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

Laura C Coates, Anna R Moverley, Lucy McParland, Sarah Brown, Nuria Navarro-Coy, John L O'Dwyer, David M Meads, Paul Emery, Philip G Conaghan, Philip S Helliwell**

Summary

Background **Early intervention and tight control of inflammation optimise outcomes in rheumatoid arthritis but these approaches have not yet been studied in psoriatic arthritis. We aimed to assess the effect of tight control on early psoriatic arthritis using a treat-to-target approach.**

Methods **For this open-label multicentre randomised controlled trial, adult patients (aged ≥18 years) with early psoriatic arthritis (<24 months symptom duration), who had not previously received treatment with any disease-modifying anti-rheumatic drugs, were enrolled from eight secondary care rheumatology centres in the UK. Enrolled patients were randomly assigned in a 1:1 ratio to receive either tight control (with review every 4 weeks and with escalation of treatment if minimal disease activity criteria not met) or standard care (standard therapy according to the treating clinician, with review every 12 weeks) for 48 weeks. Randomisation was done by minimisation incorporating a random element, to ensure treatment groups were balanced for randomising centre and pattern of arthritis (oligoarticular *vs* polyarticular). The randomisation procedure was done through a central 24-h automated telephone system based at the Leeds Institute of Clinical Trials Research (Leeds, UK). This was an open-label study in which patients and clinicians were aware of treatment group assignment. Clinical outcomes were recorded by a masked assessor every 12 weeks. The primary outcome was the proportion of patients achieving an American College of Rheumatology (ACR) 20% (ACR20) response at 48 weeks, analysed by intention to treat with multiple imputation for missing ACR components. Cost-effectiveness was also assessed. This trial is registered with ClinicalTrials.gov, number NCT01106079, and the ISCRCTN registry, number ISCRCTN30147736.**

Findings **Between May 28, 2008, and March 21, 2012, 206 eligible patients were enrolled and randomly assigned to receive tight control (n=101) or standard care (n=105). In the intention-to-treat patient population, the odds of achieving an ACR20 response at 48 weeks were higher in the tight control group than in the standard care group (odds ratio 1·91, 95% CI 1·03–3·55; p=0·0392). Serious adverse events were reported by 20 (10%) patients (25 events in 14 [14%] patients in the tight control group and eight events in six [6%] patients in the standard care group) during the course of the study. No unexpected serious adverse events or deaths occurred.**

Interpretation **Tight control of psoriatic arthritis disease activity through a treat-to-target approach significantly improves joint outcomes for newly diagnosed patients, with no unexpected serious adverse events reported.**

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*Joint senior authors

Leeds Institute of Rheumatic and Musculoskeletal Medicine (L C Coates MRCP, A R Moverley MRCP, N Navarro-Coy MPhil, Prof P Emery FRCP, Prof P G Conaghan FRACP, P S Helliwell FRCP), **Clinical Trials Research Unit, Leeds Institute of Clinical Trials Research** (L McParland MSc, S Brown MSc, N Navarro-Coy), **and Academic Unit of Health Economics, Leeds Institute of Health Sciences** (J L O'Dwyer MSc, D M Meads MSc), **University of Leeds, Leeds, UK; and Leeds NIHR Musculoskeletal Biomedical Research Unit, Leeds, UK** (L C Coates, A R Moverley, Prof P Emery, Prof P G Conaghan, P S Helliwell)

Correspondence to:
Dr Philip S Helliwell, NIHR Leeds Musculoskeletal Biomedical Research Unit, LIRMM, Chapel Allerton Hospital, Chapel Town Road, Leeds LS7 4SA, UK
p.helliwell@leeds.ac.uk

Introduction

Psoriasis affects 2–3% of the UK population and psoriatic arthritis can occur in up to 30% of those affected.[1] Most patients with psoriatic arthritis have progressive joint damage, increasing disability, and reduced life expectancy,[2] which is associated with a substantial reduction in functional ability and quality of life.[3] Observational studies in psoriatic arthritis have shown that the number of active swollen joints is a predictor of clinical[4] and radiological progression,[5] but no-one has yet attempted to address the idea of tight control of inflammation to improve outcomes in this disease.

By contrast, in rheumatoid arthritis, the pivotal TIght COntrol of Rheumatoid Arthritis (TICORA) study was the first to show that tight control of disease using predefined activity levels to guide therapeutic changes resulted in significantly better clinical and radiographic outcomes compared with routine care.[6] Following this study, a treat-to-target approach has been used in many studies in rheumatoid arthritis. Consequently, management guidelines for rheumatoid arthritis from the UK National Institute for Health and Care Excellence (NICE) now advise monthly assessments of disease activity, aiming for a predefined target.[7]

Treatment strategy trials have not been done in psoriatic arthritis, largely because of disease heterogeneity and the absence of a suitable disease-specific treatment target. A potential target for therapy in psoriatic arthritis has now been developed: the minimal disease activity (MDA) criteria. These criteria for psoriatic arthritis assess several manifestations of the disease to give a measure of low disease activity across the domains of

joints, skin, enthesitis, and patient-reported outcomes[8] and have now been validated in several cohorts.[9,10]

Observational studies have suggested that control of disease inflammation in psoriatic arthritis leads to improved long-term outcomes,[11] and more recent data suggest better outcomes in patients who are referred and treated earlier than in those referred later.[12] This evidence, together with the availability of a therapeutic target, was the impetus to study the effect of tight control of early psoriatic arthritis in a randomised controlled trial using a treat-to-target approach: the TIght COntrol of Psoriatic Arthritis (TICOPA) trial.

