The Journal of Rheumatology 2024;51 Suppl 2:58–60
doi:10.3899/jrheum.2024-0317
First Release July 15 2024

The Journal of Rheumatology

Debate at the GRAPPA 2023 Annual Meeting: Should Methotrexate Be the First Systemic Therapy in Psoriatic Disease?

Arianna J. Zhang[1], Joseph F. Merola[2], and William Tillett[3]

ABSTRACT. Despite substantial evidence that methotrexate (MTX) has inferior efficacy, safety, and tolerability compared to newer systemic therapies, MTX remains one of the most commonly prescribed first-line systemic therapies for psoriatic arthritis worldwide and for psoriasis in some countries. At the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2023 annual meeting in Dublin, Ireland, Drs. William Tillett and Joseph Merola engaged in debate over whether MTX should be the first systemic therapy used in psoriatic disease (PsD). Each presented evidence-based arguments, incorporating multiple data sources, including clinical trials, in support for and against MTX's status as first-line systemic therapy for PsD. This article summarizes their debate for the broader PsD community.

Key Indexing Terms: GRAPPA, methotrexate, psoriasis, psoriatic arthritis

Introduction

Methotrexate (MTX) was first developed in 1958 and subsequently demonstrated efficacy in treating the clinical symptoms of both psoriasis (PsO) and psoriatic arthritis (PsA).[1] MTX quickly became popular among dermatologists and rheumatologists and was approved for the treatment of PsO in 1971 by the US Food and Drug Administration.[1]

In the first phase III randomized, double-blind, placebo-controlled trial comparing the safety and efficacy of MTX to a biologic agent as a treatment for PsO, the 2007 Safety and Efficacy of Adalimumab to Methotrexate and Placebo in Subjects With Moderate to Severe Chronic Plaque Psoriasis (CHAMPION) study demonstrated superior efficacy of adalimumab (ADA) compared to MTX and placebo using the 75% improvement from baseline Psoriasis Area and Severity Index (PASI75) score as an endpoint (79.6% vs 35.5% vs 18.9%, respectively).[2] Adverse events were similar across treatment groups, and researchers of the study concluded that ADA was superior to MTX. Several subsequent studies and clinical trials have also demonstrated superiority of newer systemic therapies over MTX. Therefore, some researchers have advocated for the transition from MTX to newer systemic therapies for the treatment of PsO.[3]

During the main session of the recent Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2023 annual meeting in Dublin, Ireland, 2 experts in psoriatic disease (PsD), Drs. William Tillett and Joseph Merola, were invited to debate whether MTX should be prescribed as first-line therapy for PsD. Herein, we provide a summary of their respective arguments to provide educational insight on the controversial role of MTX as first-line therapy.

Debate summary

MTX should be used as first-line systemic therapy. Dr. Tillett opened the debate with the following question: How can MTX, unlicensed for use in PsA, remain the first-line therapy when so many other systemic therapies are more effective?

- *Cost and efficacy.* It is widely accepted that MTX is not as effective as biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) at treating the key domains of PsD including arthritis, PsO, enthesitis, dactylitis, and axial disease. Although MTX failed to produce significant differences compared to placebo in the 2003 Methotrexate in Psoriatic

As part of the supplement series GRAPPA 2023, this report was reviewed internally and approved by the Guest Editors for integrity, accuracy, and consistency with scientific and ethical standards.

AJZ receives funding from an National Insitutes of Health (NIH) research training grant (T32; T32TR004418). This project was indirectly supported by the NIH National Center for Advancing Translational Sciences. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

[1]A.J. Zhang, BA, Department of Dermatology, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts, USA; [2]J.F. Merola, MD, MMSc, Department of Dermatology and Department of Medicine, Division of Rheumatology, UT Southwestern Medical Center, Dallas, Texas, USA; [3]W. Tillett, MBChB, PhD, Royal National Hospital for Rheumatic Diseases, Bath, UK.

JFM and WT contributed equally as co-senior authors.

