

Long term follow-up of patients in the TIGHT Control of inflammation in early Psoriatic Arthritis (TICOPA) trial.

Laura C Coates MRCP<sup>1-3</sup>, Farrouq Mahmood MRCP<sup>1,2,4</sup>, Jane Freeston<sup>1,2</sup>, Paul Emery FMedSci<sup>1,2</sup>, Philip G Conaghan FRACP<sup>1,2</sup>, Philip S Helliwell FRCP<sup>1,2,4§</sup>

<sup>1</sup> Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, LS7 4SA, UK

<sup>2</sup>Leeds NIHR Musculoskeletal Biomedical Research Centre, Leeds, UK.

<sup>3</sup> Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, UK

<sup>4</sup>Bradford Teaching Hospitals Foundation Trust, Bradford, UK.

§Corresponding author

Laura C Coates, MBChB, MRCP, NIHR Clinician Scientist, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, UK  
Dr Farrouq Mahmood MRCP, Specialist Trainee, Bradford & Leeds Teaching Hospitals, UK  
Jane E Freeston, MA MD MRCP, Consultant Rheumatologist and Honorary Clinical Associate Professor, NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, UK

Paul Emery, MA, MD, FRCP, FMedSci, Arthritis Research UK Professor of Rheumatology, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, UK

Philip G Conaghan, MBBS, PhD, FRCP, FRACP, Professor of Musculoskeletal Medicine,  
Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR  
Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, UK

Philip S Helliwell, MA, PhD, DM, FRCP, Professor of Clinical Rheumatology, Leeds  
Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, and NIHR Leeds  
Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, UK

Word count: 1541

Tables: 1

Conflicts of interest:

Corresponding author

Philip Helliwell

NIHR Leeds Musculoskeletal Biomedical Research Unit

LIRMM

Chapel Allerton Hospital

Chapel Town Road

Leeds, LS7 4SA

Ph: 0113 392 3064; Fax: 0113 392 4991; Email: [p.helliwell@leeds.ac.uk](mailto:p.helliwell@leeds.ac.uk).

The TICOPA study was funded by Arthritis Research UK (grant no 18825) and Pfizer. This study was supported by the National Institute for Health Research (NIHR) infrastructure at Leeds and Oxford. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

## Abstract

**Objectives:** The TICOPA study was the first strategy trial in psoriatic arthritis using an early treat to target strategy to improve clinical outcomes. The current study aimed to review a cohort of patients who had completed TICOPA to judge if the clinical advantage gained by participants in the tight control arm was sustained, and to explore subsequent therapy.

**Methods:** A case note review was conducted for a cohort of patients who had participated in TICOPA. Current drug use and clinical status were obtained, with low disease activity judged as no tender or swollen joints, no dactylitis and enthesitis, and no change in treatment required.

**Results:** Approximately 5 years after completion of the TICOPA study, notes were reviewed for 110 patients (TC, tight control, n=54, StdC standard care, n=56). Disease activity was found to be similar in both groups (current LDA low disease activity: TC 69%, StdC 76%). Biologic use at the end of the study was higher in the TC arm (TC 33%; StdC 9%), but at review a similar percentage in both groups were taking biologic drugs (TC 54%; StdC 52%), whereas MTX use diminished.

**Conclusions:** After several years, clinical outcomes and therapeutic drug use were similar in patients in both arms of the TICOPA study, with no obvious clinical advantage after TC ended. Notably, TC did not result in greater biological use long term, and MTX use decreased in both arms of the study.

**Key words:** psoriatic arthritis; treat-to-target, outcomes

Key messages:

- In the TICOPA study a treat-to-target strategy improved clinical outcome compared to standard care over 48 weeks
- Five years later, bDMARD use increased whilst MTX use decreased leading to no difference between treatment groups for therapy and equivalent clinical outcomes
- In routine care, >50% of patients receive long-term bDMARDs; the optimal time to start them remains to be determined.

## Introduction

The concept of treat-to-target is well established in rheumatoid arthritis, and early treatment leads to better long-term outcomes both clinically and radiographically (1). The TICOPA study was the first strategy trial in psoriatic arthritis (PsA) to demonstrate that a treat-to-target strategy in early disease improves clinical outcomes over a 48 week period (2). In the TICOPA study almost 40% of patients in the tight control, treat to target, arm were in minimal disease activity at 48 weeks, compared to 25% in the standard care arm. Following exit from this study, we hypothesised that this advantage would translate to a clinical advantage in the medium-term.

## Methods

The full trial protocol and clinical results of the TICOPA study have been previously reported (2, 3). In brief, this randomised, controlled, parallel group, open label, multi-centre clinical trial recruited people with early (less than 2 years symptom duration), treatment naive PsA. The primary objective of the main trial was to compare tight control (TC) with standard care (StdC), using minimal disease activity (MDA(4)) as the treatment target. Participants received either TC or StdC for a period of 48 weeks.