Methods

Study design and participants

For this randomised, controlled, parallel-group, open-label, UK multicentre clinical trial, we recruited patients from eight secondary care rheumatology centres in the UK. Eligible participants were adults (aged ≥18 years) with recent onset (<24 months symptom duration) psoriatic arthritis diagnosed by a consultant rheumatologist, who had never previously received treatment with disease-modifying anti-rheumatic drugs. The main exclusion criteria were: previous treatment for articular disease with disease-modifying anti-rheumatic drugs, including, but not limited to, methotrexate, sulfasalazine, and leflunomide; women who were pregnant, lactating, or planning pregnancy within 6 months of their last dose of protocol treatment; and use of any investigational agents within the previous 4 weeks or within five half-lives of the investigational agent, whichever is longer, before randomisation. Full details of the trial protocol have been published previously.[13] Ethics committee approval was granted by Northern and Yorkshire Research Ethics Committee (ref: 07/H0903/72). All patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned on a 1:1 basis to receive either tight control or standard care. Randomisation was done through a central 24-h automated telephone system based at the Leeds Institute of Clinical Trials Research (Leeds, UK) and was done by minimisation incorporating a random element, ensuring treatment groups were balanced for randomising centre and pattern of arthritis (oligoarticular *vs* polyarticular).

This was an open-label study, so study physicians and patients were aware of the allocated treatment group. Follow-up assessments involving a full clinical assessment every 12 weeks were done by a research nurse who was masked to the allocated treatment group.

Procedures

Patients received either tight control or standard care for 48 weeks, with safety follow-up to 52 weeks. Patients in the tight control group were seen by the study physician every 4 weeks and treated according to a predefined treatment protocol (figure 1). At each visit, the MDA criteria were assessed by the study physicians.[8] Patients were categorised as achieving MDA if they fulfilled five of seven criteria (tender joint count ≤1; swollen joint count ≤1; Psoriasis Activity and Severity Index (PASI) ≤1; patient pain visual analogue score (VAS) ≤15 mm; patient global disease activity VAS ≤20 mm; health assessment questionnaire score ≤0·5; and ≤1 tender entheseal points). Treatment with disease-modifying anti-rheumatic drugs was increased to the maximum dose (figure 1) if patients had not achieved the MDA criteria. Any patient who could not tolerate the maximum dose because of toxicity or intolerance was allowed to continue on the highest tolerated dose and then progress to the next step in the protocol, if needed. Patients achieving the MDA criteria continued on their current treatment. Intra-articular and intramuscular steroids, administered after disease assessments, were also used in disease control. Patients were offered local joint injections to active joints or intramuscular steroid injections by the physicians if judged to be appropriate during the waiting period for the disease-modifying anti-rheumatic drugs to work.

Patients in the standard care group 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. At each study site, different physicians treated the patients in the tight control and standard care groups. All patients were required to meet the NICE criteria for the use of biologicals in psoriatic arthritis before they could receive these drugs (≥3 tender and swollen joints, and no response, or intolerance, to two standard disease-modifying anti-rheumatic drugs).

Radiographs of the hands and feet were done at baseline and at 48 weeks. They were scored according to the modified Sharp-van der Heijde scoring method for psoriatic arthritis.[14] Scoring was done by two readers (PSH and LCC) by consensus. All radiograph films were scored as a pair but the readers were masked to treatment group and time sequence.

Outcomes

The primary endpoint of the trial was the proportion of patients in each treatment group achieving an American College of Rheumatology (ACR) 20% response (ACR20) at 48 weeks post-randomisation, analysed by intention to treat. Key secondary endpoints were ACR 50% (ACR50) and ACR 70% (ACR70) response, Psoriasis Area Severity Index (PASI) 75% (PASI75),[15] and modified Sharp-van der Heijde x-ray score at 48 weeks post-randomisation.[16] Additional physician-assessed secondary outcomes included the modified Nail Psoriasis and Severity Index (mNAPSI),[17] assessment of tenderness at entheses