JFM is a consultant and/or investigator for Amgen, AstraZeneca, Boehringer Inhelheim, BMS, AbbVie, Dermavant, Eli Lilly, Incyte, Novartis, Janssen, UCB, Sanofi-Regeneron, Sun Pharma, Biogen, Pfizer, and Leo Pharma. WT has received research grants or consulting or speaker fees from AbbVie, Amgen, BMS, Celgene, Eli Lilly, Janssen, Novartis, Ono, Pfizer, and UCB. AJZ declares no conflicts of interest relevant to this article.

This paper does not require institutional review board approval.

Address correspondence to Dr. W. Tillett, Royal National Hospital for Rheumatic Diseases, Combe Park, Bath BA1 3NG, UK. Email: cwrt20@bath.ac.uk.

Accepted for publication March 21, 2024.

Arthritis (MIPA) trial, MTX may have been underdosed in this study and recruitment was slow, threatening external validity of study conclusions in clinical settings.[4] Nevertheless, other studies have shown that many patients can achieve states of low disease activity with MTX alone. In the CHAMPION study comparing MTX with placebo and ADA in PsO, 35% of patients achieved PASI75 at week 16 compared to 18% in the placebo arm.[2] A subanalysis of 188 patients in the Tight Control of Psoriatic Arthritis (TICOPA) treatment strategy trial treated with MTX found that 22.5% achieved minimal disease activity (MDA), 27% achieved PASI75, and significant improvements were seen in enthesitis, dactylitis, and nail disease. In the Study of Etanercept and Methotrexate in Subjects with Psoriatic Arthritis (SEAM-PsA) trial, which compared MTX monotherapy to etanercept (ETN) monotherapy and ETN plus MTX, 22.9% of participants in the MTX monotherapy arm achieved MDA by week 24 (compared to 35.7% in the ETN arm), rising to 36% by week 48.[5,6] The findings of the SEAM-PsA study are consistent with rates of MDA attainment in many b/tsDMARD clinical trials, with typical MDA attainment rates of between 20% and 40%. Additionally, the Comparing Methotrexate Monotherapy With Methotrexate Plus Leflunomide Combination Therapy in PsA (COMPLETE-PsA) trial found that 59% of patients achieved MDA by week 16 when taking MTX in addition to leflunomide, suggesting that even when used first-line, MTX could be combined with other therapies to achieve improved efficacy.[7] Dr. Tillett went on to argue that the low cost of MTX (£0.15 per 2.5 mg tablet in the United Kingdom),[8] considered with its modest efficacy, meant that MTX was the logical choice as first-line systemic therapy. MTX remains the least expensive conventional synthetic DMARD (csDMARD) and is several orders of magnitude cheaper than b/tsDMARDs.

• *MTX safety and tolerability.* With regard to safety and tolerability, Dr. Tillet argued that MTX has a well-established safety profile and is generally well tolerated by most patients; potential side effects can be managed effectively with monitoring. The percentage of participants taking MTX monotherapy who experienced an adverse event in the SEAM-PsA trial was 75% for MTX monotherapy vs 67% for ETN monotherapy. Nausea, a common side effect with MTX, was noted in 13% of participants on MTX monotherapy, meaning that a majority (87%) did not experience this side effect.[6]

• *MTX positioning in treatment recommendations.* Finally, Dr. Tillett reviewed the positioning of MTX in the European Alliance of Associations for Rheumatology (EULAR) and GRAPPA treatment recommendations. EULAR recommend MTX as the preferred csDMARD for those with polyarthritis and relevant skin involvement.[9] In the GRAPPA treatment recommendations, MTX is strongly recommended for the treatment of PsO and peripheral arthritis, conditionally recommended for enthesitis and dactylitis, and can be considered in nail disease. Further, MTX was conditionally recommended in the setting of concurrent inflammatory bowel disease or uveitis.

In summary, Dr. Tillett contested that the effectiveness of MTX in PsD was better than its reputation deserved. Because of the convenience of oral weekly dosing and the favorable cost-benefit ratio, he argued that it should remain as the first-line systemic in most cases of PsD.

