ACR Open Rheumatology
Vol. 3, No. 8, August 2021, pp 578–580
DOI 10.1002/acr2.11303

American College of Rheumatology
Empowering Rheumatology Professionals

JOURNAL CLUB

Sustained Remission in Rheumatoid Arthritis: Time to Withdraw Treatment?

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With increasing numbers of patients with rheumatoid arthritis achieving sustained remission, medication withdrawal is an important consideration to reduce polypharmacy and associated adverse events. An article from the journal *Arthritis & Rheumatology* (1) explores the treatment withdrawal options for patients on etanercept and methotrexate combination therapies and suggests methotrexate withdrawal has the least impact on disease worsening. There are limitations in the study, including the use of only one disease activity score and no assessment of radiographic progression, but, overall, the article provides a good framework for future studies on treatment withdrawal options and the possibility of medication reduction for patients.

Since the development of biologics, such as tumor necrosis factor inhibitors (TNFIs), for the treatment of rheumatoid arthritis, patients have been able to achieve sustained remission with decreased radiographic progression, improved physical functionality, and improved patient-reported outcomes. A question that arises with patients achieving such good outcomes with prolonged remission is the possibility of withdrawing treatments and maintaining remission. Reducing medication exposure will help reduce the development of side effects and complications, especially with an aging population with polypharmacy concerns and complications. The authors of a recent article published in *Arthritis & Rheumatology* titled "Etanercept or Methotrexate Withdrawal in Rheumatoid Arthritis Patients in Sustained Remission." help explore this idea of medication withdrawal through the Study of Etanercept and Methotrexate in Combination or as Monotherapy in Subjects with Rheumatoid Arthritis (SEAM-RA) clinic trial and database (1).

Prior guidelines about therapy tapering have been reported by both the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) (2,3). The authors do not explicitly discuss the tapering regimen from the ACR or EULAR, other than stating that all medications should not be stopped in the Introduction. As the authors mention, the overall data on the best way to taper treatment are limited. Prior studies have also had inconsistent definitions of sustained remission as well as limited comparisons with monotherapy regimens when either methotrexate or etanercept are withdrawn in combination regimens. The authors suggest in the Introduction that the SEAM-RA trial had a more consistent and stringent definition of remission and more closely looked at monotherapy regimens.

The trial design involved an international multicenter study with a 24-week open-label run-in period in which patients continued combination therapy and sustained remission, a 48-week randomized double-blind controlled period in which treatment was withdrawn, and a 30-day safety follow-up. Patients had to have rheumatoid arthritis and receive both methotrexate and etanercept and achieve a Simplified Disease Activity Index (SDAI) score of less than 3.3, which met ACR and EULAR criteria for remission. The randomized treatment withdrawing groups consisted of etanercept withdrawal, methotrexate withdrawal, or no change in therapy (a placebo was used for medication being withdrawn in combination with the remaining drug). Dosages of continued medications were unchanged. SDAI scores were followed to monitor for disease worsening. The trial population is consistent in terms of at least 6 months of good disease control (although still based on investigator opinion so variations in disease activity/severity may have been present) and stable dosage of medications for at least 8 weeks. The primary end point was no disease worsening based on the SDAI score 48 weeks after randomization. Secondary end points included adverse events as well as return to remission with rescue therapy if needed after withdrawal of treatments. Statistical analyses performed were appropriate with two-sided χ^2 tests,

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No potential conflicts of interest relevant to this article were reported.
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Submitted for publication June 15, 2021; accepted in revised form June 16, 2021.

univariate analysis, and Kaplan-Meier curves. Power analysis to determine the number of patients needed is potentially problematic because the effect size difference between etanercept and methotrexate monotherapy groups was based on prior treatment withdrawal groups, and the authors explicitly state that prior studies were inconsistent in their definitions of treatment outcomes and remission and consisted of limited studies in terms of comparisons with monotherapy regimens. However, some baseline difference is needed to perform the power calculation, and these were the best available data at the time for the calculation.

The baseline demographics of the patients were consistent between the randomized groups, with female predominance, an average age around 55 years old, a predominance of White race, similar treatment dosages and disease activities, and positive serological test results. No statistical comparisons between the groups are shown for these baseline characteristics. There were trends toward a higher percentage of White patients in methotrexate monotherapy (91.1%) versus combination therapy (82.4%) and of combination therapy being more seropositive for rheumatoid factor (RF) and anti-cyclic citrullinated peptides (CCP) antibodies than methotrexate monotherapy, which can all affect results, but the statistical significance of these differences is not shown or mentioned, limiting interpretation.