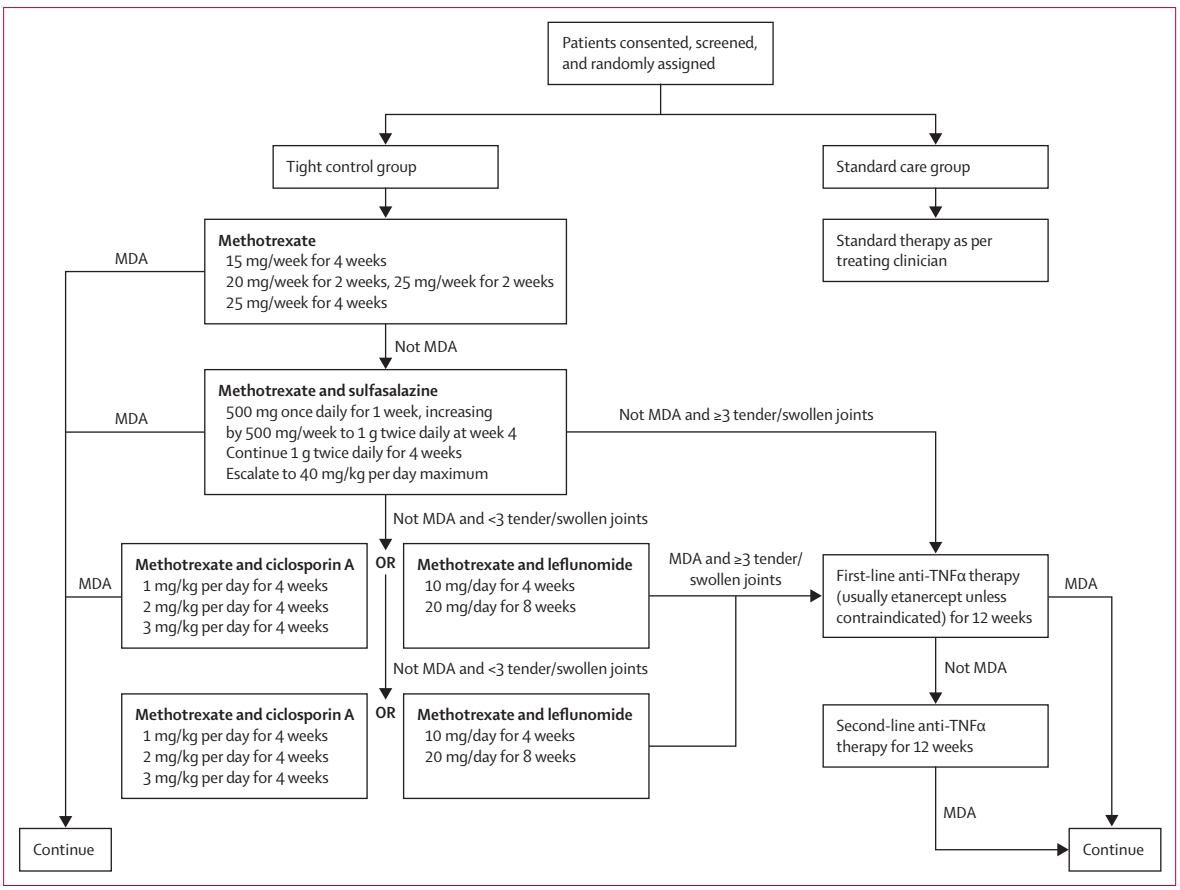

Figure 1: **Treatment protocol**
MDA=minimal disease activity. TNF=tumour necrosis factor.

(comprising the Maastricht ankylosing spondylitis enthesitis index,[18] the Leeds Enthesitis Index,[19] and tenderness at the plantar fascia), dactylitis (assessed by the Leeds Dactylitis Index[20]), and a 66 swollen joint count and 68 tender joint count. Patient-completed outcomes were visual analogue scale scores (patient global disease activity and pain score, and physician global disease activity score), the health assessment questionnaire (HAQ), the Bath ankylosing spondylitis functional questionnaire (BASFI),[21] the Bath ankylosing spondylitis disease activity index (BASDAI),[22] psoriatic arthritis quality-of-life index (PsAQoL),[23] and the EQ-5D. Additionally, information about clinic visits, investigations, and employment status was gathered for use in economic analyses.

Statistical analysis

We calculated that a sample size of 93 evaluable patients per group (thus a total sample size 186 participants) would provide 80% power to detect a 20% difference in the primary outcome (ACR20 at 48 weeks) between the two treatment groups, under the assumption of a 50% response rate in the standard care group, and based on a χ^2 test without continuity correction at the two-sided 5% significance level. To allow for a 10% dropout rate, a total of 206 patients were recruited. We fitted a multivariable logistic regression model to assess the effect of treatment on the odds of patients achieving ACR20 (in the intention-to-treat population) at 48 weeks post-randomisation, with adjustment for the minimisation factors. We used multiple imputation[24] to impute missing ACR component data (eg, tender joint count) at baseline and follow-up assessments; we then combined parameter estimates using Rubin's rules[25] to obtain an overall estimate of the treatment effect.

Additionally, we did a univariable analysis on those patients with an evaluable ACR20 response at 48 weeks. We compared the difference in the proportion of patients achieving an ACR20 response between the treatment groups using the χ^2 test. We did sensitivity analyses to assess the robustness of the primary analysis using multiple imputation and the assumptions regarding the missing data, the results of which will be presented separately.

We used a multivariable logistic regression analysis, adjusting for the minimisation factors, to assess the effect of treatment on the key secondary outcomes of ACR50 and ACR70 (in the intention-to-treat population)

and PASI75 (in the evaluable patient population) at 48 weeks post-randomisation. We compared the difference in the proportion of patients in the evaluable patient population achieving each outcome between treatment groups using the χ^2 test. To ascertain the pattern of the treatment effect on ACR20 over time, we did a repeated-measures analysis on ACR20 response across all follow-up timepoints (in the evaluable patient population), for which we used generalised estimating equations to adjust for the correlated outcome data. The analysis adjusted for the minimisation factors, time since baseline, and treatment group; we also assessed the treatment-by-time interaction.

We compared the difference in the median change in modified Sharp-van der Heijde x-ray score (baseline–week 48) between treatment groups using the Wilcoxon rank-sum test.

Additional secondary outcomes (physician-assessed disease activity and patient-reported outcomes) are summarised for those patients with non-missing data; we did not do any formal statistical comparisons between the groups for these outcomes. PASI, enthesitis, dactylitis, and mNAPSI are also summarised for those patients with corresponding disease at baseline.

