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SEAM-PsA: Seems like methotrexate works in Psoriatic Arthritis?

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In this issue of *Arthritis and Rheumatology*, Mease and colleagues report the results of an important trial, 'SEAM-PsA', evaluating the efficacy of methotrexate monotherapy, etanercept monotherapy, or methotrexate/etanercept in combination, in early psoriatic arthritis (PsA).⁽¹⁾ The primary endpoint in this study was the American College of Rheumatology 20% Response Criteria (ACR20) and minimal disease activity (MDA) was a key secondary/co-primary endpoint. MDA requires achievement of five of seven points of low disease activity including swollen and tender joint counts, psoriasis, enthesitis, patient global assessment, patient pain assessment and the health assessment questionnaire. Among patients in the etanercept monotherapy arm, 61% achieved ACR20 and 36% achieved MDA. This was very similar to the combination therapy arm (65% and 36% respectively). Both etanercept monotherapy and etanercept+methotrexate combination therapy were significantly more efficacious than the methotrexate monotherapy arm (ACR20 51% and MDA 23%).

The SEAM-PsA trial brings to the forefront several important concepts that remind us of where we are in the management of PsA in 2019. This trial represents many "firsts" in PsA: the first appropriately-powered randomized double blind trial to test a head-to-head comparison of therapies (although more head-to-head trials are in progress); the first large RCT not to include a placebo arm; the first study to include MDA as a key secondary (co-primary) outcome and one of the first trials to examine the management of early PsA and initial treatment selection. SEAM-PsA represents one of a few handful of trials to infer methotrexate monotherapy does indeed have benefit in the treatment-naïve patient with PsA, although without a placebo control this is not possible to confirm definitively.

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Methotrexate in PsA: a mixed history

While the benefits of methotrexate alone and in combination with tumor necrosis factor inhibitor (TNFi) therapy have been clearly demonstrated in RA,(2, 3) the same cannot be said for PsA.(4) Studies of methotrexate monotherapy in PsA have been largely underwhelming(5–7) or at least mixed(8–11).

The Methotrexate in Psoriatic Arthritis ('MIPA') study, a key placebo-controlled trial of methotrexate published in 2012, found no significant advantage of methotrexate over placebo in ACR20.(5) On the other hand, the TIGHT CONTROL in PsA (TICOPA) study in the United Kingdom, a treat to target study which used methotrexate as a backbone therapy (at higher doses than in MIPA), found benefits with oral DMARDs frequently used in combination to achieve ACR20 responses.(10, 12). In the open label RESPOND trial which compared infliximab plus methotrexate to methotrexate monotherapy, an ACR20 response was achieved in 66.7% of patients in the methotrexate arm, but the combination therapy arm was significantly more effective than monotherapy.(8)

Aside from the (3) trials mentioned above, support for methotrexate in PsA has mainly been drawn from observational data including one study demonstrating similar persistence on methotrexate among patients with RA and PsA in Norway(11) and another demonstrating that initiation of methotrexate resulted in an ACR20 response in 41% of patients with active PsA in clinical practice.(13) In fact, the relative lack of efficacy of methotrexate in RCTs led to the ACR/National Psoriasis Foundation (NPF) PsA Treatment Guidelines deviating from prior treatment recommendations to conditionally recommend the use of a TNFi biologic *over methotrexate* or other oral small molecules in the patient with active treatment naïve PsA.(14)

SEAMs like methotrexate works? Etanercept as active comparator

Taken even at face value, a methotrexate monotherapy arm ACR20 response rate of 50.7% should bring some enthusiasm. Etanercept may serve as a very useful "active comparator" in informing our understanding of methotrexate efficacy in this study. Given the breadth of studies to date for which we have efficacy data on etanercept in PsA, etanercept efficacy here mirrored that seen in the previous pivotal phase 3 trial, among others.(15) With that anchor, the methotrexate monotherapy in SEAM-PSA did relatively well: ACR20 50.7%, MDA 22.9%, enthesitis resolution in 43.1% and psoriasis was clear or almost clear in 66.3% at 24 weeks. Even with a potentially high placebo rate (placebo rates are presumed to be higher in trials enrolling treatment naïve patients who know they will receive a treatment), these values might suggest that we not close the door on the clinical story around methotrexate in the treatment of psoriatic disease. Again, however, it is unfortunately impossible for us to tell with certainty the effect of MTX monotherapy without a placebo arm in SEAM-PSA.

What was different in this study compared to prior methotrexate studies?

What was different in previous studies, in particular the MIPA trial, has been the under-dosing of methotrexate and under-powering of a study for the expected response.(16) In

SEAM-PsA, the median oral methotrexate dose was 20mg, a dose considered appropriate by most experts, whereas MIPA target dose was 15mg weekly with as many as 11% on lower doses.

The future of methotrexate in PsA?

