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**Short running head**

Radiographic outcomes from TICOPA

**Full title of manuscript**

Does tight control of disease impede radiological progression? The radiographic outcomes of the TICOPA study

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**Key Indexing Terms**

Psoriatic arthritis; treat-to-target; radiographic damage / progression

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## **Conflict of interest:**

LJ: none

PSH reports advisory boards for Amgen and speaker fees for Novartis.

PGC reports advisory boards for Abbvie, Roche and Novartis and speaker fees for Abbvie, Roche, Merck, Pfizer, and UCB.

PE reports clinical trials and provided expert advice to Abbott/Abbvie, Bristol Myers Squibb, Pfizer, UCB, MSD, Roche, Novartis, Takeda and Lilly

EH: none

LCC has worked as a paid consultant for AbbVie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Gilead, Galapagos, Janssen, Moonlake, Novartis, Pfizer and UCB., LCC has received grants/research support from AbbVie, Amgen, Celgene, Eli Lilly, Janssen, Novartis, Pfizer and UCB.

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## **Statement of ethics and consent:**

Ethics committee approval was granted by Northern and Yorkshire Research Ethics Committee (ref: 07/H0903/72). All patients were provided written informed consent.

## **Abstract**

### **Objective**

The Tight Control of Psoriatic Arthritis (TICOPA) study was the first to undertake treat-to-target approach in PsA. Our aim was to further investigate the radiographic changes in the TICOPA study.

### **Methods**

The TICOPA trial recruited patients with early DMARD naïve psoriatic arthritis (PsA). Plain radiographs of the hands and feet were taken at weeks 0 and 48. Clinical outcomes were recorded by a blinded assessor every 12 weeks. In post-hoc analysis, bootstrapped quantile regression, adjusting for baseline values and minimisation factors, was used to compare radiographic scores (modified van der Heijde-Sharp; mvdH-S) defined according to treatment arm or disease activity states.

### **Results**

Paired baseline and week 48 radiographs were available for 169/206 (82.0%) at week 48; 84 tight-control, 85 standard therapy. There was no difference in change in total mvdH-S score median (IQR) seen with tight control compared to standard therapy [0.0 (-2.0, 0.5) vs 0.0 (-2.0, 0.0); difference (95% CI) 0.0 (0.0, 0.0)]. Median total mvdH-S score change was lower in those achieving MDA, DAPSA remission and VLDA.

The number of people with radiographic progression (a total erosion score of  $\geq 2$  at week 48) was numerically lower in the tight control group (5/84 [5.9%] versus 12/85 [14.1%]). Patients with radiographical progression presented with polyarticular disease, high C-reactive protein and had poorer clinical outcomes at weeks 12 and 24.

## **Conclusion**

These data confirm the benefit of achieving low disease activity states on subsequent radiographic outcome but did not show a significant impact related to a tight-control management approach.

## **Background:**

Psoriatic arthritis (PsA) is a systemic inflammatory condition that presents with varying levels of severity that can manifest in six distinct domains, including peripheral arthritis, axial disease, enthesitis, dactylitis, and psoriatic skin and nail disease[1].

PsA in the peripheral joints can exhibit radiographic damage, including bone erosions, joint space narrowing (JSN), periostitis, pencil-in-cup-like joint deformity, acro-osteolysis, subluxation, and ankylosis. However, the extent and progression of this damage can vary significantly between patients.[2] It is possible for radiographic damage to be present before any physical symptoms, such as limited movement, deformities, and ankylosis [3].

Uncontrolled inflammation, particularly the number of active swollen and tender joints, has been shown to accelerate radiological damage progression [4]. Radiological damage can negatively impact patients' physical function and lead to poor functional outcomes[2, 5].

Identifying patients with PsA who suffer from destructive arthritis is crucial for effective treatment measures. In 2016, the GRAPPA-OMERACT PsA working group advised that drug evaluations in studies should include at least one measurement of structural damage, such as through imaging.[6]

The modified van der Heijde-Sharp (mvdH-S) scoring method is commonly used to evaluate radiographic changes in PsA[7]. Previous studies have shown that an increase in mvdH-S score negatively affects functional outcomes, which is indicated by a higher score on the Health Assessment Questionnaire (HAQ)[8]. This method meets many aspects of the OMERACT filter, making it an important tool in the assessment of PsA[6] assessing both erosion and JSN.

The Tight Control of PsA (TICOPA) study [9] was the first to address treat-to-target in PsA using the minimal disease activity (MDA) criteria[10], confirming a benefit in terms of minimising disease activity, normalisation of function, social participation and improve health-related quality of life (HRQoL) [9].

**Aim:**

This report investigates whether treat-to-target or achieving low disease activity states impacts on radiographic change/progression based on the TICOPA study results.