We did a prospective economic evaluation to assess the cost-effectiveness of tight control compared with standard care over 48 weeks. Health service costs were combined with EQ-5D-derived quality-adjusted life-years outcomes. Resource use was captured through the use of 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 done from the perspective of the health-care provider. When appropriate, incremental cost-effectiveness ratios were calculated using the willingness-to-pay threshold of £20 000 per quality-adjusted life-year gain. The probability of cost-effectiveness was established by bootstrapping analysis and the construction of cost-effectiveness acceptability curves[26] using a range of willingness-to-pay thresholds for quality-adjusted life-year gains. Multiple imputation was used to account for missing cost and EQ-5D data.

SAS version 9.2 and Stata version 12.0 were used for all statistical analyses. This trial is registered with ClinicalTrials.gov, number NCT01106079, and the ISCRCTN registry, number ISCRCTN30147736.

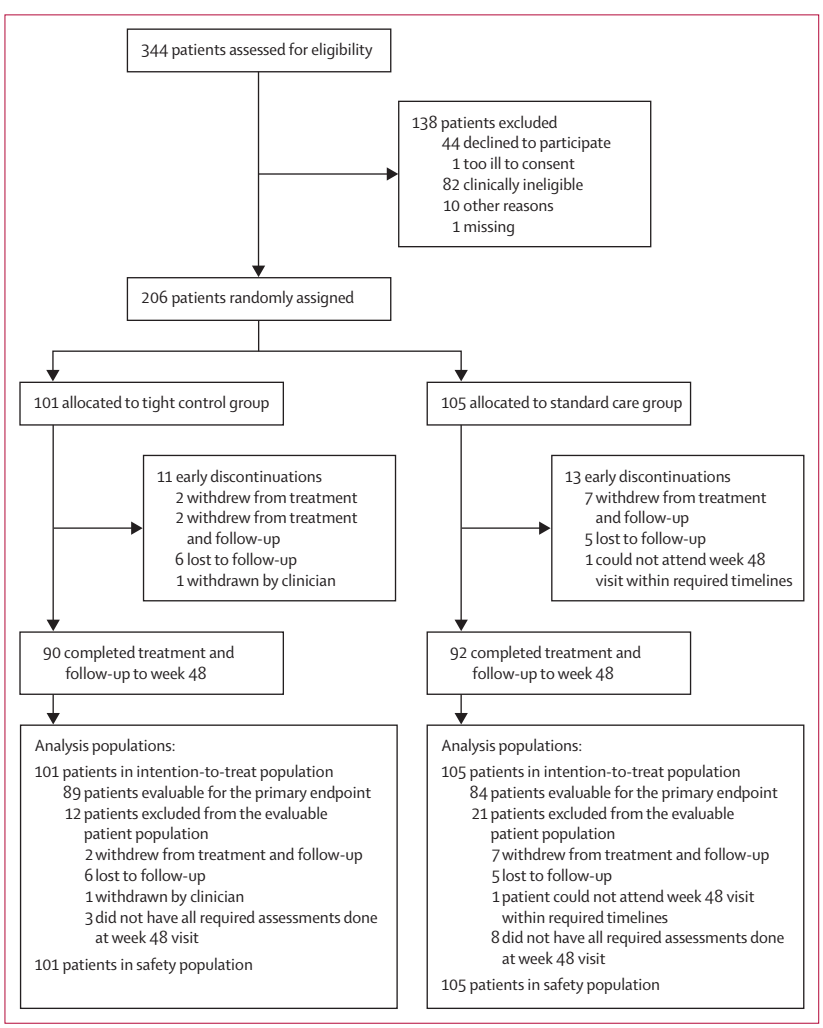

Figure 2: **Trial profile**

Role of the funding source

The funders 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

Between May 28, 2008, and March 21, 2012, a total of 344 patients were screened for eligibility. 206 (60%) of these patients were enrolled and randomly assigned to either tight control (101 patients [49%]) or standard care (105 patients [51%]; figure 2). In the tight control group, 90 (89%) of 101 patients completed treatment and follow-up to week 48, and a similar proportion (92 [88%] of 105) did so in the standard care group. No patients were found to be ineligible for the trial post-randomisation. A similar proportion of patients discontinued early from the trial in the tight control group (11 patients [12%]) as in the standard care group (13 patients [12%]).

Baseline characteristics were similar across the treatment groups, although more patients in the tight control group presented with current enthesitis and dactylitis, whereas fewer presented with distal inter-phalangeal joint disease and current psoriasis than in the standard care group (table 1). Most patients (188 [91%]) fulfilled the ClASsification of Psoriatic ARthritis (CASPAR) criteria for psoriatic arthritis

(ie, score ≥3), with 202 (98%) patients scoring 2 or more points. Most patients (146 [71%]) presented with polyarticular disease (≥5 joints involved) in keeping with other psoriatic arthritis cohorts, and had psoriasis at baseline (174 [85%]) although in these patients, psoriasis disease activity was low (median PASI 2·6 [IQR 1·2–4·8]).

Of the 206 randomly assigned patients, 33 (16%) had some or all of the component data missing needed for the derivation of the ACR20, more of whom were in the standard care group (21 patients [20%], *vs* 12 [12%] in the tight control group; figure 2). The intention-to-treat population consisted of all 206 randomly assigned patients. The evaluable patient population consisted of patients with an ACR20 response at 48 weeks, before any imputation, and included 173 patients (84 [80%] in the standard care group and 89 [88%] in the tight control group). The safety patient population comprised all 206 randomised patients.

