·0 (1·0, 9·0)	2·0 (1·0, 8·0)
Non-missing N (total N)	57 (62)	53 (62)
Total joint count (TJC), median improvement (IQR)	4·0 (1·0, 11·0)	3·0 (-1·0, 9·5)
Non-missing N (total N)	92 (101)	92 (105)
Swollen joint count (SJC), median improvement (IQR)	4·0 (2·0, 7·5)	2·5 (1·0, 6·0)
Non-missing N (total N)	92 (101)	92 (105)
Patient reported outcomes		
BASDAI score (cm), median improvement (IQR)	2·4 (0·9, 5·2)	1·5 (-0·2, 3·3)
Non-missing N (total N)	81 (101)	79 (105)
BASDAI MCID, N (%)	57/81 (70·4)	44/79 (55·7)
BASDAI score (cm)[5], median improvement (IQR)	3.9 (-0·3, 5·8)	0.9 (-0·1 , 3·0)
Non-missing N (total N)	18 (20)	21 (23)
BASFI score (cm), median improvement (IQR)	1.2 (0·3, 3·7)	0.2 (-0·6, 1·7)
Non-missing N (total N)	81 (101)	80 (105)
BASFI MCID, N (%)	49/81 (60·5)	32/80 (40·0)
BASFI score (cm)[6], median improvement (IQR)	2.0 (0·0, 5·5)	-0·1 (-0·6, 1·3)
Non-missing N (total N)	18 (20)	21 (23)
PsAQoL, median improvement (IQR)	3.0 (0·0, 7·0)	0.5 (-1·0, 3·5)
Non-missing N (total N)	80 (101)	84 (105)
HAQ score, median improvement (IQR)	0·5 (0·1, 0·9)	0·1 (0·0, 0·5)
Non-missing N (total N)	91 (101)	90 (105)
HAQ MCID, N (%)	53/91 (58·2)	37/90 (41·1)
ASAS 20, N (%)	49/80 (61·3)	33/79 (41·8)
ASAS 40, N (%)	37/80 (46·3)	25/81 (30·9)

[1] Patients with skin psoriasis at baseline

[2]Patients with enthesitis at baseline

[3]Patients with dactylitis at baseline

[4]Patients with nail disease at baseline

[5]Patients with axial disease at baseline

[6]Patients with axial disease at baseline

Improvement (baseline – 48 weeks), where a positive score indicates an improvement Summaries correspond to those patients with non-missing data at baseline and week 48
BASDAI MCID, change in score from baseline to week 48 of at least 1.0cm
BASFI MCID, change in score from baseline to week 48 of at least 0.7cm
HAQ MCID, change in score from baseline to week 48 of at least 0.35
PASI, Psoriasis Area Severity Index; mNAPSI, Modified Nail Psoriasis Severity Index; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; MCID, Minimum Clinically Important Difference; BASFI, Bath Ankylosing Spondylitis Functional Index; PsAQoL, Psoriatic Arthritis Quality of Life Questionnaire; ASAS, ASsessment in Ankylosing Spondylitis; HAQ, Health Assessment Questionnaire.

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Table 7

Commonly reported adverse events (Safety patient population)

AE description	Tight control N (%)	Standard care N (%)	Total N (%)
Abdominal / GI upset, n (%)	35 (5·6)	13 (5·3)	48 (5·5)
Number of patients, n (%)	31 (30·7%)	12 (11·4%)	43 (20·9%)
Fatigue (Asthenia, lethargy, malaise), n (%)	33 (5·3)	8 (3·3)	41 (4·7)
Number of patients, n (%)	22 (21·8%)	8 (7·6%)	30 (14·6%)
Headache / Migraine, n (%)	27 (4·4)	11 (4·5)	38 (4.4)
Number of patients, n (%)	20 (19·8%)	7 (6·7%)	27 (13·1%)
Infection (Common cold), n (%)	46 (7·4)	14 (5·7)	60 (6·9)
Number of patients, n (%)	34 (33·7%)	13 (12·4%)	47 (22·8%)
Liver enzyme abnormalities, n (%)	37 (6·0)	39 (15·9)	76 (8·8)
Number of patients, n (%)	23 (22·8%)	28 (26·7%)	51 (24·8%)
Musculoskeletal pain, n (%)	28 (4·5)	8 (3·3)	36 (4·2)
Number of patients, n (%)	22 (21·8%)	6 (5·7%)	28 (13·6%)
Nausea, n (%)	54 (8·7)	38 (15·4)	92 (10·6)
Number of patients, n (%)	36 (35·6%)	27 (25·7%)	63 (30·6%)

Number and % of events is out of 620 events in the TC arm and 246 events in the StdC arm.
Number and % of patients is out of 101 patients in the TC arm and 105 patients in the StdC arm.