Article:
Coates, LC and Helliwell, P (2016) Methotrexate Efficacy in the Tight Control in Psoriatic Arthritis Study. Journal of Rheumatology, 43 (2). pp. 356-361. ISSN 0315-162X

https://doi.org/10.3899/jrheum.150614

Methotrexate efficacy in the Tight Control in Psoriatic arthritis (TICOPA) study

Laura C Coates, Philip S Helliwell

Background

Methotrexate is a commonly used DMARD in psoriatic arthritis (PsA) but there is conflicting evidence to support its efficacy.

Methods

Within the tight control of psoriatic arthritis (TICOPA) study, patients were treated with methotrexate, as part of the tight control protocol or standard care. Outcomes were recorded at the 12 week visit including joint counts, skin, nail, enthesitis, dactylitis and patient reported measures.

Results

Of the 206 patients enrolled, 188 received methotrexate in the first 12 weeks of the trial with 104 receiving a mean dose >15mg/week. The proportions of patients achieving the ACR outcomes at 12 weeks were: ACR20 40.8%, ACR50 18.8% and ACR70 8.6% with 22.4% achieving minimal disease activity (MDA). Improvements were seen in psoriasis with 27.2% reaching a PASI75. The proportion of patients with dactylitis, and Leeds dactylitis instrument (LDI) scores, decreased significantly (62.7% decrease in patients with dactylitis; median change LDI -59.7 (-157.4, -26.4), p = 0.033). The decrease in proportion of patients with enthesitis (25.7%) was significant but the median change in enthesitis score was 0. There was a trend to higher proportions of patients receiving over 15mg/week achieving ACR20, 50 and PASI 75.

Conclusion

Despite the open-label nature of the data, improvements in multiple clinical outcomes are seen. The proportion reaching ACR20 is higher than in MIPA (41 vs 34%) but no comparative data are available for other outcomes. There is a suggestion of a dose-response but this is hard to assess when patients doing well may be maintained on lower doses.

Key Indexing terms – psoriatic arthritis, DMARD, Treatment, Methotrexate, outcome measures

Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK and Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, UK.

Funding statement – the Tight Control of Psoriatic Arthritis (TICOPA) study was funded by Arthritis Research UK (grant number 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.

Conflict of interest – The authors declare that there are no relevant conflicts of interest to declare.

Dr Laura C Coates, NIHR Clinical Lecturer, MBChB, MRCP, PhD

Dr Philip S Helliwell, Senior Lecturer, MA, MD

Corresponding author

Dr Philip S Helliwell

Leeds Institute of Rheumatic and Musculoskeletal Medicine

University of Leeds

2nd Floor, Chapel Allerton Hospital

Harehills Lane

Leeds, LS7 4SA

Tel - +44 113 392 3064

Fax - +44 113 392 4991

Email – p.helliwell@leeds.ac.uk

Word count – 2428, table count – 3, figure count - 0

Psoriatic arthritis (PsA) is an inflammatory arthritis causing a significant burden of joint damage and related disability(1). Recent studies have highlighted a poorer outcome for those with a significant delay between symptom onset and diagnosis presumably related to a delay in initiation of therapy(2-5). One of the most common first line therapies used for patients with PsA is methotrexate. In Norway it was the most commonly used disease-modifying anti-rheumatic drug (DMARD) in PsA between 2000 and 2005(6) and 39% of patients in the ClASsification of Psoriatic ARthritis (CASPAR) study, recruited worldwide, were given methotrexate as their first DMARD(7). Even in recent years the Swedish early PsA registry (SwePsA) found that over half of the patients had received methotrexate(8).

Despite its frequent use, the evidence for methotrexate efficacy in PsA is lacking. Until recently, there were only 2 small RCTs assessing its use against placebo. The first, published in 1964, investigated the use of IV pulsed methotrexate. Despite an improvement seen with methotrexate, one patient died of marrow aplasia and several other adverse events were reported(9). The second study evaluated low dose oral methotrexate with a weekly dose of 7.5-15mg spread over three consecutive days. This did show a superior response in terms of a physicians' assessment of arthritis and body surface area (BSA) of psoriasis(10).