A total of 206 patients were recruited into TICOPA; 101 in the TC arm and 105 in the StdC arm. In 2018, approximately 5 years after the end of the study, the notes of all the available patients who participated in the TICOPA study at St Luke's Hospital, Bradford and Chapel Allerton Hospital, Leeds were reviewed. From the case notes, information was obtained on current treatment, treatment since the end of the study, and current clinical state. A patient was judged to be in low disease activity if there were no swollen or tender joints, no record of active enthesitis and dactylitis, and no escalation or change of treatment (unless the patient changed therapy because of adverse events). If the psoriasis was recorded as requiring further

treatment, then the patient was not judged to be in low disease activity. Unfortunately, not enough participants had current radiographs of the hands and feet to make meaningful comparisons with radiographs and radiographic scores at the end of the study.

## Results

Across the two sites 77 patients were randomised to the TC arm and 81 to StdC (Table 1). There had been four deaths in the TC arm, none of whom had been on biologics (causes of death: multi-organ failure, non-HIV Kaposi's sarcoma, recurrent glioblastoma, septicemia/diabetes). Data were available for 54 patients from the TC arm, 56 patients from the StdC arm of the study. Methotrexate use at the end of the study was similar between the groups (93% in TC, 80% in StdC). Methotrexate use at review was similar between groups but reduced overall (44% in TC, 54% in StdC). Biologic use at the end of the study was, as previously reported, higher in the TC arm (33% in TC, 9% in StdC) but at review, a similar percentage in both groups were taking biologic drugs (54% in TC, 52% in StdC). The treatment algorithm in TICOPA included the use of combination conventional synthetic disease modifying drugs (csDMARDs) and this was reflected in the percentage of patients taking combination csDMARDs (30% in TC, 15% in StdC). At review these figures had decreased with just one patient (2%) in the TC arm and 4 patients (7%) in the StdC arm on combination csDMARDs. In terms of disease activity at the end of the study, more patients were in MDA in the TC arm (50%) than the StdC arm (32%) but at follow up the percentage of patients considered to be in low disease activity was similar across the two arms (69% in TC; 76% in StdC). Although no formal statistics have been performed, it is clear that there are no differences between the outcomes for PsA patients in the different arms of the study, in terms of treatment and assessed disease activity, some 5 years after study completion.

To explore predictors of people being on biologic drugs in the moderate term, logistic regression was performed with current biologic use as the dependent variable and baseline age, gender, arthritis classification (oligoarthritis v polyarthritis), patient global VAS and PASDAS as independent variables. In this analysis, where all variables were entered simultaneously, only age was a predictor of future biologic use, with younger patients more likely to be taking biologic drugs (OR 0.95, 95% CI 0.92-0.99).

## Discussion

The TICOPA study confirmed the benefit of a treat to target strategy in PsA, but as the patients completed the study they returned to routine rheumatology care. There were equivalent numbers of patients judged to be in low disease activity at the review period suggesting that the benefit of treat to target may not continue beyond the use of this strategy. There were also significant changes in prescribing patterns after the study ended. In TICOPA the majority of patients were on methotrexate at the end of the study but this reduced to around 50% at follow up, demonstrating a substantial reduction in MTX use in both arms of the study over time. Although considerably more patients in the TC arm had escalated to biologics at 48 weeks, the number of patients on biologics at this 5 year review was similar between groups. Very few patients in either arm were on combination conventional synthetic disease modifying drugs (csDMARDS).

What useful information can be gleaned from this review? Despite an early intervention at the time of diagnosis with a treat to target strategy for one year, the benefit identified in TICOPA at 48 weeks does not seem to extend to a longer term improvement in disease activity once patients return to routine care. This argues for the importance of continuing with a treat to target approach for PsA patients in the long term to ensure that ongoing active disease is addressed and outcome maximised.

In the TICOPA study treatment costs were higher in the TC arm, due mainly to two factors: the higher use of biologic drugs and the more frequent appointments over the 48 weeks study period. However, at the follow up review, equivalent numbers in both treatment arms were on biologic drugs. Thus, the use of biologics in the StdC arm was later in the course of the disease but, eventually became equivalent to the TC arm. In both arms, at 50%, use of biologic drugs at the review was comparable to other published cohorts (5). Given that a number of biologic studies have shown higher response rates when used in patients with shorter disease duration (6, 7), this may justify the earlier use of biologics in those failing DMARD therapy despite the slight increase in cost over the patient's lifetime. There is also the benefit of improved quality of life (and benefit for work) during the 2 years of TC, which were not quantified. In this study the only significant predictor of future biologic use was younger age: disease sub-group, disease activity, and gender were not predictors, but the numbers were small in this analysis.