## Methods:

The TICOPA clinical trial was conducted across eight UK rheumatology secondary care centres between May 2008 and March 2012. Ethics committee approval was granted by Northern and Yorkshire Research Ethics Committee (ref: 07/H0903/72). It was a randomised, controlled, parallel group, open label trial that recruited patients with early treatment-naïve PsA who were randomly assigned to tight control or standard care. The trial is registered with ClinicalTrials.gov (NCT01106079); and with Current Controlled Trials (ISRCTN 30147736). The complete protocol details can be found in the published paper.[9]

<https://pubmed.ncbi.nlm.nih.gov/26433318/>

The PsA disease activity was evaluated objectively using the following criteria: American College of Rheumatology improvement scores of 20%, 50% and 70% (ACR20/50/70), Disease Activity in Psoriatic Arthritis (DAPSA) remission and Minimal or Very Low Disease Activity (MDA/VLDA) defined as meeting all seven of the MDA cut points at any at any given time[10]. Clinical outcomes were documented by a blinded assessor.

The participants underwent radiographs of their hands and feet at weeks 0 and 48. These radiographs were centrally read by two independent readers (PSH and LCC) using the mvdH-S scoring method. The scores were determined by consensus between LCC and PSH. The radiographic readers were blinded to all aspects, including treatment allocation, demographics, outcomes, and the order of the X-rays. In a post-hoc analysis, bootstrapped quantile regression was employed to compare changes in radiographic scores.

### **Statistical analysis:**

All statistical analyses were carried out in SAS version 9.2 and Stata V12.0. Adjusting for baseline values and minimisation factors, bootstrapped quantile regression was used to compare changes in radiographic scores defined according to treatment or disease states at the 50th, 75th and 90th percentiles. The bootstrap method provides a simple way to create confidence intervals in a small sample study[11]. Additionally, the method's estimations are not required to rely on the underlying distributional assumptions[11].

### **Results:**

The TICOPA study included 206 participants randomly assigned to either the tight control (TC) (n=101, 49.0%) or standard care (StdC) (n=105, 51.0%) group. Of the TC participants, 87.6% (92) completed treatment and follow-up to week 48, which was comparable to the percentage of StdC patients who did the same (87.6%, n=92). Additionally, 188 of the 206 patients (91.3%) met the Classification of Psoriatic ARthritis (CASPAR) criteria for PsA, and the study population had similar baseline characteristics across both treatment arms ***(Supplementary file 1)***.

Radiographs were available for 195 (94.7%) participants at baseline and 176 (85.4%) at week 48; 169 (82.0%; 84 TC, 85 StdC) had both sets. In total, 25.1% of participants had erosive disease and 84.6% JSN at baseline. The total mvdH-S scores (erosions + JSN) at baseline

were low with an overall median (IQR) score of 8·0 (2·0, 16·0), predominantly due to JSN.

**Table 1** shows that the total scores median (IQR) were similar at baseline in both treatment arms. Both treatment arms experienced a slight increase in radiological damage at 48 weeks.

### **The impact of tight control vs standard care**

At the median (50<sup>th</sup> percentile) there was no evidence of a difference in the change in mvdH-S scores between the treatment arms at week 48 ( $p=1.000$ ; **Table 2**), with median change of zero in both arms (**Table 1**).

As there was no difference at the median, we also investigated differences at the 75<sup>th</sup> and 90<sup>th</sup> percentiles (**Table 2**). Using this analysis there was no difference in radiographic progression between the two arms of the study. The differences in changes in erosion scores were not clinically or statistically significant. The cumulative probability of total mvdH-S score change, and erosion only change, between the two arms showed no difference (**Figures 1a and 1b**).

### **Impact of clinical disease control**

Regardless of allocated treatment group, achieving good clinical outcomes was associated with lower radiographic progression. The cumulative probability of total mvdH-S score

change was lower in those achieving MDA at 48 weeks (**Figure 1c**). This was consistent across different disease activity measures (**Table 2**).

### **Characteristics of radiographic progressors in the TICOPA dataset**

On evaluation of radiographic progression (defined as a total erosion score of  $\geq 2$ ), at week 48, 17/169 patients (10.1%) were found to have radiographic progression, representing 14.1% (12/85) of the StdC arm versus 5.9% (5/84) of the TC arm. When comparing those with radiographic progression to those who did not, 82% were found to have polyarticular disease, compared to 68%. Additionally, 77% (13 out of 17) of the patients with radiological progression had nail disease, compared to 58% in the non-radiographic progression group. Almost half of the radiographic progression group had dactylitis (47%, 8 out of 17) versus 28% in the non-radiographic progression group. The mean CRP at baseline in those with radiographic progression was higher than that in those who did not (CRP 34 mg/L, CRP 17.5 mg/L, respectively).

The fifth metatarsophalangeal (MTP) joint was found to be the most commonly eroded joint in the feet, followed by MTP 1 and MTP 2. In the hand joints, the second distal interphalangeal (DIP) and second metacarpophalangeal (MCP) joints were the most commonly affected. Male patients exhibited a higher likelihood of experiencing foot erosion (71%) compared to female patients (29%), while hand erosion rates were equal between the StdC and TC arm.

