

Methotrexate reduces withdrawal rates of TNF-inhibitors due to ineffectiveness in rheumatoid arthritis but only in patients who are seropositive

Mandy Greenwood¹, Muhammad Shipa¹, Su-Ann Yeoh¹, Euthalia Roussou², Dev Mukerjee³, Michael R Ehrenstein¹

1. Centre for Rheumatology, Division of Medicine, UCL, London, UK
2. Department of Rheumatology, Barking, Havering and Redbridge University Hospital NHS Trust, Romford, UK
3. Department of Rheumatology, North Middlesex University Hospital NHS Trust, London, UK

Correspondence to

Professor Michael Ehrenstein, Centre for Rheumatology, Division of Medicine, London WC1E 6JF, UK; m.ehrenstein@ucl.ac.uk

The benefits of co-prescribing methotrexate with TNF-inhibitors are well documented in rheumatoid arthritis (RA), though rheumatoid factor (RF) and anti-CCP status have not always been taken into account (1). Increasing doubt about the value of combination methotrexate and anti-TNF therapy in psoriatic arthritis (2, 3) led us to evaluate whether methotrexate reduced withdrawal rates due to ineffectiveness for anti-TNF therapy equally in seropositive and seronegative RA. Treatment durations for adalimumab or etanercept were analysed for 301 patients with RA using retrospective, real-world data from a single centre. All had started adalimumab or etanercept as a first-line biologic from 2003 onwards. Rates of ineffectiveness-related withdrawal during the first 5 years of anti-TNF therapy, were analysed using Kaplan-Meier and Cox regression, with comparison of rates with respect to concomitant methotrexate at anti-TNF initiation. 52 withdrawals for adverse events, and 10 for other reasons constituted censored cases as did 136 still on anti-TNF at 5 years and 60 still on anti-TNF with < 5 years follow up.

Kaplan-Meier plots (Figure 1) revealed seropositive patients had a significantly lower rate of withdrawal for ineffectiveness if on methotrexate at anti-TNF initiation. In contrast, the rate in seronegative patients was, unexpectedly, significantly higher with methotrexate, though the number of patients in the seronegative group is relatively small. A separate validation cohort of 534 patients from two other hospitals confirmed these findings (Figure S1). Concomitant sulfasalazine, hydroxychloroquine or number of concomitant DMARDs were not significantly associated with ineffectiveness withdrawal rates regardless of seropositivity. Discontinuation of anti-TNF for ineffectiveness in patients not on methotrexate was much greater in seropositive compared to seronegative patients ($p=0.002$, $p=0.001$ in the validation cohort).

Cox regression with a backward stepwise method was used to select variables from a list comprising methotrexate, seropositivity and anti-TNF type (and all three of their interactions) plus all factors with univariate $p<0.20$, and to estimate hazard ratios (HR) for ineffectiveness-related anti-TNF withdrawals (Supplemental Table 1). Seropositive status (HR 6.17, $p=0.012$), methotrexate (HR 4.47, $p=0.049$) and their interaction (HR 0.12, $p=0.007$) remained significant after controlling for disease duration <3 years at anti-TNF initiation (HR 2.04, $p=0.001$), 4+ DMARD trials (HR 2.50, $p<0.005$), male gender (HR 0.49, $p=0.017$), and biologic-naïve global VAS in cm (HR 1.27, $p<0.0005$). Anti-TNF type and its interactions with methotrexate or seropositive status did not make a significant enough impact for inclusion in the model, and neither did age, date of anti-TNF initiation, other baseline data (tender and swollen joint counts, elevated ESR or CRP), prednisolone use, SLZ, HCQ or number of concomitant DMARDs. When the impact of anti-CCP and RF were considered separately, both

were also significant as main effects (anti-CCP HR 5.03, $p=.002$ and RF HR 4.73, $p=.010$) and in interaction with methotrexate (anti-CCP*methotrexate HR 0.14, $p=.002$, RF*methotrexate HR 0.16, $p=0.007$).

Despite being significantly related to rate of discontinuation for ineffectiveness, neither methotrexate nor seropositive status, nor their interaction, explained a significant amount of the variance in DAS28-CRP at the first review appointment or in the change from biologic-naïve baseline.

These results support the co-prescription of methotrexate for patients with RA on adalimumab or etanercept but only for seropositive patients. The reason for the discordance associated with seropositivity is unclear but perhaps highlight specific mechanisms of disease response to combination methotrexate and TNF inhibitors dependent upon RF or CCP status. It is tempting to draw parallels with other seronegative inflammatory arthropathies, specifically psoriatic arthritis, where the benefits of concomitant methotrexate with TNF inhibitors remain unproven (2, 3). We analysed etanercept and adalimumab, as the relevance of immunogenicity is likely to be less for the former (4), but did not find any difference between these two types of anti-TNF with respect to methotrexate influencing discontinuation due to ineffectiveness. Further analysis of concomitant methotrexate in seronegative RA patients treated with TNF inhibitors is warranted.

Figure 1 Legend

Kaplan-Meier survival curves for discontinuation of anti-TNF due to ineffectiveness in seropositive and seronegative patients with and without concomitant methotrexate

Contributors MG and MRE were involved in the design of the study, data interpretation and wrote the manuscript. MG performed the research, collected and analysed the data. MS, S-A Y, ER, DM collected and verified patient data, and analysed the validation cohort. All authors approved reviewed and approved the manuscript's content before submission.