In the intention-to-treat population (n=206), the odds of achieving an ACR20 response at 48 weeks were higher in the tight control group than in the standard care group after adjustment 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 patients in the tight control group achieved an ACR20 response at 48 weeks than in the standard care group (17·8% difference [95% CI 3·1–32·4], p=0·0194; table 3).

In the intention-to-treat population, the odds of achieving ACR50 (OR 2·36 [95% CI 1·25–4·47], p=0·0081) and ACR70 (2·64 [1·32–5·26], p=0·0058) at 48 weeks were higher in the tight control group than in the standard care group. Furthermore, in the evaluable patient population (n=156), the odds of achieving a PASI75 response at 48 weeks were higher in the tight control group than in the standard care group (OR 2·92 [95% CI 1·51–5·65], p=0·0015). Table 3 shows the difference in the proportion of patients achieving each response status (ACR50/70 and PASI75) for the evaluable patient populations.

The odds of achieving an ACR20 response throughout the whole study duration were higher in the tight control group than in the standard care group (OR 1·69 [95% CI 1·10– 2·60], p=0·0158). The odds of achieving an ACR20 response also increased significantly over time (OR 1·02 [95% CI 1·01–1·03], p=0·0009). However, there was no evidence that the treatment effect varied over time (treatment-by-time interaction p=0·7255).

At baseline, 49 (25%) of all enrolled and randomised patients had some erosive disease and 165 (85%) had joint space narrowing, with a slightly higher proportion of these patients in the tight control group (appendix p 1). The total modified Sharp-van der Heijde scores (erosions + joint space narrowing) at baseline were low, with an overall median score of 8 (IQR 2–16), mainly caused by joint space narrowing; median scores were similar in the two treatment groups (appendix p 2). By week 48, the number of patients with erosive disease had been observed to increase, whereas the proportion of patients with joint space narrowing remained similar to that at baseline (appendix p 2). The median total modified Sharp-van der Heijde scores at week 48 remained similar across the treatment groups (appendix p 2). There was no evidence of a difference in the change in the total modified Sharp-van der Heijde scores between the treatment groups at week 48 (p=0·9779), with median change of 0 in both groups.

More patients in the tight control group than in the standard care group achieved PASI20 and PASI90 responses (appendix p 3). For the remaining measures of disease activity, a similar median improvement at week 48 was recorded between treatment groups, with the exception of dactylitis for which a greater median improvement was observed in the standard care group,

See Online for appendix

	Tight control (n=101)	Standard care (n=105)
Male sex	53 (53%)	55 (52%)
Age (years)	46 (38–55)	45 (36–51)
White ethnic origin	92 (91%)	96 (91%)
Disease duration at randomisation (months)	0·9 (0·5–2·1)	0·7 (0·4–1·8)
Number of swollen joints (0–66)	6 (3–10)	4 (2–8)
Number of tender joints (0–68)	9 (3–19)	9 (4–17)
C-reactive protein (mg/dL)	7·5 (5·0–24·0)	6·3 (5·0–15·5)
Rheumatoid factor negative	94 (93%)	101 (96%)
CCP negative	87 (86%)	85 (81%)
Early morning stiffness	88 (87%)	96 (91%)
Duration of early morning stiffness in patients with this symptom (h)	1·0 (0·5–2·0)	1·0 (0·5–2·0)
Arthritis pattern		
Polyarthritis (≥5 joints)	72 (71%)	74 (71%)
Oligoarthritis (<5 joints)	29 (29%)	31 (30%)
Distal inter-phalangeal joint disease	18 (18%)	27 (26%)
Axial involvement	20 (20%)	23 (22%)
Arthritis mutilans	0	0
CASPAR criteria met (score ≥3)	90 (89%)	98 (93%)
CASPAR score ≥2	99 (98%)	103 (98%)
Current psoriasis	81 (80%)	93 (89%)
PASI score (all patients)	1·7 (0·4–4·2)	2·1 (0·8–4·2)
PASI score (condition at baseline)	2·6 (1·2–4·8)	2·5 (1·2–4·7)
Current enthesitis	82 (81%)	80 (76%)
Enthesitis score (all patients)	3 (1–6)	2 (1–6)
Enthesitis score (condition at baseline)	4 (2–7)	4 (2–7)
Current dactylitis	35 (35%)	27 (26%)
Dactylitis score (all patients)	0 (0–22)	0 (0–0)
Dactylitis score (condition at baseline)	36 (20–67)	41 (16–112)
Current nail disease	62 (61%)	62 (59%)
mNAPSI score (all patients)	2·0 (0·0–10·0)	1·5 (0·0–11·5)
mNAPSI score (condition at baseline)	8·5 (3·0–15·0)	8·0 (2·0–23·0)

Data are n (%) or median (IQR). CCP=cyclic citrullinated peptide antibody. CASPAR=ClASsification of Psoriatic ARthritis. PASI=Psoriasis Area Severity Index. mNAPSI=modified Nail Psoriasis Severity Index.

Table 1: **Baseline characteristics**

	Odds ratio (95% CI)	p value
Treatment group: 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

ACR20=American College of Rheumatology 20% response. This analysis was done on the intention-to-treat population with multiple imputation. Following multiple imputation of the 206 patients, two patients had an undefined relative improvement for the Health Assessment Questionnaire, which was needed to ascertain the ACR20 value. Other sites were: 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.