MTX should not be used as first-line systemic therapy. Dr. Merola presented the argument that MTX should not be used as the first-line systemic therapy in PsD. In his opening statement, he likened MTX to a blunt, primitive weapon compared to the newer targeted b/tsDMARDs that selectively affect key pathways in PsD pathogenesis and often address associated comorbidities as well. Dr. Merola asked, "Why then, are we not upgrading our first-line therapy from MTX to something we know is not only much more effective, but also safer and far better-tolerated?"

• *Limited evidence of MTX efficacy.* To start, Dr. Merola underscored that there is weak evidence of MTX's efficacy in joints compared to newer targeted therapies. In the MIPA trial, which did not meet its primary endpoint, MTX failed to show significant effects on Psoriatic Arthritis Response Criteria (PsARC), 20% improvement from baseline American College of Rheumatology Criteria (ACR20), Disease Activity Score in 28 joints (DAS-28), synovitis, C-reactive protein, and pain; only improvements in patient and provider global assessment instruments were found.[4] Although some have argued that MTX was underdosed at 15 mg/week in the MIPA trial, the Comparison Between Adalimumab Introduction and Methotrexate Dose Escalation in Patients With Inadequately Controlled PsA (CONTROL) trial demonstrated that dose escalation had marginal benefit compared to the addition of ADA in patients who had failed MTX 15 mg (13% vs 41% achieving MDA at 16 weeks).[10] Further, there appears to be no convincing evidence that MTX inhibits radiographic progression of PsA, unlike several other b/tsDMARDs.[11] With regard to including MTX in combination therapy, Dr. Merola countered that data were mixed; MTX and tumor necrosis factor inhibitor (TNFi) therapy showed modest, if any, benefit over TNFi therapy alone in the Norwegian Disease-Modifying Antirheumatic Drugs Register (NOR-DMARD) study, and no benefit to the addition of MTX to interleukin (IL)-17 inhibitor and other newer targeted therapies in the SPIRIT-H2H and SEAM-PsA trials.[12,13] Finally, with regard to efficacy in skin, MTX pales in comparison to numerous other therapies. Review of literature revealed that the number needed to treat to achieve PASI90 was 43.5 for MTX compared to 1.4 to 4.8 for newer targeted therapies targeting IL-17, IL-12/23, and TNF.[3,14]

• *Safety and tolerability.* A cornerstone of the argument against MTX as first-line therapy are issues of MTX tolerability and safety. Dr. Merola emphasized that tolerability affects treatment adherence, citing a study that found patients were 3 times more likely to have nausea compared to placebo, and one-third of patients eventually stopped taking MTX due to gastrointestinal intolerability.[15] Poor tolerability leads to poor adherence and worse disease control with poorer outcomes. Additionally, 27% of patients with PsO taking MTX developed liver enzyme abnormalities, which may be especially alarming given evidence suggesting that PsD is itself an independent risk factor for liver

disease.[15] Finally, MTX has been associated with increased risk of lung and bone marrow complications that threaten patient safety, resulting in the need for routine monitoring, which may be inconvenient for patients.

• *MTX positioning in treatment guidelines.* In alignment with the evidence shared, Dr. Merola pointed out that the ACR/National Psoriasis Foundation (NPF) guidelines for the management of active PsA recommended starting a TNFi over oral small-molecule therapy, including MTX. According to GRAPPA guidelines, MTX efficacy is limited in several key domains of PsD, including axial, enthesial, skin, and nail disease. Finally, Dr. Merola presented data from polling at the GRAPPA 2019 annual meeting, in which 69% of respondents said they would use a TNFi as first-line therapy for PsA if cost was no object. When asked what treatment was preferred as first line for moderate-to-severe plaque PsO, only 14% voted for MTX compared to 30% and 43% for an IL-23 inhibitor or IL-17 inhibitor, respectively.

In summary, Dr. Merola argued that MTX should not be used as first-line systemic therapy for PsD due to weak evidence of effectiveness in joints, inferior effectiveness in skin compared to newer therapies, and an unfavorable safety and tolerability profile. He posited that continuing to use MTX as a first-line therapy may delay delivery of more targeted therapies that are more effective, safe, and tolerable.