Methotrexate use, on the other hand, decreased over the 5 years after the end of the study, at a rate of just under 10% per year, consistent with other reports in this disease (8). Combination csDMARDs was relatively high in the TC cohort, reflecting the treatment algorithm used in TICOPA, but their use at review was much less. There is extremely limited data supporting the use of combination DMARDs in PsA, but in the UK, failure of at least 2 csDMARDs is required prior to the use of biologics. As previously reported, combination csDMARDs were used in approximately 50% of those in MDA at 48 weeks in TICOPA, but this benefit either didn't continue or there were unacceptable adverse events – there was insufficient detail during the notes review of the current study to answer this point. Of interest, 50% of patients on combination csDMARDs at the end of the study were on biologics at the review, so not all patients made the transition to biologic drugs



The study has several limitations. When evaluating these results, it must be noted that there was no formal intention to continue the treatment strategy, nor to continue detailed clinical and radiographic observations beyond the end of the TICOPA study. Other studies are needed to answer the question of the long-term benefits of an early continuous treat to target strategy. Secondly, the current status of the patients was based on notes review only and formal assessments, such as MDA, were rarely found in these routine clinic appointments. Disease status data are therefore uncertain, although this uncertainty applies equally to both treatment groups. Thirdly, an objective measure of disease status would have provided more tangible evidence of the medium-term benefit, or otherwise, of an early treat to target strategy in PsA but insufficient radiographs were available.

In summary, 5 years after study end, clinical outcomes and therapeutic drug use were similar but with considerable changes in patients who had been in the TICOPA study, with no obvious long term clinical advantage to the 48 week TC intervention. Without a formal intention to continue a treat to target strategy, this result reflects clinical practice in routine rheumatology care. No data were available on disease status to reflect a benefit of early tight control of disease activity.

## References

1. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis* 2016;75:3-15
2. Coates LC, Moverley AR, McParland L, Brown S, Navarro-Coy N, O'Dwyer J, et al. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. *Lancet* 2015;386:2489-98
3. Coates LC, Navarro-Coy N, Brown SR, Brown S, McParland L, Collier H, et al. The TICOPA protocol (Tight Control of Psoriatic Arthritis): a randomised controlled trial to compare intensive management versus standard care in early psoriatic arthritis. *BMC Musculoskelet Disord* 2013;14:101
4. Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. *Ann Rheum Dis* 2010;69:48-53
5. Gorlier C, Orbai A-M, Puyraimond-Zemmour D, Coates LC, Kiltz U, Leung Y-Y, et al. Comparing patient-perceived and physician-perceived remission and low disease activity in psoriatic arthritis: an analysis of 410 patients from 14 countries. *Ann Rheum Dis* 2019;78:201-8
6. Coates LC, Gladman D, Nash P, FitzGerald O, Kavanaugh A, Rasouliyan L, et al. Secukinumab provides sustained PASDAS related low disease activity in psoriatic arthritis: 2 year results from the FUTURE 2 study. *Ann Rheum Dis* 2017;76:948
7. Baranauskaite A, Raffayova H, Kungurov N, Kubanova A, Venalis A, Helmle L, et al. Infliximab plus methotrexate is superior to methotrexate alone in the treatment of psoriatic arthritis in methotrexate naive patients: the RESPOND study. *Ann Rheum Dis* 2012;71:541-8

8. Maetzel A, Wong A, Strand V, Tugwell P, Wells G, Bombardier C. Meta-analysis of treatment termination rates among rheumatoid arthritis patients receiving disease-modifying anti-rheumatic drugs. *Rheumatology* 2000;39:975-81

Table 1.

Treatments and disease outcome for patients in the TICOPA study (the numbers in parentheses represent the percentage of the patients reviewed)

	Tight Control Arm	Standard Care Arm
N at completion of TICOPA	77	81
N reviewed	54	56
MTX therapy at end of study	50 (93)	45 (80)
MTX therapy now	24 (44)	30 (54)
Biologic treatment at end of study	18 (33)	5 (9)
Biologic Treatment now	29 (54)	29 (52)
Combination csDMARD at end of study	16 (30)	8 (15)
Combination csDMARD now	1 (2)	4 (7)
No DMARD currently	8 (15)	7 (13)
In MDA at end of study	27 (50)	18 (32)
In LDA now	37 (69)	41 (76)

MDA = meets minimal disease activity criteria

LDA = meets low disease activity criterion used for this study

MTX: methotrexate

csDMARD: conventional systemic disease modifying drug