Table 2: **Multivariable logistic regression analysis for the effect of treatment on the primary endpoint (ACR20 at 48 weeks post randomisation)**

	Tight control	Standard care	% difference in proportions (95% CI)	p value
ACR20	55/89 (62%)	37/84 (44%)	17·8% (3·1–32·4)	0·0194
ACR50	44/86 (51%)	21/84 (25%)	26·2% (12·1–40·2)	0·0004
ACR70	33/87 (38%)	15/86 (17%)	20·5% (7·5–33·5)	0·0026
PASI75	44/75 (59%)	27/81 (33%)	25·3% (10·2–40·5)	0·0015

Data are n/N (%) unless otherwise indicated. ACR=American College of Rheumatology. PASI=Psoriasis Area Severity Index.

Table 3: **Univariable analysis (χ^2 test of independence) for the proportion of patients in the evaluable patient population achieving a response at 48 weeks post randomisation for the key secondary endpoints**

although the number of patients with disease at baseline were small and scores were highly variable (appendix p 3).

For the patient-reported outcomes, patients with axial disease at baseline reported a greater median improvement in BASDAI and BASFI scores in the tight control group than in the standard care group (appendix p 3). From baseline to week 48, a higher proportion of patients in the tight control group than in the standard care group met the minimum clinically important difference threshold for improvement[27] for the BASDAI, BASFI, and HAQ scores (appendix p 3). Patients in the tight control group also reported a greater median improvement in PsAQoL score (appendix p 3).

Throughout the trial, methotrexate monotherapy was administered to 27 (27%) of 101 patients in the tight control group, compared with 63 (60%) of 105 in the standard care group. A higher proportion of patients in the tight control group than in the standard care group were treated with combination disease-modifying anti-rheumatic drugs (74 [73%] in the tight control group *vs* 30 [29%] in the standard care group) and biological therapies (39 [39%] *vs* 7 [7%]). All 101 patients in the tight control group reached a methotrexate dose level of at least 15 mg per week by week 12 compared with 70 (67%) of those in the standard care group. By week 12, more patients in the tight control group than in the standard care group reached a methotrexate dose level of at least 20 mg per week (91 patients [90%] *vs* 31 patients [30%]) and of at least 25 mg per week (83 [82%] *vs* 8 [8%]). At 12 weeks, most patients in both groups were reported to be on methotrexate monotherapy (57 [56%] in the tight control group and 72 [69%] in the standard care group), with more tight control patients (37 [37%]) than standard care patients (4 [4%]) moving onto combination disease-modifying anti-rheumatic drug therapy. By week 48, just less than half (51 [49%] of 105 patients) in the standard care group were reported to still be on methotrexate monotherapy, whereas in the tight control group, only 26 (26%) of 101 patients continued on methotrexate monotherapy, with more patients in this group on combination disease-modifying anti-rheumatic drugs alone (24 [24%] in the tight control group *vs* 11 [11%] in the standard care group) or any biologicals (37 [37%] *vs* seven [7%]). Throughout the trial, patients in the tight control group received more steroid treatment in the form of intra-articular or intramuscular injections than did those in the standard care group (median dose 120 mg [IQR 0–260] per patient over 48 weeks in the tight control group *vs* 80 mg [0–160] in the standard care group) but doses overall were quite low.

At week 12, 83 (82%) of the 101 patients in the tight control group reached 25 mg per week of methotrexate, with 33 (33%) following the exact methotrexate escalation schedule as per the tight control treatment protocol (figure 1). Overall, 24 (24%) of patients in the tight control group had reached MDA by week 12; of the 75 patients who did not reach MDA, treatment was escalated in 53 (71%). Between weeks 12 and 48, 73 patients (72%) reached MDA at least once, with 57 patients (56%) reaching MDA on at least two consecutive visits. Furthermore, on average, patients reached MDA at 41% of assessments attended and, of those assessments where MDA was not met, treatment was escalated 37% of the time. Reasons for non-escalation included: on current disease-modifying anti-reheumatic drug therapy for less than 12 weeks; concurrent disease; on maximum therapy already; recent missed treatment; or unable to tolerate escalated dose.

Serious adverse events were reported in 20 (10%) of 206 patients and were more common in the tight control group, in which 25 serious adverse events occurred in 14 patients (14%) compared with eight events in six patients (6%) in the standard care group. In patients who had an event, a similar median number of serious adverse events were reported between the treatment groups (1 [range 1–6] in the tight control group *vs* 1 [1–2] in the standard care group). Ten serious adverse events were suspected to be related to drug treatment, with eight in the tight control group (cellulitis [n=2], pneumonia [n=2], musculoskeletal chest pain [n=1], raised liver function tests [n=1], collapse and pancytopenia [n=1], and anaphylaxis [n=1]) and two in the standard care group (migraine and septic arthritis), all of which required hospital admission, but none were judged to be life-threatening. No unexpected serious adverse events or deaths occurred in the trial.

Adverse events were reported in 179 (87%) of 206 patients and were reported more often by patients in the tight control group (98 patients [97%]) than in the standard care group (81 patients [77%]). In patients who had an event, a higher median number of adverse events was reported in the tight control group (6 events [range 1–20]) than in the standard care group (3 events [1–10]). Of all 866 adverse events reported, the most commonly reported were nausea, liver abnormalities, and infections (common cold; appendix p 5). Nausea, fatigue, the common cold, headache or migraines, musculoskeletal pain, and gastrointestinal upset were reported more frequently in the tight control group than in the standard care group, although abnormalities in liver function tests were reported equally in both groups (appendix p 5). A similar proportion of adverse events were suspected to be related to drug treatment in both groups (68% of those in the tight control group and 73% of those in the standard care group).