Even though methotrexate *seems* to have ‘worked’ in SEAM-PsA, only 50% of patients starting methotrexate improved by 20%, (ACR20) and only 30% improved by 50% (ACR50) at 24 weeks (compared to 61% and 44% for patients initiating etanercept). These results were produced within the ideal setting of a typical phase III trial in which adherence to therapy is generally higher than what we expect in the ‘real world.’ It is safe to say *we still have a long way to go* in achieving better outcomes. Furthermore, at 48 weeks, there is suggestion of more radiographic progression among those treated with methotrexate (although few patients progressed in either arm). Thus, there is still limited evidence for methotrexate halting radiographic progression in PsA; this requires further exploration.

Additionally, the results of SEAM-PsA suggest that, unlike combination therapy in RA, there was no meaningful benefit to combination therapy in PsA. That being said, SEAM-PsA does not test the potential benefit of combination therapy in prolonging persistence of etanercept or effect on etanercept blood levels and cannot be necessarily extrapolated to other TNFi mechanisms given etanercept’s unique structure as a fusion protein.(17–19)

With regard to patient satisfaction, more limited tolerability was seen with methotrexate including nausea and vomiting, and from clinical experience, we believe more fatigue would likely have been reported if it had been measured. There was otherwise no appreciable difference in infection risk or other major adverse events between etanercept and methotrexate. A further consideration is that of methotrexate safety in the long term among a patient population with a known high prevalence of obesity, fatty liver disease and metabolic co-morbidities. (20–22) In the era of multiple effective target therapies for PsA, these factors should be weighed in the patient-physician discussion of appropriate treatment options.

Still a lot to learn...

The SEAM-PsA trial will continue to contribute to our knowledge of PsA management over the coming months and years as important sub-analyses are performed. This trial of over 800 patients is an ideal dataset in which to address many questions including predictors or biomarkers of treatment response among methotrexate and TNFi users, and how to design comparative efficacy and/or effectiveness trials. For example, the ACR20 is the primary outcome used in all PsA regulatory trials but fails to capture important elements in PsA, including enthesitis, axial disease and skin psoriasis. The gap between ACR response criteria and MDA in this study underscores the difference in measured domains of disease in a psoriatic disease trial. Subsequent analyses in this trial will help us understand whether one of the alternative outcome measures may in fact be a better primary outcome measure for future comparative efficacy trials.

SEAM-PsA greatly underscores the need for more head-to-head trials in PsA to inform treatment guidelines, comparative effectiveness, and cost research. Of equal importance are

more comparative effectiveness studies in the ‘real world’ to appropriately inform clinical practice.(23, 24) SEAM-PsA enrolled patients typical of trial patients but that represent less than half of our patients in clinical practice.(25) This trial was mainly composed of patients with a polyarticular phenotype (with an average of 12 swollen joints and 20 tender joints). In contrast, pragmatic trials enroll patients representative of those seen in clinical practice - approximately half of which would have an oligoarticular phenotype.(25) Such trials are needed to inform the treatment of ‘real-world’ patients, including phenotypic subsets of disease that may not be captured in traditional trials or by traditional outcome measures extrapolated from RA such as the ACR response criteria. We still have very little data to inform how to treat the patients with PsA that we see in our day to day practices.

In summary, SEAM-PsA represents an important piece of the puzzle in our larger understanding of treatment approaches to PsA. We learned that combination therapy offers little benefit over etanercept monotherapy and gained important, albeit inferred and without placebo control, insights into the efficacy of methotrexate monotherapy. These data should invigorate the community to take a deeper look into methotrexate efficacy, effectiveness and safety/tolerability in our patients with psoriatic disease; such data are certain to inform future treatment guidelines. We hope that this is a turning point in trial design and drives the initiative for more head-to-head trials, pragmatic trials and other novel clinical trial designs in PsA. It is from these direct comparisons that we actually learn how to treat our patients.

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References

1. Mease PG D.D.; Collier DH; Ritchlin CT; Helliwell PS; Liu L; Kricorian G; Chung JB:. Etanercept and Methotrexate as Monotherapy or in Combination for Psoriatic Arthritis: Primary Results From a Randomized, Controlled Phase 3 Trial. *Arthritis Rheumatol* 2019;In Press.
2. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalten J, Malaise M, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* (London, England). 2004;363(9410):675–81. [PubMed: 15001324]
3. van der Heijde D, Klareskog L, Rodriguez-Valverde V, Codreanu C, Bolosiu H, Melo-Gomes J, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis and rheumatism* 2006;54(4):1063–74. [PubMed: 16572441]
4. Rajitha P, Biswas R, Sabitha M, Jayakumar R. Methotrexate in the Treatment of Psoriasis and Rheumatoid Arthritis: Mechanistic Insights, Current Issues and Novel Delivery Approaches. *Current pharmaceutical design* 2017;23(24):3550–66. [PubMed: 28571554]
5. Kingsley GH, Kowalczyk A, Taylor H, Ibrahim F, Packham JC, McHugh NJ, et al. A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. *Rheumatology* (Oxford, England) 2012;51(8):1368–77.
6. 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 and rheumatism* 1984;27(4):376–81. [PubMed: 6712754]
7. 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;189:743–7. [PubMed: 14174051]