The primary end point of sustained remission based on SDAI scores showed that etanercept monotherapy and combination therapy maintained equivalent sustained remission for 48 weeks at around 50% (but not directly compared statistically), whereas methotrexate monotherapy only had 28.7% maintained remission. Additionally 62.4% of patients on methotrexate monotherapy had disease worsening, whereas 35% to 40% of patients on etanercept and combination therapies had worsening disease. The time to disease worsening was also shorter for methotrexate monotherapy. In terms of patients who received rescue therapy (returning to combination therapy with prior dosing), patients had similar remission responses between the methotrexate and etanercept monotherapies and responses similar to those seen with the continued combination regimen. Looking at covariates in terms of how they affect maintenance of remission suggested that seronegativity for RF and anti-CCP antibodies, lower disease activity, and lower body mass index were all positive predictors of maintained remission, but more detailed analysis was not performed on these and other variables.

Safety outcomes were seemingly similar between the groups, but there appears to be increased musculoskeletal and connective tissue disorders in the methotrexate-only group compared with the etanercept-only and combination therapy groups. There also appears to be fewer overall adverse events in the etanercept monotherapy group compared with the other groups. However statistical analysis is not shown or commented on, so the overall significance of these differences remains unclear.

Overall, the authors provide additional insight into therapy withdrawal in patients with sustained remission and suggest etanercept withdrawal and methotrexate monotherapy have higher rates and earlier occurrence of disease worsening compared with continued combination therapy or etanercept monotherapy with methotrexate withdrawal. There is also concern for increased adverse events with continued methotrexate use, suggesting additional benefit in methotrexate withdrawal to help prevent these complications.

There are a number of concerns with this article, including the disease activity evaluations. Only the SDAI score is used, and no evaluation of radiographic changes is done. The authors acknowledge this limitation, as prior studies have shown differences in radiographic changes with withdrawal of different medications. Other disease scoring criteria could also be used to help validate the results and help show that the results are not specific to one disease activity scoring system.

In terms of the medication regimens patients were on, it is unclear if methotrexate and etanercept was the first combination of medications the patients were on or if other medications had been tried before, including other biologics. Exposures to other medications could have altered the disease responses to the current medications or altered the disease pathology in ways not currently appreciated. More detail in disease and treatment history in the patient demographics would have been useful, as well as statistical analysis of the baseline demographics.

The authors also discuss in their Introduction the importance of studying drug withdrawal and comparing with monotherapy regimens, but few comparisons are done between treatment groups. Etanercept monotherapy is not statistically compared with combination therapy, and no patients with sustained remission after initial monotherapy are studied. Adding these groups would have made statistical analysis more difficult and would have required substantially more patients, but the same concerns the authors bring up in their Introduction remain with this article in terms of comparing different regimens and drug withdrawal options.

One aspect of TNFI and methotrexate combination therapy the authors do not discuss is the reduction of anti-drug antibodies against etanercept by methotrexate. There has been a strong emphasis on the benefit of continuing methotrexate with TNFIs and biologics to help reduce the development of these anti-drug antibodies (4). Looking for the presence of these anti-drug antibodies would be useful in terms of the importance of continuing methotrexate and would help compare the combination regimen with etanercept monotherapy, a comparison that is limited currently. Although 48 weeks is a fairly long period to assess for continued remission, even longer periods could be beneficial, especially regarding the development of anti-drug antibodies.

Finally, the article highlights how sustained remission remains difficult to maintain even with continued combination therapy, with only around 52% of patients remaining in remission. With such high rates of disease worsening, it could be argued that drug withdrawal is not the best consideration at this point because our current regimens are not able to sustain

remission for a large portion of patients. This again brings up the concern of anti-drug antibodies, which could be resulting in the failure to sustain remission.

The authors of this article explore an interesting aspect of treating rheumatoid arthritis that deserves to be explored because patients are often concerned about the duration of treatment and whether they will have to continue these treatments throughout their lifetime. Drug withdrawal is becoming increasingly more important with improving treatment options and more patients able to achieve remission. However, there are still high rates of patients who are not able to sustain remission even with continued therapies. Methotrexate may be the best medication to withdraw when compared with etanercept withdrawal, but various implications of medication cessation are not addressed, including radiographic changes and anti-drug antibody formation. The article is also limited in terms of all the medication combinations and regimens available currently. The authors provide a good framework for further studies and research regarding medication withdrawal, and the article serves as a lesson to providers to not be complacent with medication regimens and consider medication reduction to prevent polypharmacy and associated complications.

AUTHOR CONTRIBUTIONS

Dr. Sungur drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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