In the economic analysis, the mean cost per patient in the tight control group was £4198 (SD 2758) compared with £2000 (2349) for those in the standard care group (appendix p 6). Mean quality-adjusted life-years were 0·602 (0·195) for tight control and 0·561 (0·244) for standard care. These values yielded a deterministic incremental cost-effectiveness ratio of £53 948 per quality-adjusted life-year. Bootstrapped uncertainty analysis produced a mean simulation incremental cost-effectiveness ratio of £50 723 and suggested that tight control had a 0·07 probability of being cost effective at a £20 000 threshold. Scenario analyses, which reduced total costs in both groups by 25% and reduced consultations for patients in the tight control group who achieved MDA on two consecutive occasions (with an assumed reduction to 3-monthly follow-up visits), yielded an incremental cost-effectiveness ratio 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 psoriatic arthritis (panel). Treat to target using a tight control strategy significantly improved the primary outcome (ACR20), with the greatest benefits recorded with more stringent outcome measures such as ACR70 and PASI75. Benefits were recorded across both articular and skin outcomes and for a range of patient-reported outcomes. Radiographic progression did not differ between the two groups, 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 group than in the standard care group.

Physicians might be reluctant to treat to target in patients with psoriatic arthritis, or even to treat these patients at all, as shown by the high proportion of people without any or only topical treament for psoriasis and psoriatic arthritis in the USA.[29] This reluctance to treat affected patients might be due to a perception that psoriatic arthritis is not a progressive disabling disease, despite evidence showing that its consequences are similar to those of rheumatoid arthritis.[3] The process of treating to a low disease activity target in rheumatoid arthritis is believed to lead to better outcomes, both clinical and radiographic,[30] and the present study supports this strategy, for clinical outcomes, in psoriatic arthritis. However, to achieve this state consistently across a patient group, patients need to be reviewed regularly and treated by an aggressive algorithm. Importantly, the patient should be involved in the decision to use a treat-to-target approach, and every patient might have their own preference for both target and the means to achieve it, which should be respected.

Which aspect of care led to better outcomes is difficult to ascertain. Certainly patients appreciated the more intense visit schedule mandated by the tight control group, even when they were in stable MDA and, theoretically, did not need to visit the hospital every month. This aspect of the treat-to-target approach should be assessed in future studies. Clearly the higher use of biologicals in the tight control group increased the chance of achieving an ACR20 response, but the data indicate that more patients in this group reached an ACR20 at weeks 12 and 24, which is before biologicals would have been introduced. As with treat to target 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 achieve it.

Panel: Research in context

Systematic review

In 2014, the European League Against Rheumatism (EULAR) published a systematic literature review of the MEDLINE, Embase, and Cochrane databases, examining the evidence for treat to target in the spondyloarthritides including psoriatic arthritis. Search terms included: "psoriatic arthritis", "treat* adj to target*", "tight", "aggressive", "control", and "strategy".[28] The investigators were mainly looking for "strategic studies that compared a therapy steered towards a prespecified treatment target versus a conventional non-steered approach" but no such studies were identified in any of the spondyloarthritides. Five studies in psoriatic arthritis were identified in which doses of drugs (most often TNF inhibitors) could be escalated for all patients if a predefined improvement in joint counts was not met. No randomised controlled trials of tight control in psoriatic arthritis were identified.

Interpretation

This is the first randomised, controlled, treat-to-target trial in psoriatic arthritis. Patients in the tight control group showed significant improvements in joint and skin disease activity as well as benefits in function and quality of life when compared with those in the standard care group. Radiographic outcome did not differ between the groups because of very low rates of radiographic progression in the study. The number of adverse events, including serious adverse events, was higher in the tight control group than in the standard care group, but no unexpected serious adverse events were reported. Our findings provide clinicians with clear evidence of the benefits of a treat-to-target approach in psoriatic arthritis with a clinically feasible target.

Similarly, assessment of the gains achieved is complex. Although a 20% improvement in the ACR response criteria (the primary outcome) is equivalent to only modest clinical benefit, a 50% and 70% improvement is very noticeable by the patient. These gains are also shown by the increased proportion of patients achieving the minimal clinically 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 regimen but, overall, quality of life improved, albeit modestly.

In the UK and elsewhere,[31] methotrexate is often the first drug to be used in psoriatic arthritis, unless the patient has only axial disease. However, the methotrexate in psoriatic arthritis (MIPA) study reported that methotrexate is ineffective in psoriatic arthritis.[32] We accept that treatment approaches evolve and that, at the time when the MIPA trial was started, lower doses of methotrexate were used. Doses are now higher[33] and in the present study methotrexate 25 mg weekly was taken by 82% of patients in the tight control group by 12 weeks. Furthermore, throughout the study, methotrexate monotherapy was used in just over a quarter of the tight control group, with these patients consistently achieving MDA.

Radiographic progression did not differ between the two groups. This finding is perhaps unsurprising in view of the fact that the patients had very early disease, a variable clinical phenotype with around 30% with oligoarticular disease, and both study groups were given active treatment. Previous work has shown that a quarter of patients have bone erosions at first presentation, increasing to 43% at 2 years, despite treatment, but numbers of erosions per patient were low.[34] In the present study, 25% of patients had at least one erosion at baseline, with this figure increasing to 31% at 48 weeks. The infrequent erosions at baseline, and the relative absence of deterioration over 48 weeks, implies that longer intervals, or alternative imaging techniques such as MRI, are needed to show structural damage progression in psoriatic arthritis with the use of modern treatment paradigms.

