Current treatment strategies in rheumatoid arthritis after methotrexate are not enough to maintain sustained remission: There is no holy grail!

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The ideal state for a patient with rheumatoid arthritis (RA) is sustained remission (1). Contemporary treatment strategies such as early initiation of DMARD(s), optimal methotrexate dosing and treating to a target with validated outcomes have improved the likelihood of remission in RA (1). Remission, however defined, is not always achieved and even less often will patients with RA maintain sustained remission over time (2,3). The EULAR and the ACR recommendations for the treatment of rheumatoid arthritis suggest that patients with poor prognostic features should be treated with advanced therapies such as biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs such as JAK inhibitors) after a methotrexate incomplete response (2,4). Källmark et al published an observational study of patients with RA from the Swedish National Register Study comparing sustained remission on triple therapy (methotrexate, hydroxychloroquine and sulfasalazine) to methotrexate with bDMARDs after methotrexate monotherapy (4). The study spanned 12 years. Sustained remission was defined as 24 months or longer of DAS28(ESR)<2.6, a validated metric. A total of 1502 patients were included of whom ¼ were treated with triple therapy. They observed that in patients starting bDMARDs, sustained remission occurred more frequently than with triple therapy. The odds of long-term sustained remission at 2 years were 1.62 (0.94-2.79). Short-term sustained remission was more frequent with new starts of bDMARDs compared to triple therapy at one and two years with adjusted OR 1.79 (1.18-2.72) and 1.92 (1.21-3.06) respectively favoring bDMARDs. Whereas, for those remaining on either drug regimen at any time over follow up, there were no between-groups differences, but that is expected as analyses are biased towards responders. They concluded that although there was more sustained remission for those initiating bDMARDs, triple therapy may have a role in some patients who can tolerate the regimen (as those remaining on treatment had equal likelihood of sustained remission) but there was less retention in the patients treated with triple therapy (5).

The Källmark study is important as the use of triple therapy has become less prominent in RA recommendations and guidelines, although it is mentioned in the EULAR recommendations and not highly recommended in the ACR 2020 guidelines (2,4). As the study was not randomized, it is likely that there was a bias and confounding in patients selected by the treating physicians to received triple
therapy, such as perceptions of less active disease, year in which therapy was commenced, comorbidities, etc., as the majority (approximately 75%) received a bDMARD (5). However, the results are consistent with a systematic review of randomized controlled trials by Fleischmann et al which demonstrated in RA patients who were inadequate responders to methotrexate, triple therapy was 65% less likely to obtain an ACR70 at 6 months compared to TNFi added to methotrexate (6). Results from the meta-analysis at 1 and 2 years had large confidence intervals around the rates of ACR70 responses that were superior numerically for TNFi but not statistically.

This Swedish Register study did not consider the costs of treatment as they were primarily interested in the clinical effectiveness of both regimens, which clearly would benefit triple therapy compared to bDMARDs, even with the use of biosimilar biologic DMARDs (7).

There are implications from the findings of Källmark et al (5). Treatment after methotrexate with a bDMARD compared to adding csDMARDs as triple therapy is more likely to result in sustained DAS28(ESR) remission and be continued because of the better clinical benefit and tolerability. However, patients who do respond and tolerate triple therapy, are just as likely to achieve and maintain sustained DAS28(ESR) remission; just a smaller percent of initial patients do so (5).

It is important to recognize that either treatment strategy was not effective for all patients with 64% vs. 52% at 1 year and 43% vs. 35% at 2 years of bDMARD plus MTX vs. triple therapy, respectively, remaining on therapy. Unfortunately, as is true in virtually all registries, precise reasons for discontinuation such as loss of efficacy and/or adverse events were unavailable. Long term sustained remission at 2 years in completers was approximately 1 in 6 patients and for those who discontinued their therapy the odds were 1 in 10. This analysis suggests that despite advances in treatment strategies and therapeutic options, the likelihood of sustained remission over 2 years with either strategy in their rheumatology practices remains low with more than half the patients discontinuing treatment by 2 years (5). These results do not bode well for a lifelong chronic disease. In contradiction to this analysis, data were slightly better in a large incident cohort of patients with RA (the Canadian CATCH cohort) whereby using a more rigorous definition of remission, 55% achieved SDAI
remission (SDAI ≤3.3) and 47% maintained remission at one year (25% of the entire cohort) with 40% at 2 years (1 in 5 patients in sustained remission) (8). If DAS28(ESR) was the metric used in the CATCH analysis, the percent of patients achieving remission would approximately double. A structured approach to RA therapy following best practices is more likely to achieve desirable goals for the patients, but, despite our current therapies, not all patients respond well.

The chance of remission and drug survival is often worse for patients with RA not on background methotrexate (2). Approximately 1/3 of RA patients in the real-world on bDMARDs are receiving monotherapy (9); we would expect achieving and maintaining sustained remission to be less likely with monotherapy using advanced therapies. As predictors of tolerability and response to medications are lacking, our current treatment paradigm of blindly choosing a specific treatment option after methotrexate failure in RA is sub-optimal.

The NORD-STAR trial compared various treatment strategies in early RA patients including conventional synthetic DMARDs or biologics (10). The primary outcome was the clinical disease activity index (CDAI) at 24 weeks. Although biologic strategies in general numerically had a slight advantage, there were no differences between the strategies.

We propose that other treatment options/strategies need to be investigated in hopes of obtaining a prolonged remission in RA. Tofacitinib, baricitinib (4 mg) and upadacitinib in combination with MTX are at least as effective and in some circumstances more effective than a TNFi (adalimumab) but there are some questions about their relative risk with respect to safety (11). All therapies need to be balanced with respect to their benefit and risk. Perhaps other molecules with different mechanisms of action, may yield better and more sustained responses in RA or we will have combinations of treatment that yield higher and longer responses.

We can argue that the problem is not remission in RA but our measurements of remission. DAS28(CRP) gives more remission than a more stringent metric such as the SDAI. Many remission definitions include a patient reported outcome (PRO) such as patient global, which if removed would
result in more “remission” as patient global is often strongly related to pain which may be driven by factors unrelated to active RA (i.e. not from clinically detected inflammation (12). If remission translates into no detectable disease with metrics such as the CDAI in combination with a PRO such as the RAPID3 and no detectable inflammation on imaging, then remission would be very rare.

So, with all the money spent on advanced therapies in rheumatoid arthritis, we haven’t yet achieved remission in most and sustained remission for 2 years or more is achieved in a minority. Perhaps biomarkers will provide more rationale treatment choices and inform us when to start or stop a medication but the search for such biomarkers has been disappointing. We may learn lessons from oncology where pragmatic trials comparing one strategy to another are frequent with front end loading of medications and frequent alterations to treatment if biomarkers change. We have come a long way over the last 30 years from waiting rooms filled with RA patients, with severe subluxations who were wheelchair-bound and with shortened survival, but much scientific enquiry is still needed for patients with RA to achieve the holy grail of sustained remission for all - our ultimate goal!
References


