ARD Online First, published on May 24, 2016 as 10.1136/annrheumdis-2016-209791

Why methotrexate suboptimal dosing is a potential source of bias in biologic drugs clinical trials

We appreciate the editorial Dr Kremer[1] wrote regarding our article[2] and we want to clarify some of the issues he raises.

Dr Kremer states that there is no evidence of benefit from increasing the methotrexate dose from 20 to 25 mg 'given the appropriate parenteral route of administration'. What he states is accurate; it is a bit misleading, as evidence does exist of the benefit of switching from oral to subcutaneous methotrexate, which was a focus of our paper. In a crossover trial by Schiff *et al*[3] that we cite in our article, subjects achieved a higher effective therapeutic level with no increase in adverse events when switching from oral to subcutaneous methotrexate. It is precisely the lack of use of parenteral methotrexate, which we believe is the most important potential source of bias, and this is stated in our discussion. He questions the adverse event profile of methotrexate in a dose >20 mg, but in a comparative effectiveness trial in early rheumatoid arthritis published in 2015 by Hazlewood *et al*,[4] only 3 out of 112 subjects who received parenteral methotrexate in a dose >20 mg failed treatment due to toxicity. In his editorial, Dr Kremer cites a study associating genetic polymorphisms with toxicity, which actually found that 'In the overall population, the prevalence of adverse events among patients taking 25 mg/week MTX was not significantly different from that among patients taking 15 mg/week study'.[5] In addition, he argues that the methotrexate consensus paper that recommends a higher methotrexate dose cited in our discussion was based on expert opinion, but the recommendations made in this paper considered a literature review that included a randomised controlled trial comparing oral versus subcutaneous methotrexate that showed the superiority of the latter and also studies comparing different dosing regimens of methotrexate, one of which compared 15 vs 25 mg of methotrexate as a starting dose and found no difference in withdrawals and dose reductions between groups.[6] In addition to the two randomised controlled trials which showed a greater efficacy with subcutaneous methotrexate,[7 8] multiple observational studies have reinforced this evidence.[9 10] We acknowledge that the use of methotrexate in its recommended dose is not widespread, at least in the USA, but this does not justify the suboptimal dosing of methotrexate when used as a comparator in trials.

Finally, our study is not meant to be applicable to Asians, as they use methotrexate in much lower doses (<15 mg/week).

Josefina Durán,[1] David T Felson[2,3]

[1]Department of Rheumatology, Pontificia Universidad Catolica de Chile, Santiago, Region Metropolitana, Chile

[2]Clinical Epidemiology Unit, School of Medicine, Boston University, Boston, Massachusetts, USA

[3]Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Institute of Inflammation and Repair, University of Manchester, Manchester, UK

Correspondence to Dr Josefina Durán, Department of Rheumatology, Pontificia Universidad Catolica de Chile, Santiago, Region Metropolitana, Chile; jgduran@uc.cl

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

To cite Durán J, Felson DT. *Ann Rheum Dis* Published Online First: [*please include* Day Month Year] doi:10.1136/annrheumdis-2016-209791

Received 26 April 2016
Accepted 29 April 2016

Linked

- http://dx.doi.org/10.1136/annrheumdis-2016-209505
- http://dx.doi.org/10.1136/annrheumdis-2016-209383

Ann Rheum Dis 2016;**0**:1. doi:10.1136/annrheumdis-2016-209791

REFERENCES

1 Kremer JM. Bias? Not so fast. *Ann Rheum Dis* 2016; Published Online First 20 Apr 2016. doi:10.1136/annrheumdis-2016-209505
2 Durán J, Bockorny M, Dalal D, *et al*. Methotrexate dosage as a source of bias in biological trials in rheumatoid arthritis: a systematic review. *Ann Rheum Dis* 2016; Published Online First 18 Apr 2016. doi: 10.1136/annrheumdis-2016-209383
3 Schiff MH, Jaffe JS, Freundlich B. Head-to-head, randomised, crossover study of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis: drug-exposure limitations of oral methotrexate at doses ≥15 mg may be overcome with subcutaneous administration. *Ann Rheum Dis* 2014;73:1549–51.
4 Hazlewood GS, Thorne JC, Pope JE, *et al*. The comparative effectiveness of oral versus subcutaneous methotrexate for the treatment of early rheumatoid arthritis. *Ann Rheum Dis* 2016;75:1003–8.
5 Wessels JA, de Vries-Bouwstra JK, Heijmans BT, *et al*. Efficacy and toxicity of methotrexate in early rheumatoid arthritis are associated with single-nucleotide polymorphisms in genes coding for folate pathway enzymes. *Arthritis Rheum* 2006;54:1087–95.
6 Visser K, Katchamart W, Loza E, *et al*. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. *Ann Rheum Dis* 2009;68:1086–93.
7 Braun J, Kästner P, Flaxenberg P, *et al*. Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. *Arthritis Rheum* 2008;58:73–81.
8 Islam MS, Haq SA, Islam MN, *et al*. Comparative efficacy of subcutaneous versus oral methotrexate in active rheumatoid arthritis. *Mymensingh Med J* 2013;22:483–8.
9 Müller RB, von Kempis J, Haile SR, *et al*. Effectiveness, tolerability, and safety of subcutaneous methotrexate in early rheumatoid arthritis: a retrospective analysis of real-world data from the St. Gallen cohort. *Semin Arthritis Rheum* 2015;45:28–34.
10 Gunn J, Panopolou A, Steuer A. Efficacy and tolerability of subcutaneous methotrexate for inflammatory arthritis: a retrospective observational cohort study [abstract]. *Arthritis Rheum* 2014;66:S1079.

Ann Rheum Dis: first published as 10.1136/annrheumdis-2016-209791 on 24 May 2016. Downloaded from http://ard.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Copyright Article author (or their employer) 2016. Produced by BMJ Publishing Group Ltd (& EULAR) under licence.