Given this lack of evidence, the Methotrexate in Psoriatic Arthritis (MIPA) study started in 2003. This compared methotrexate versus placebo in 221 patients with PsA. The study found no significant difference in ACR20, DAS28 or PsARC responses at 6 months, although they did see an improvement in both patient and physician assessments of PsA and psoriasis area and severity index (PASI) compared to placebo(11). This study cast doubt on the efficacy of methotrexate in PsA but there are concerns about its design. The target dose of methotrexate was just 15mg and only 11% of patients received doses higher than this (with a further 11% receiving less than 15mg/week). There were a large number of drop outs in the study and there has been concern about selection bias as patients and physicians were aware that half of the patients would receive placebo only for 6 months. There

was no assessment of radiographic damage in the study given its short time frame and no effort to assess other features of PsA such as enthesitis, dactylitis or axial involvement.

Some observational studies have suggested an effect with methotrexate in terms of peripheral joints(12) and also with enthesitis and dactylitis in small numbers(13, 14). Interestingly an updated assessment in the Toronto PsA database using a case control design found a significant response to methotrexate and a trend towards lower radiographic progression with patients receiving higher doses of methotrexate(15) which had not been seen in an earlier study in 1995 when doses were much lower(16).

The aim of this study was to investigate the effectiveness of methotrexate in early DMARD naïve PsA on different disease manifestations and to investigate whether differing dosages of methotrexate may impact outcome in a post-hoc analysis.

Methods

A total of 206 patients with early PsA were recruited into the Tight Control of Psoriatic Arthritis (TICOPA) trial (ISCRCTN30147736 and NCT01106079). Eligibility criteria were adults with recent onset (<24 months symptom duration) PsA naïve to disease modifying anti-rheumatic drugs (DMARDs). Full details of the trial protocol are published(17). In brief summary, patients were randomised to receive tight control (TC) (n=101) or standard care (StdC) (n=105). In the ITT patient population, the odds of achieving an ACR20 at 48 weeks were greater 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) at 48 weeks were also greater.

A greater improvement was observed for other outcomes including PASI, Bath ankylosing spondylitis disease activity index (BASDAI), Bath ankylosing spondylitis functional index (BASFI), PsA quality of life questionnaire (PsAQoL), ASAS 20/40 and health assessment questionnaire (HAQ) score in the TC arm.

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

Within this randomized controlled trial, patients could be treated with methotrexate. In the tight control arm, patients were treated according to an algorithm which mandated monotherapy methotrexate as the first DMARD unless contraindicated for at least the first 12 weeks. All patients in this arm were treated with rapidly escalating doses (15mg/week for 4 weeks, 20mg/week for 2 weeks and 25mg/week thereafter if tolerated). Patients in the standard care arm could be treated with methotrexate at the discretion of their treating physician but it was not a requirement.

A variety of clinical outcome measures were collected every 12 weeks, including ACR outcomes, minimal disease activity (MDA)(18), PASI(19), modified nail psoriasis severity index (mNAPSI)(20), enthesitis scores (Leeds Enthesitis Index (14), Impact and Maastricht ankylosing spondylitis enthesitis score(21) scores) and dactylitis measures (Leeds dactylitis instrument(13)). At this visit, all patients were assessed by a blinded assessor who did not know what therapy they were receiving. This analysis examines the 12 week outcomes as at that point, the majority of patients were on methotrexate monotherapy rather than in combination with other DMARDs. Although some patients continued on methotrexate monotherapy throughout the 48 week study period, these were, by definition, methotrexate responders and therefore analysis at later time points would introduce selection bias.

Response rates were compared using chi squared tests. Changes in joint counts and continuous measures were assessed using the Wilcoxon signed rank test or Mann-Whitney U test as appropriate. To assess the impact of higher doses of methotrexate, sub-analyses were performed on those receiving above 15mg/week doses. These analyses were not pre-specified in the trial protocol.

Results

Of the 206 patients enrolled in TICOPA, 188 received oral methotrexate in the first 12 weeks of the trial. Of these, 175 patients reached a dose of at least 15mg by 12 weeks, with 122 reaching a dose of at least 20mg and 86 reaching the top dose of 25mg. Only 5 patients received parenteral methotrexate and these were not included in the analysis as the number was so low. The baseline characteristics of the full trial population and the 188 patients who received methotrexate by week 12 are shown in table 1.