The economic assessment suggests that tight control is unlikely to be regarded as cost effective according to willingness-to-pay thresholds of £20 000–30 000 per quality-adjusted life-year. Tight control conferred a small incremental quality of life benefit (0·041 quality-adjusted life-years), at an additional cost (especially for drugs and consultation). In reality, patients would not be reviewed as often as the protocol demanded, especially once they had achieved low disease activity. The sensitivity analyses, including reduced consultations for patients in the tight control group achieving MDA after two consecutive visits, yielded an incremental cost-effectiveness ratio that approached an acceptable level of cost-effectiveness. Drug costs are also likely to fall, given the imminence of biosimilars, but at present it is not possible to ascertain the effect of those changes on the incremental cost of a tight control strategy. For now, we must accept that, with the use of the existing treatment algorithm, the costs for tight control remain higher than the existing standard of care. Further subgroup and sensitivity analyses are needed.

Adverse events were reported more frequently in the tight control group than in the standard care group. Notably, rates of liver enzyme abnormalities were similar in both groups. By contrast, symptoms such as nausea, fatigue, and gastrointestinal upset were reported more frequently in the tight control group than in the standard care group. The higher rate of adverse events in this group is probably related to the more intensive treatment schedule, including rapid escalation of disease-modifying anti-rheumatic drug therapy, especially methotrexate. Recall bias could be another factor, with patients in the tight control group having more opportunity to recall events over a 4-week period compared with those seen every 12 weeks in the standard care group. Serious adverse events, including those suspected to be related to the study drugs, were also reported more frequently in the tight control group than in the standard care group. Half of these serious events were infections, as might be expected with treatments that suppress the immune system. All serious adverse events necessitated admission to hospital but none were judged to be life-threatening or resulted in death, and no unexpected serious adverse events were reported.

The open-label design of this trial might have caused unintentional bias in favour of the tight control group; to avoid this problem, a masked assessor was used. However, we were unable to test the efficacy of the masking. Patients in the standard care group were more likely to experience resentful disillusionment, although early discontinuation occurred in only 13 patients in this group compared with 11 in the tight control group. A blunting of the efficacy of tight control might also have occurred because the patients who received standard care were all treated by consultant rheumatologists working in teaching hospitals and might therefore already be following a more aggressive approach in their treatment of this disease. The intended treatment effect might also have been diluted by deviations from the treatment escalation protocol. Despite this potential problem, 82% of patients in the tight control group achieved a 25 mg dose of methotrexate by week 12. Finally, the primary outcome measure could be argued to be suboptimal for assessing response, since the ACR response criteria were originally designed for rheumatoid arthritis. Use of a composite outcome that represents the whole range of disease manifestations of psoriatic arthritis would be more appropriate,[35] and such measures have been shown to have more power.[36] However, these composite measures were not available when this study commenced.

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

Contributors

PSH, LCC, PE, and PGC conceived the study. PSH and LCC designed the study. The Leeds Institute of Clinical Trials Research gathered and coordinated the study data. LM, SB, JLO'D, and DMM analysed the data. PSH and LCC had full access to all the data. PSH takes responsibility for the data and analysis. All authors approved the final version of the report.

TICOPA study centres and investigators

Chapel Allerton Hospital, Leeds, UK: P S Helliwell, L Coates, A Moverley, S Bingham, P Conaghan, P Emery, H Marzo-Ortega, D McGonagle, M Martin, C Pease. St Luke's Hospital, Bradford, UK: P S Helliwell, G Ibrahim, T Aslam, H MacIver. York District Hospital, York, UK: A Isdale, M Quinn. Manchester Royal Infirmary, Manchester, UK: P Ho. Royal National Hospital for Rheumatic Diseases, Bath, UK: N McHugh, E Korendowych. North Tyneside Hospital, Newcastle, UK: D Walker. Harrogate District Hospital, Harrogate, UK: A Gough, M Green. St Bartholomew's Hospital, London, UK: C Pitzalis.

TICOPA trial study committees

Trial Steering Committee: C Deighton (Chair), A Parkinson (patient representative), V Dale (statistician), J Packham (clinical representative). Data Monitoring and Ethics Committee: Z Karim (Chair), M Lewis (statistician), P Ho (clinical representative until started recruiting), P Jobanputra (clinical representative). Leeds Institute of Clinical Trials Research: H Collier (data management), J Langridge (data management), S Hartley (trial management), S R Brown (statistician), N Corrigan (statistician), I Garraway (data entry).

Declaration of interests

LCC has served on advisory boards for, and received research funding and speakers' fees from, Abbvie, Pfizer, MSD, UCB, and Celgene. PE has worked on clinical trials for, and provided expert advice to, Abbott/Abbvie, Bristol-Myers Squibb, Pfizer, UCB, MSD, Roche, Novartis, Takeda, and Lilly. PGC has served on advisory boards for Abbvie, Roche and Novartis and has received speakers' fees from Abbvie, Roche, Merck, Pfizer, and UCB. PSH has served on advisory boards for and received speakers' fees from Amgen, Abbvie, BMS, Janssen, Pfizer, MSD, UCB, and Celgene, and has received research funding from Abbvie and Pfizer. ARM, LM, SB, NN-C, JLO'D, and DMM declare no competing interests.

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