Patients with radiological progression were less likely to show clinical improvement, particularly at the 3- and 6-month timepoints (**Supplementary File 2**). By week 48, clinical outcomes were similar in progressors vs non-progressors. At this time, of the 17 patients showing radiographic progression, twelve continued on single DMARD therapy, three were receiving combination DMARDs (methotrexate and sulfasalazine) and two were receiving biologic DMARD therapy.

## **Discussion**

The TICOPA study has confirmed that a treat-to-target strategy can be beneficial in clinical outcomes for PsA patients, especially when implemented early to improve clinical outcomes. During the study, individual radiographs of PsA patients were examined to determine if tight disease control could affect radiographic outcomes in people with early PsA (those with less than 2 years of symptom duration and no prior treatment). However, it was found that radiographic progression did not vary between the groups, and tight control had no impact on the erosion score. This could be attributed to the study's design, which included a population with early milder disease (30% of participants had oligoarthritis), no comparison with a placebo, and a step-up treatment protocol.

Comparisons at the 75th and 90th percentiles, i.e. at the upper distribution of the change scores, representing those with the most progression, showed that reaching MDA, DAPSA

remission, or VLDA is a strong indicator of the overall MvdH-S score at 48 weeks. Individuals who accomplished these disease states had a lower total MvdH-S scores. In exploratory analysis, it appeared that early achievement of good clinical outcomes such as MDA was associated with less radiographic progression. The study found that those who had radiographic progression had higher levels of CRP at the beginning and were less likely to achieve good clinical outcomes at 12 and 24 weeks on treatment. This is in keeping with other studies in PsA and other forms of inflammatory arthritis.

Complementing our data, low clinical activity or remission was associated with minimal radiographic progression has been consistently reported in earlier studies[4, 12-14]. In addition, there is evidence that biologics such as adalimumab effectively prevent radiographic progression, independent of clinical activity control suggesting an added benefit related to the biologic mechanism of action[15, 16]. This was also confirmed in trials of golimumab[17]. In TICOPA, most individuals who experienced radiographic progression (n=17) continued with single DMARD therapy which may explain their ongoing radiographic progression. Due to the small sample size, drawing definitive conclusions is challenging.

This study assessed the radiological outcomes in the foot and ankle which are often overlooked in clinical practice despite their potential for causing significant functional problems. A higher percentage of male patients experienced foot erosions than female patients, while radiological progression scores in both hands and feet remained similar. Dactylitis is often linked with more erosive forms of PsA and can act as an early indicator of

the disease[18]. The foot is the common site of dactylitis, with the fourth MTP joint being the most affected joint[19]. The current study found that the fifth MTP joint is the most commonly affected with joint erosions in the feet, while the second DIP and second MCP joints are the most frequently affected in the hands. The findings were similar to the recently published results from the SpARRO cohort study[20].

### **Limitations**

This study has a few limitations in that it only analysed radiographs of hands and feet. Plain radiographs may not accurately depict the extent of damage in patients with a complex 3D structure, which is difficult to assess using a 2D imaging modality. Given the subjective interpretation of radiographic changes, assessing radiographic progression might be prone to measurement errors and variability. While this raises concerns about score reliability, the reporters mitigated errors by independently scoring the radiographs while being blinded. Furthermore, it may not reflect the radiographic damage in patients who had oligoarthritis affecting large joints that are not included in the x-ray imaging. However, reassuringly, 3D imaging in a sub-set of patients from the TICOPA trial also failed to demonstrate between treatment group differences[21].

Another potential drawback is the limited duration of follow-up. However, newer drug trials have confirmed the finding of limited progression of structural damage over a longer period of follow-up. For instance, patients treated with tofacitinib for up to 5 years showed limited progression of structural damage, with similar results found for both monotherapy and

combination therapy for up to 3 years.[22] Similarly, a 10-year observational cohort study demonstrated a slowing of radiographic progression following treatment with anti-TNF treatment as measured by the mSvdHS[23].

Additionally, the mvdH-S score does not measure bone proliferation, which means that it may not fully reflect the extent of structural damage[24]. Alternative PsA-specific scoring methods include the Psoriatic Arthritis Ratingen score (PARS)[25]. PARS is a validated framework based on the extent of joint-surface damage per joint, while also taking into account bone pathology changes involving destruction and proliferation[2].

The study observed no significant difference in radiographic progression between the StdC and TC groups. This outcome is not unexpected given that the participants were in the early stages of the disease, and all underwent active treatment. Consistent with other studies, this analysis indicated that maintaining low disease activity minimises radiographic damage and progression. Nevertheless, it is important to interpret these results cautiously due to the small number of people showing radiographic damage. To date, no comparable studies on tight control have been conducted.

## **Acknowledgements:**

The TICOPA study was funded by the Arthritis Research UK (grant 18825) and Pfizer. The research team acknowledges the support of the National Institute for Health Research and the Comprehensive Clinical Research Network in supporting this research.

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