Response to: 'Metering the METEOR in methotrexate failure: is propensity score a falling star?' by Ahmed *et al*

We thank Dr Ahmed for his response to our article and for his interest in the methodology we used.¹ The aim of our study was twofold: to compare, in daily practice, treatment options after failure of initial methotrexate (MTX) in rheumatoid arthritis (RA) patients, but also to introduce the multiple propensity score (PS) in rheumatology.

As Dr Ahmed mentioned, previous research has been performed into treatment options after MTX failure, including the mentioned network meta-analysis based on clinical trials.² These trials mostly included a selected population and reported response to one or at most two treatment options, either including a biologic disease modifying anti-rheumatic drug (bDMARD) or conventional synthetic (cs) DMARD triple therapy. But in daily practice, there are many scenarios in which rheumatologists consider multiple treatment options aimed to specifically benefit their individual patient, rather than following predefined study protocols. In our large, international daily practice database, we were able to compare three treatment strategies simultaneously, including a combination of csDMARD(s) with glucocorticoids. This is a therapy that has never been compared with triple therapy in clinical trials, but as shown by our data it was the therapy that was most frequently prescribed after MTX failure in daily practice.³

Next, Dr Ahmed asked for the proportion of patients that fulfil the American College of Rheumatology response criteria, which we cannot provide as it is not used in daily practice to monitor individuals' response to treatment and therefore not included in the Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology (METEOR) database. In addition, Dr Ahmed¹ is interested in the 24-month results of our data. Although undoubtedly long-term outcomes are of interest in a potentially chronic disease as RA, we were specifically interested in the short-term effectiveness of the treatment strategy after MTX failure. With longer follow-up, many patients who do not respond to treatment will have switched to a next treatment step according to a treat-to-target approach. When analysing longer term results, we would not be able to discern the effects of the second treatment strategy, but rather evaluate the treat-to-target concept. Previous studies have shown that long-term outcomes can be greatly improved if a consequent treat-to-target approach aimed at remission or at least low disease activity is maintained.⁴⁻⁶ These long-term benefits make it possible to return to the acute symptoms of having active RA and the intention to suppress disease activity as quickly as possible, hence our focus on short-term outcomes of treatment choices.

Only data regarding treatment effectiveness will not allow us to draw definitive conclusions on the best treatment step after initial MTX failure in daily practice. For this decision, also other factors such as adverse events and cost-effectiveness should be considered. We do not agree that the dose of methotrexate (within a certain range) has a significant impact on short-term outcomes, as in our previous studies in the same database such an association was not found, neither for MTX in combination therapies nor for MTX monotherapy.^{7,8}

Next to the clinical research question, multiple PS played an important role in our study. From the onset of this study, we have been careful to consider bias. We have acknowledged that there was a large risk of confounding by indication and that the

multiple PS would be an appropriate method to handle this bias. Indeed, several of the included baseline variables were unbalanced at baseline. However, it is impossible to determine the eventual influence of the multiple PS on the effect estimates beforehand, and the relatively small differences between crude and adjusted analyses should not be a reason to not include the multiple PS afterwards. We have shown both crude and adjusted analyses, such that the reader can judge both.

Using the multiple PS enabled us to compare three treatment groups simultaneously, which was not done in previous studies, but more in line with relevant scenarios in daily practice. A multiple PS reflects to some extent the prescriber's perspective on a patient's disease severity and prognosis.⁹ As in all methods used to adjust for bias in observational research, unknown or unmeasured factors that influence treatment decisions (cultural, socioeconomic, emotional, other) cannot be included in multiple PS.⁹ We agree that we should always remain critical when interpreting its results. Nevertheless, a well-applied multiple PS can help us shine light on outcomes of daily practice observational studies, specifically in the situation in which multiple treatment options are available.

Sytske Anne Bergstra,¹ Cornelia F Allaart,¹ Robert B M Landewé^{2,3}

¹Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands

²Amsterdam Rheumatology & Immunology Center, Amsterdam, The Netherlands

³Department of Rheumatology, Zuyderland Medical Center, Heerlen, The Netherlands

Correspondence to Sytske Anne Bergstra, Department of Rheumatology, Leiden University Medical Center, Leiden 2333 ZA, The Netherlands; s.a.bergstra@lumc.nl

Handling editor Josef S Smolen

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Commissioned; internally peer reviewed.

© Author(s) (or their employer(s)) 2019. No commercial re-use. See rights and permissions. Published by BMJ.

To cite Bergstra SA, Allaart CF, Landewé RBM. *Ann Rheum Dis* 2019;**78**:e132.

Received 2 November 2018

Accepted 4 November 2018

Published Online First 14 November 2018

► <http://dx.doi.org/10.1136/annrheumdis-2018-214612>

Ann Rheum Dis 2019;**78**:e132. doi:10.1136/annrheumdis-2018-214652

REFERENCES

- 1 Ahmed S, Bergstra SA, Winchow LL. Metering the Meteor in methotrexate failure: is propensity score a falling star? *Ann Rheum Dis* 2019;**78**:e131.
- 2 Fleischmann R, Tongbram V, van Vollenhoven R, *et al*. Systematic review and network meta-analysis of the efficacy and safety of tumour necrosis factor inhibitor-methotrexate combination therapy versus triple therapy in rheumatoid arthritis. *RMD Open* 2017;**3**:e000371. doi:10.1136/rmdopen-2016-000371
- 3 Bergstra SA, Winchow LL, Murphy E, *et al*. How to treat patients with rheumatoid arthritis when methotrexate has failed? the use of a multiple propensity score to adjust for confounding by indication in observational studies. *Ann Rheum Dis* 2019;**78**:25–30.
- 4 Markusse IM, Akdemir G, Dirven L, *et al*. Long-term outcomes of patients with recent-onset rheumatoid arthritis after 10 years of tight controlled treatment: a randomized trial. *Ann Intern Med* 2016;**164**:523–31.
- 5 Rantalaiho V, Korpela M, Laasonen L, *et al*. Early combination disease-modifying antirheumatic drug therapy and tight disease control improve long-term radiologic

- outcome in patients with early rheumatoid arthritis: the 11-year results of the Finnish Rheumatoid Arthritis Combination Therapy trial. *Arthritis Res Ther* 2010;12:R122.
- 6 Boers M, Verhoeven AC, Markusse HM, *et al*. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet* 1997;350:309–18.
 - 7 Bergstra SA, Allaart CF, Stijnen T, *et al*. Meta-regression of a dose-response relationship of methotrexate in mono- and combination therapy in disease-modifying antirheumatic drug-naïve early rheumatoid arthritis patients. *Arthritis Care Res* 2017;69:1473–83.
 - 8 Bergstra SA, Allaart CF, van den Berg R, *et al*. Similar short-term clinical response to high-dose versus low-dose methotrexate in monotherapy and combination therapy in patients with rheumatoid arthritis. *Arthritis Res Ther* 2017;19:258.
 - 9 Spreeuwenberg MD, Bartak A, Croon MA, *et al*. The multiple propensity score as control for bias in the comparison of more than two treatment arms: an introduction from a case study in mental health. *Med Care* 2010;48:166–74.