Funding MG (and MRE in part) are supported by the University College London Hospital Biomedical Research Centre.

Acknowledgements We thank Professor Kimme Hyrich for critical review of the manuscript.

References

1. Hyrich KL, Watson KD, Silman AJ, Symmons DP. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Rheumatology (Oxford)*. 2006;45(12):1558-65.
2. Behrens F, Koehm M, Arndt U, Wittig BM, Greger G, Thaci D, et al. Does Concomitant Methotrexate with Adalimumab Influence Treatment Outcomes in Patients with Psoriatic Arthritis? Data from a Large Observational Study. *The Journal of rheumatology*. 2016;43(3):632-9.
3. Mease PJ, Gladman DD, Collier DH, Ritchlin CT, Helliwell PS, Liu L, et al. Etanercept and Methotrexate as Monotherapy or in Combination for Psoriatic Arthritis: Primary Results From a Randomized, Controlled Phase III Trial. *Arthritis & rheumatology*. 2019;71(7):1112-24.

4. Jani M, Barton A, Warren RB, Griffiths CEM, Chinoy H. The role of DMARDs in reducing the immunogenicity of TNF inhibitors in chronic inflammatory diseases. *Rheumatology*. 2013;53(2):213-22.

Figure S1.

Kaplan-Meier survival curves of discontinuation of anti-TNF due to ineffectiveness in seropositive and seronegative RA patients with and without concomitant methotrexate (validation cohort).

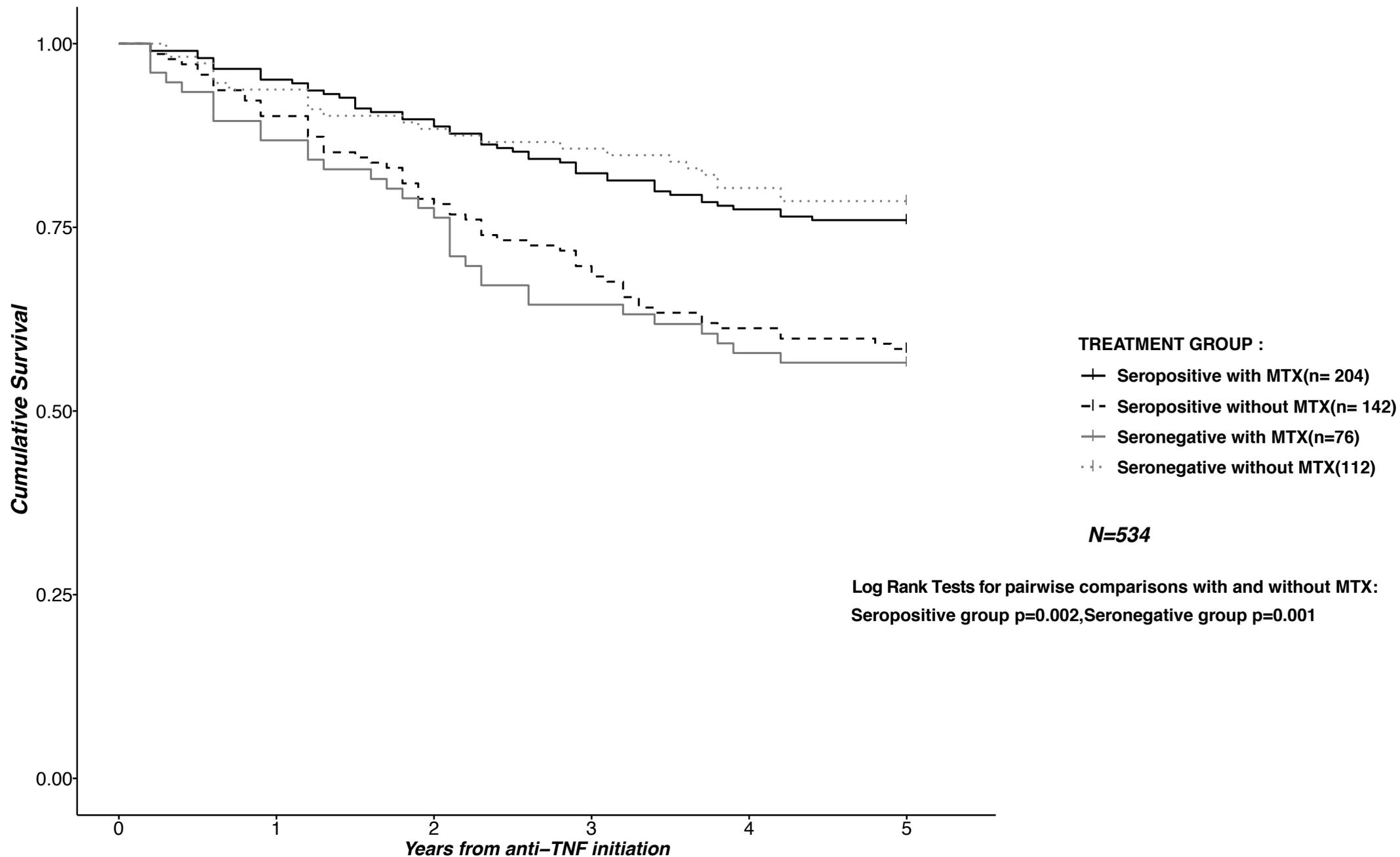


Figure 1.