At 12 weeks, 40.8% (69/169 with no missing data) achieved an ACR20 outcome. Lower proportions of patients achieved the ACR50 and ACR70 outcomes (table 2). Considering individual joint counts, there was a significant reduction in tender and swollen joint counts by 12 weeks (table 1, $p<0.0005$). A significantly higher proportion of patients with polyarthritis (≥5 active joints) achieved ACR20 compared to those with oligoarthritis ($p=0.022$) but the difference was not significant for either ACR50 or ACR70. A total of 22.4% achieved minimal disease activity (MDA) at 12 weeks. Conversely the oligoarthritis patients were more likely to achieve MDA than those with polyarticular disease ($p=0.005$). Comparing the actual reduction in tender and swollen joint counts, a significantly better response was seen in polyarticular disease (median reduction TJC poly -3, oligo -1, SJC poly -4, oligo -1, $p<0.004$ for both) but comparing percentage reduction in tender and swollen joint counts found no significant difference between the groups.

Improvements were seen in the 158 patients with psoriasis with 27.2% reaching a PASI75. Nail involvement was present in 117 patients and showed a median change in mNAPSI score of -2 (IQ range -8, 0). The median change in the nail plate score was 0 (IQ range -3.75, 1) due to the short follow up time, with a median change of -1 (IQ range -4.75, 0) seen in the nail bed.

For those with baseline dactylitis (n=59), there was a significant reduction in LDIbasic scores ($p=0.033$) and by 12 weeks 37 of the 59 showed complete resolution (table 2). Only 9 new cases of dactylitis were identified in the patients without baseline involvement. There was a significant change in the proportion of patients with dactylitis from baseline to 12 weeks ($chi^2 = 22.3$, $p<0.001$).

For those with enthesitis at baseline (n=148) the median change in enthesitis score was 0 independent of which entheseal index was used (table 2). Of those with active enthesitis, 38 had full resolution of their symptoms at 12 weeks. Only 8 patients developed new enthesitis not identified at baseline. There was a significant change in the proportion of patients with enthesitis from baseline to 12 weeks ($chi^2 = 32.8$, $p<0.001$).

There was an improvement also seen in individual patient reported outcome measures including the patient VAS for pain, fatigue and global disease activity and the PsAQoL and HAQ score (table 1). In total, 69/188 (36.7%) achieved the MCID for HAQ (reduction of ≥0.35) at 12 weeks.

Using the psoriatic arthritis disease activity score (PASDAS)(22), the median score at baseline was 5.26 (IQR 3.98, 6.19) indicating active disease according to defined cut-offs(23). The score was higher in the polyarticular patients (median 5.52, IQR 4.38, 6.51) compared to the oligoarticular patients (median 3.98, IQR 3.47, 5.18). However the change in PASDAS score over the 12 weeks was similar in both groups (table 1). Using the PASDAS response criteria(23) found that 57.4% achieved a moderate or good response and 18.5% achieved a good response. The proportions of good and moderate responses were similar in polyarticular and oligoarticular patients (table 2). The proportions of patients reaching PASDAS low disease activity threshold (≤3.2) were higher in the oligoarticular patients (table 2) as they had a lower baseline value.

Over the 12 week period, 104 of the 188 patients received over 180mg cumulative dose of methotrexate, equivalent to an average of 15mg/week. There was no significant difference in the response rates seen in patients taking over 15mg/week of methotrexate for the ACR outcomes, MDA, PASI or PASDAS responses despite higher proportions of patients in the higher dose group achieving ACR20, 50, PASI 75 and PASDAS moderate response.

During the first 12 weeks, there were 233 adverse events reported among patients receiving methotrexate. Adverse events possibly related to methotrexate are listed in table 3. Of note, there

were 40 instances of nausea, 30 of raised liver function tests and 3 episodes of neutropenia but none of these met the criteria for a serious adverse event. The majority of AEs reported were classified as mild (157/233, 67.4%) with only 5 severe AEs (2.1%). Only 14 patients discontinued their methotrexate due to an AE, although in 77 patients the dose was modified or temporarily suspended (eg in the case of a current infection).

There were a total of four serious AEs (SAEs) reported in this cohort: one each of angina, migraine, PsA flare and kidney stones, which were all classified as serious because they led to a hospital admission. None were life-threatening.

By the end of the study at 48 weeks, 88 patients had received only methotrexate monotherapy for their PsA. In the tight control arm, where a target of MDA was required at each 4 week visit, 25 of 101 patients continued on methotrexate throughout the study.