Discussion

The role of MTX as first-line systemic therapy for treatment of PsD remains controversial. Despite substantial evidence that MTX has inferior efficacy and tolerability compared to newer systemic therapies, it remains the most commonly prescribed first-line systemic therapy.[3] Further, many healthcare settings require trial of MTX prior to allowing access to biologics and other systemic therapies.

MTX is a relatively safe, somewhat effective, and very affordable option for many patients with PsO. Although newer b/tsDMARDs have demonstrated superior efficacy compared to MTX, it is likely that cost and availability considerations contribute to MTX's continued widespread use, at least in PsA. Meanwhile, substantial evidence suggests that MTX has a relatively unfavorable efficacy, safety, and tolerability profile compared to newer therapies. Although it is likely that MTX will continue to be a prominent treatment for PsD, there is substantial evidence to suggest that its role as first-line therapy should be carefully considered by relevant stakeholders.

ACKNOWLEDGMENT

We thank DerMEDit (www.dermedit.com) for editing services in preparation of this manuscript.

REFERENCES

1. Luber A, Lee D. History of methotrexate and use in psoriasis. Psoriasis Forum 2012;18a:164-73.
2. Saurat JH, Stingl G, Dubertret L, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br J Dermatol 2008;158:558-66.
3. Coates LC, Merola JF, Grieb SM, Mease PJ, Callis Duffin K. Methotrexate in psoriasis and psoriatic arthritis. J Rheumatol Suppl 2020;96:31-5.
4. Kingsley GH, Kowalczyk A, Taylor H, et al. A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. Rheumatology 2012;51:1368-77.
5. Merola JF, Ogdie A. SEAM-PsA: seems like methotrexate works in psoriatic arthritis? Arthritis Rheumatol 2019;71:1027-9.
6. Mease PJ, Gladman DD, Collier DH, et al. Etanercept and methotrexate as monotherapy or in combination for psoriatic arthritis: primary results from a randomized, controlled Phase III trial. Arthritis Rheumatol 2019;71:1112-24.
7. Mulder MLM, Vriezekolk JE, van Hal TW, et al. Comparing methotrexate monotherapy with methotrexate plus leflunomide combination therapy in psoriatic arthritis (COMPLETE-PsA): a double-blind, placebo-controlled, randomised, trial. Lancet Rheumatol 2022;4:e252-61.
8. NHS Electronic Drug Tariff. Part VIIIA – Basic prices of drugs. [Internet. Accessed April 8, 2024.] Available from: www.drugtariff.nhsbsa.nhs.uk/#/00553921-DA/DA00553911/Part%20VIIIA%20-%20Basic%20Prices%20of%20Drugs
9. Gossec L, Baraliakos X, Kerschbaumer A, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. Ann Rheum Dis 2020;79:700-12.
10. Coates LC, Tillett W, D'Agostino MA, et al. Comparison between adalimumab introduction and methotrexate dose escalation in patients with inadequately controlled psoriatic arthritis (CONTROL): a randomised, open-label, two-part, phase 4 study. Lancet Rheumatol 2022;4:e262-73.
11. Felten R, Lambert De Cursay G, Lespessailles E. Is there still a place for methotrexate in severe psoriatic arthritis? Ther Adv Musculoskelet Dis 2022;14:1759720X221092376.
12. Fagerli KM, Lie E, van der Heijde D, et al. The role of methotrexate co-medication in TNF-inhibitor treatment in patients with psoriatic arthritis: results from 440 patients included in the NOR-DMARD study. Ann Rheum Dis 2014;73:132-7.
13. Smolen JS, Sebba A, Ruderman EM, et al. Efficacy and safety of ixekizumab with or without methotrexate in biologic-naïve patients with psoriatic arthritis: 52-week results from SPIRIT-H2H study. Rheumatol Ther 2020;7:1021-35.
14. Leonardi CL, See K, Burge R, et al. Number needed to treat network meta-analysis to compare biologic drugs for moderate-to-severe psoriasis. Adv Ther 2022;39:2256-69.
15. Nikiphorou E, Negoescu A, Fitzpatrick JD, et al. Indispensable or intolerable? Methotrexate in patients with rheumatoid and psoriatic arthritis: a retrospective review of discontinuation rates from a large UK cohort. Clin Rheumatol 2014;33:609-14.