Editorial

Methotrexate in Giant Cell Arteritis Deserves a Second Chance — A High-dose Methotrexate Trial Is Needed

Giant cell arteritis (GCA) is a chronic inflammatory disease of the large- to medium-sized arteries and shows a relapsing course in up to 75% of patients. In sharp contrast to other autoimmune/inflammatory diseases, the treatment of GCA still heavily relies on high-dose, longterm glucocorticoids (GC)[1]. After 5 years of GC treatment, > 50% of patients still have active disease and are continuing the treatment. The well-known side effects of GC add to the burden of the disease itself, decreasing the quality of life of these elderly patients with GCA.

Are there good alternatives for GC in the treatment of GCA? Recently, a successful randomized controlled trial (RCT) was performed with the interleukin (IL-) 6 receptor blocker tocilizumab (TCZ) in GCA. More than 50% of the treated patients reached the primary endpoint of the study and were in sustained GC-free remission at 1 year[2].

Although TCZ is an important addition to the therapeutic tools against GCA, there are also several drawbacks. First, almost 50% of patients still develop a relapse despite TCZ. Second, under treatment with TCZ, one cannot rely on the acute-phase reactants as biomarkers of disease activity in GCA. Currently there are no IL-6–independent validated biomarkers for routine use in GCA. Also, as with other new treatments with potential therapeutic effect in GCA, the costs of TCZ are significant. In contrast to the upcoming trials with new, expensive treatment modalities in GCA (upadacitinib NCT03725202, ustekinumab NCT03711448, NCT02955147, sarilumab NCT03600805, baricitinib NCT03026504, granulocyte-macrophage colony-stimulating factor blockade), there is a limited number of studies and a limited amount of evidence on the effects of conventional disease-modifying antirheumatic drugs in GCA. This is in contrast to rheumatoid arthritis (RA), for which cheap and safe drugs such as methotrexate (MTX) and leflunomide are effective. Another important drawback of the above-mentioned registered trials is that they are short-term, mostly 1–2 years, and that no longterm data are generated in a disease in which > 50% of patients still have active disease after 5 years[1].

In this issue of *The Journal*, Koster, *et al*[3] report the results of their study on longterm MTX use in patients diagnosed with GCA at the Mayo Clinics between 1998 and 2013. They included 83 patients with GCA in both arms of the study (GC only and GC + MTX) who were matched for age, sex, and laboratory variables at baseline as well as for mean initial prednisone doses. Disease duration before the start of MTX was 39 weeks, with an interquartile range of 13–80 weeks. The median followup time was 4 years. Their main finding was that MTX plus GC led to a 2-fold greater relapse rate reduction compared to GC alone. Importantly, the patients who received MTX [median dose 13.5 (10–15) mg per week] had a higher relapse rate at baseline than those who did not receive MTX. In the MTX group the relapse rate decreased from 11.8 relapses per 10 person-years prior to the start of MTX to 3.72 relapses per 10 person-years thereafter. In those patients not receiving MTX, the relapse rate was 4.45 relapses per 10 person-years before the index date and 2.68 relapses per 10 person-years following the index date ($p < 0.004$). Unfortunately, the authors did not find a GC-sparing effect. The MTX-treated patients received a cumulative higher GC dose because of the already-higher GC dose at the time of MTX introduction [24.4 vs 20.5 mg; MTX group 1 yr: 5.0 g (3.9–8.4); 2 yrs: 8.1 g (5.4–14.1) vs GC alone, 1 yr: 3.5 g (1.7–7.4), 2 yrs: 5.7 g (2.2–9.1)].

Despite its retrospective nature, this study adds important data on the effectiveness and side effects of MTX in patients with GCA in daily clinical practice[3]. Its particular strength comes from the longterm followup in a well-defined, large cohort.

The finding by Koster, *et al* that MTX was not GC-sparing seems to be in contrast with previous studies summarized in the metaanalysis by Mahr, *et al*[4]. The 3 trials included in this metaanalysis used MTX for treatment

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induction, rather than in relapsing patients with GCA as in the study by Koster, *et al*[3]. Further, the 3 trials used a relatively low dose of MTX (starting dosage ranged from 7.5 to 10 mg/week, increasing to a maximum dose range of 10 to 20 mg/week and a GC starting dose of a maximum of 60 mg per day in the Jover, *et al* and Hoffmann, *et al* trials)[5,6,7].

The metaanalysis of individual patient data from the 3 clinical trials did identify a protective effect of MTX against relapse, with the risk of first relapse being reduced by 35% and second relapse by 51%.

In addition, there was an overall reduction in the exposure to GC. However, only 1 of the 3 MTX trials (Jover, *et al*, using 10 mg MTX/week for 24 mos) demonstrated a GC-sparing effect of 1.12 g (CI –1.99 to –0.24 g)[5]. This study also showed a benefit in relapse reduction that was not found by the other 2 studies. Based on an extraction of the original data, Mahr, *et al* were able to draw survival curves that demonstrated an overall relapse-preventing and GC-sparing benefit of MTX[4]. Yates, *et al* also included, in their metaanalysis on MTX treatment in GCA, the same 3 MTX studies as Mahr, *et al*, but used pooled and not individualized data[8]. As a result of varying doses of MTX and GC, the differences in the definition of relapse and the baseline variation in the characteristics of the patients with GCA being studied, they reported that it was very hard to draw any conclusions[8].

Overall, studies with MTX in GCA are hampered by either the use of low-dose MTX (7.5–10 mg per week) or short followup. In the double-blind, placebo-controlled study by van der Veen, *et al*, 21 patients with GCA/polymyalgia rheumatica (PMR) were followed for 2 years on average[9]. No differences were found between the MTX group and the placebo group concerning time to achieve remission, duration of remission, number of relapses, or cumulative prednisone doses in the total group containing GCA and PMR patients[9]. Interestingly, in a recent longterm (1991–2013), open-label, cross-sectional study with MTX at a mean dose of 10 mg per week, Leon, *et al* found that MTX decreased the chance of getting a relapse from 65% to 34% and that the GC dose at the time of relapse was lower in the MTX-treated patients (3.75 mg vs 5.0 mg)[10].

Especially in the light of ageing populations and the associated rise of healthcare costs, there is an unmet need for cheap and safe GC-sparing and relapse-preventing drugs in GCA. Several factors may have played a role in the marginal effect of MTX in the studies mentioned above: their retrospective design, a selection bias (MTX being started in relapsing patients), and a low dose of MTX. Although the evidence is marginal, MTX should get a second chance in GCA because it is a cheap, safe, and effective drug in other autoimmune diseases, such as RA.

The ideal study to test the efficacy of MTX would be a 3-year prospective multicenter RCT with newly diagnosed patients with GCA who start high-dose MTX (25 mg per week) or placebo along with 40–60 mg prednisolone, followed by a short 26-week taper.

ELISABETH BROUWER, MD, PhD,
Associate Professor;
KORNELIS S.M. VAN DER GEEST, MD, PhD;
MARIA SANDOVICI, MD, PhD;
Department of Rheumatology and Clinical Immunology,
University Medical Center Groningen (UMCG),
University of Groningen,
Groningen, the Netherlands.

Dr. E. Brouwer, as an employee of the UMCG, received speaker fees and consulting fees from Roche, which were paid to the UMCG. Address correspondence to Dr. E. Brouwer, Department of Rheumatology and Clinical Immunology, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9713 GZ Groningen, the Netherlands.
E-mail: e.brouwer@umcg.nl

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