Discussion

This analysis demonstrates an improvement in psoriatic peripheral joint disease, skin disease, enthesitis, dactylitis and nail disease seen over the course of a 12 week period when patients were treated with methotrexate. In addition to improvements in composite arthritis measures, there was a significant decrease in tender and swollen joint counts by 12 weeks. The majority of patients were treated with at least 15mg/week methotrexate with more than half receiving higher doses. There was a significant difference seen between response in polyarticular and oligoarticular patients but this was dependent on the measure used. A response measure such as ACR20 showed a greater benefit in polyarticular patients and a measure of disease state such as MDA showed a greater benefit in oligoarticular disease. The PASDAS again showed a greater proportion of oligoarticular patients achieving a low disease activity state but interestingly showed similar response rates for both oligoarticular and polyarticular patients. These findings suggest that the difference is due to the outcome measure rather than a true differential response to methotrexate. Improvements were

seen in PASI in keeping with known efficacy in psoriasis but there was also a suggestion of improvement in nail disease. Improvements were seen in the number of patients affected and the disease activity in dactylitis. Despite no change in the median enthesitis scores, the proportion of patients with active enthesitis decreased. In the tight control arm of the study, one quarter of patients remained on methotrexate throughout indicating that their disease was consistently well controlled.

The main limitation of these data is that the open label nature of the study. A high placebo response can be seen in PsA trials and so results of open label studies must be interpreted with caution(24). The ACR20 proportions are higher than seen in the MIPA study (40.8% vs 34% in MIPA) which could be explained by the open label design or could represent benefit seen with higher methotrexate doses.

There was some suggestion of better outcomes for those receiving above 15mg/week of methotrexate. This analysis is complex because there is a bias by intention introduced by the trial design. Patients doing well on low doses of methotrexate will continue at this dose, while those with active disease are more likely to have their dose increased leading to an underestimation of the dose effect. However despite this bias, there was some evidence supporting higher dose methotrexate.

Despite the design problems of the MIPA trial, it is highly unlikely that a further RCT of methotrexate in PsA will ever be conducted. Open label evidence must therefore be considered. Methotrexate remains a commonly prescribed drug in PsA and, whilst it will not be effective for all patients, it does have a role in the treatment of the articular manifestations of PsA. Methotrexate has the further advantage of working for the skin and it may have efficacy for other aspects of the disease, such as enthesitis and dactylitis. It is worth noting that the limitations of the clinical data are compounded by the lack of data on structural progression but it must be noted that this statement is also true for the other oral DMARDs, including the more recent drugs such as apremilast(25).

In conclusion, data from the TICOPA study have shown improvement in musculoskeletal manifestations, skin and nails in PsA. The results should be interpreted in the context of the open label design of the study, and placed alongside the other observational studies that support its use in this disease.