8. Baranaukaite A, Raffayova H, Kungurov NV, Kubanova A, Venalis A, Helmle L, et al. Infliximab plus methotrexate is superior to methotrexate alone in the treatment of psoriatic arthritis in methotrexate-naïve patients: the RESPOND study. *Annals of the rheumatic diseases* 2012;71(4): 541–8. [PubMed: 21994233]
9. Chandran V, Schentag CT, Gladman DD. Reappraisal of the effectiveness of methotrexate in psoriatic arthritis: results from a longitudinal observational cohort. *The Journal of rheumatology* 2008;35(3):469–71. [PubMed: 18085735]
10. Coates LC, Helliwell PS. Methotrexate Efficacy in the Tight Control in Psoriatic Arthritis Study. *The Journal of rheumatology* 2016;43(2):356–61. [PubMed: 26669913]
11. Lie E, van der Heijde D, Uhlig T, Heiberg MS, Koldingsnes W, Rodevand E, et al. Effectiveness and retention rates of methotrexate in psoriatic arthritis in comparison with methotrexate-treated patients with rheumatoid arthritis. *Annals of the rheumatic diseases* 2010;69(4):671–6. [PubMed: 19740904]
12. Coates LC, Moverley AR, McParland L, Brown S, Navarro-Coy N, O'Dwyer JL, et al. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. *Lancet (London, England)* 2015;386(10012):2489–98.
13. Cantini F, Niccoli L, Nannini C, Cassara E, Pasquetti P, Olivieri I, et al. Frequency and duration of clinical remission in patients with peripheral psoriatic arthritis requiring second-line drugs. *Rheumatology (Oxford, England)* 2008;47(6):872–6.
14. Singh JA, Guyatt G, Ogdie A, Gladman DD, Deal C, Deodhar A, et al. Special Article: 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. *Arthritis & rheumatology (Hoboken, NJ)* 2019;71(1):5–32.
15. Combe B, Behrens F, McHugh N, Brock F, Kerkmann U, Kola B, et al. Comparison of Etanercept Monotherapy and Combination Therapy with Methotrexate in Psoriatic Arthritis: Results from 2 Clinical Trials. *The Journal of rheumatology* 2016;43(6):1063–7. [PubMed: 27134249]
16. Mease PJ. Spondyloarthritis: Is methotrexate effective in psoriatic arthritis? *Nature Reviews Rheumatology* 2012;8(5):251–2.
17. Fagerli KM, Lie E, van der Heijde D, Heiberg MS, Lexberg AS, Rodevand E, 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. *Annals of the rheumatic diseases* 2014;73(1):132–7. [PubMed: 23291385]
18. Goss SL, Klein CE, Jin Z, Locke CS, Rodila RC, Kupper H, et al. Methotrexate Dose in Patients With Early Rheumatoid Arthritis Impacts Methotrexate Polyglutamate Pharmacokinetics, Adalimumab Pharmacokinetics, and Efficacy: Pharmacokinetic and Exposure-response Analysis of the CONCERTO Trial. *Clinical therapeutics* 2018;40(2):309–19. [PubMed: 29402521]
19. Mantravadi S, Ogdie A, Kraft WK. Tumor necrosis factor inhibitors in psoriatic arthritis. *Expert review of clinical pharmacology* 2017;10(8):899–910. [PubMed: 28490202]
20. Dubreuil M, Rho YH, Man A, Zhu Y, Zhang Y, Love TJ, et al. Diabetes incidence in psoriatic arthritis, psoriasis and rheumatoid arthritis: a UK population-based cohort study. *Rheumatology (Oxford, England)* 2014;53(2):346–52.
21. Ogdie A, Grewal SK, Noe MH, Shin DB, Takeshita J, Chiesa Fuxench ZC, et al. Risk of Incident Liver Disease in Patients with Psoriasis, Psoriatic Arthritis, and Rheumatoid Arthritis: A Population-Based Study. *The Journal of investigative dermatology* 2018;138(4):760–7. [PubMed: 29104161]
22. Ogdie A, Schwartzman S, Husni ME. Recognizing and managing comorbidities in psoriatic arthritis. *Current opinion in rheumatology* 2015;27(2):118–26. [PubMed: 25603040]
23. Ogdie A, Coates L. The Changing Face of Clinical Trials in Psoriatic Arthritis. *Curr Rheumatol Rep* 2017;19(4):21. [PubMed: 28365920]
24. Ford I, Norrie J. Pragmatic Trials. *The New England journal of medicine* 2016;375(5):454–63. [PubMed: 27518663]
25. Ogdie AP, Greenberg J, Curtis JR, Harrold LR, Solomon DH, Kavanaugh A, Kremer JM, Mease P. Predictors of achieving remission among patients with psoriatic arthritis initiating a TNF inhibitor. *J Rheumatol* 2019;In Press.