References

1. Sokoll KB, Helliwell PS. Comparison of Disability and Quality of Life in Rheumatoid and Psoriatic Arthritis. J Rheumatol. 2001;28(8):1842-6.
2. Gladman DD, Thavaneswaran A, Chandran V, Cook RJ. Do patients with psoriatic arthritis who present early fare better than those presenting later in the disease? Ann Rheum Dis. 2011 Dec;70(12):2152-4.
3. Tillett W, Jadon D, Shaddick G, Cavill C, Korendowych E, de Vries CS, et al. Smoking and delay to diagnosis are associated with poorer functional outcome in psoriatic arthritis. Ann Rheum Dis. [Research Support, Non-U.S. Gov't]. 2013 Aug;72(8):1358-61.
4. Haroon M, Gallagher P, Fitzgerald O. Diagnostic delay of more than 6 months contributes to poor radiographic and functional outcome in psoriatic arthritis. Ann Rheum Dis. 2014 Feb 27.
5. Theander E, Husmark T, Alenius GM, Larsson PT, Teleman A, Geijer M, et al. Early psoriatic arthritis: short symptom duration, male gender and preserved physical functioning at presentation predict favourable outcome at 5-year follow-up. Results from the Swedish Early Psoriatic Arthritis Register (SwePsA). Ann Rheum Dis. 2013 Jan 25.
6. Kvien TK, Heiberg, Lie E, Kaufmann C, Mikkelsen K, Nordvag BY, et al. A Norwegian DMARD register: prescriptions of DMARDs and biological agents to patients with inflammatory rheumatic diseases. Clinical and experimental rheumatology. 2005 Sep-Oct;23(5 Suppl 39):S188-94.
7. Helliwell PS, Taylor WJ, Group CS. Treatment of psoriatic arthritis and rheumatoid arthritis with disease modifying drugs -- comparison of drugs and adverse reactions. J Rheumatol. 2008 Mar;35(3):472-6.
8. Theander E, Husmark T, Alenius GM, Larsson PT, Teleman A, Geijer M, et al. Early psoriatic arthritis: short symptom duration, male gender and preserved physical functioning at presentation predict favourable outcome at 5-year follow-up. Results from the Swedish Early Psoriatic Arthritis Register (SwePsA). Ann Rheum Dis. 2014 Feb;73(2):407-13.
9. Black RL, O'Brien WM, Vanscott EJ, Auerbach R, Eisen AZ, Bunim JJ. Methotrexate Therapy in Psoriatic Arthritis; Double-Blind Study on 21 Patients. Jama. 1964 Sep 7;189:743-7.
10. Willkens RF, Williams HJ, Ward JR, Egger MJ, Reading JC, Clements PJ, et al. Randomized, double-blind, placebo controlled trial of low-dose pulse methotrexate in psoriatic arthritis. Arthritis Rheum. 1984 Apr;27(4):376-81.
11. Kingsley GH, Kowalczyk A, Taylor H, Ibrahim F, Packham JC, McHugh NJ, et al. A randomized placebo-controlled trial of MTX in PsA. Rheumatology (Oxford). 2012 Jun 21.
12. Heiberg MS, Kaufmann C, Rodevand E, Mikkelsen K, Koldingsnes W, Mowinckel P, et al. The comparative effectiveness of anti-TNF therapy and methotrexate in patients with psoriatic arthritis: 6 month results from a longitudinal, observational, multicentre study. Ann Rheum Dis. 2007 Aug;66(8):1038-42.
13. Healy PJ, Helliwell PS. Measuring dactylitis in clinical trials: which is the best instrument to use? J Rheumatol. 2007 Jun;34(6):1302-6.
14. Healy PJ, Helliwell PS. Measuring clinical enthesitis in psoriatic arthritis: assessment of existing measures and development of an instrument specific to psoriatic arthritis. Arthritis Rheum. 2008 May 15;59(5):686-91.
15. Chandran V, Schentag CT, Gladman DD. Reappraisal of the effectiveness of methotrexate in psoriatic arthritis: results from a longitudinal observational cohort. J Rheumatol. 2008 Mar;35(3):469-71.
16. Abu-Shakra M, Gladman DD, Thorne JC, Long J, Gough J, Farewell VT. Longterm methotrexate therapy in psoriatic arthritis: clinical and radiological outcome. J Rheumatol. 1995 Feb;22(2):241-5.
17. 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.

[Comparative Study Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2013;14:101.

18. Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. Ann Rheum Dis. 2010 Jan;69(1):48-53.
19. Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. Dermatologica. 1978;157(4):238-44.
20. Cassell SE, Bieber JD, Rich P, Tutuncu ZN, Lee SJ, Kalunian KC, et al. The modified Nail Psoriasis Severity Index: validation of an instrument to assess psoriatic nail involvement in patients with psoriatic arthritis. J Rheumatol. 2007 Jan;34(1):123-9.
21. Heuft-Dorenbosch L, Spoorenberg A, van Tubergen A, Landewe R, van ver Tempel H, Mielants H, et al. Assessment of enthesitis in ankylosing spondylitis. Ann Rheum Dis. 2003 Feb;62(2):127-32.
22. Helliwell PS, FitzGerald O, Fransen J, Gladman DD, Kreuger GG, Callis-Duffin K, et al. The development of candidate composite disease activity and responder indices for psoriatic arthritis (GRACE project). Ann Rheum Dis. 2013 Jun;72(6):986-91.
23. Helliwell PS, FitzGerald O, Fransen J. Composite disease activity and responder indices for psoriatic arthritis: a report from the GRAPPA 2013 meeting on development of cutoffs for both disease activity states and response. J Rheumatol. 2014 Jun;41(6):1212-7.
24. Jones G, Crotty M, Brooks P. Interventions for psoriatic arthritis. Cochrane database of systematic reviews (Online). 2000(3):CD000212.
25. Acosta Felquer ML, Coates LC, Soriano ER, Ranza R, Espinoza LR, Helliwell PS, et al. Drug therapies for peripheral joint disease in psoriatic arthritis: a systematic review. J Rheumatol. 2014 Nov;41(11):2277-85.