The approach to treatment of RA has evolved substantially in recent years with the introduction of highly effective novel therapies that have resulted in new treatment paradigms, such as treat-to-target and the treatment of patients earlier in their disease course [1, 2]. Clinicians are very interested in studies that compare the effectiveness of medications that could help them achieve optimal treatment outcomes for their patients. Extrapolation of the results of such studies into clinical practice depends on accurate assessment of data from the clinical trials. This assessment has become increasingly challenging as study designs have become increasingly complex, with multiple arms and changes in treatments over the course of a trial. There are many methods to analyse a given set of data; with the same data set, depending on the method of analysis, different conclusions can be reached. To help standardize this process, a European League Against Rheumatism (EULAR)/ACR committee created guidelines on reporting data from clinical trials [3]. The complexities of this analysis are illustrated by a recent example.

The Randomized Comparative Effectiveness Study of Oral Triple Therapy versus Etanercept plus Methotrexate in the Early, Aggressive Rheumatoid Arthritis (TEAR) trial was designed to address two important clinical questions: (i) is it better to intensively treat all early RA patients with multiple DMARDs, or reserve this treatment only for those who do not appropriately respond to MTX monotherapy? and (ii) is the combination therapy of MTX plus etanercept (ETN) superior to triple combination therapy of MTX, SSZ and HCQ (TT), either initially or after insufficient efficacy of MTX at 6 months? [4]. Patients with early RA were randomly assigned to receive MTX monotherapy, MTX plus ETN or TT. At 6 months, patients treated with MTX monotherapy who did not achieve DAS28 < 3.2 were stepped up to add either ETN or move to TT and treated for 102 weeks.

The primary outcome, by the protocol, was the area under the curve (AUC) of DAS28 from weeks 48 to 102. The primary outcome reported in the manuscript was an observed analysis only for patients who continued in the trial from week 48 to 102 patients had to have done well clinically and not had a significant adverse event to remain in the study through week 48. A more traditional statistical analysis, such as a non-responder imputation or last observation carried forward from day 0 to week 102 might have given different results.

The first question posed, whether it is more effective to start either combination or MTX monotherapy, was not answered; the results are not presented for those patients initially treated with MTX who achieved DAS28 < 3.2 at week 26 and then continued to week 102. The primary outcome reported in the manuscript was an observed group analysis of change in the mean DAS28-ESR from week 48 to 102 and the AUC of the DAS28 during this time period. The authors stated that their statistical analysis plan was confirmed by their secondary analyses, which did include non-responder imputation and last observation carried forward. However, these analyses were also performed only on patients in the study from week 48 to 102.

In addition to design and statistical considerations, some of the data can be interpreted differently from the authors, and this might be worth some further examination. For instance, the authors reported that there was no difference in the change in DAS28, or other clinical measures, between the patient groups studied. However, there was a treatment difference at week 102 between the ETN and TT groups for ACR70 (18.2 ± 11.3%, P = 0.02). This would suggest that ETN plus MTX was more effective in achieving a profound response. This difference in profound response may have led to the significant difference in radiographic progression reported with ETN and MTX treatment vs TT at week 102. The radiographic difference was noted despite the fact that X-rays were not done in patients who withdrew early; in other studies, results at the time of exit have been extrapolated to the final endpoint to allow comparison. In this case, radiological data are only in those observed or study completers; by definition, such patients usually fare quite well and patients who do well have less progression of joint damage.

Initial TT and initial MTX monotherapy with step-up had similar ACR20/50/70 response rates at 2 years, showing
no advantage of either approach; however, there is the possibility that switching from MTX to another monotherapy might have resulted in similar clinical and structural efficacy as stepping up, as was seen in the Behandel Strategieën (BeSt) trial [1]. The primary focus on observed data from weeks 48 to 102 makes this design similar in some ways to long-term extension (LTE) phases of clinical trials rather than the traditional double-blind studies that compare the efficacy of one agent(s) with another agent(s). The analysis of LTE studies is much more complicated than traditional double-blind, randomized controlled trials [5]. There are issues in LTE related to efficacy, as the aim of LTE is to confirm maintenance of the initial response. Also of note in this study is that there was a relatively high dropout rate in both groups, with only 65% of the ETN and MTX group and 58.5% of the TT group remaining at week 102. The sample size determination for 80% power to prove the primary endpoint was based on a dropout rate of 10%, and thus, with this number of dropouts, the study was underpowered to show a statistical difference between the groups.

Methodological issues are crucial for the accurate interpretation of clinical trial data [6–8]. Clinicians must be aware of how subtle differences in data presentation affect results, so that they can arrive at accurate answers to important clinical questions, such as the most appropriate therapeutic approach to the treatment of early RA. With this wealth of data available from the TEAR study, a re-analysis of the data using the suggested approaches could be considered, assuming that the high dropout rate does not preclude it, to try to directly answer the very important question, should a physician start therapy with MTX, dosed appropriately for no more than 3–6 months, and then, if low disease activity is not reached, is a switch to combination DMARDs as effective as addition of a biologic or not?

This study explored concepts that are of significant practical importance to rheumatologists and patients; moreover, the authors should be congratulated on the undertaking. However, further analyses of this data set will help in its application to clinical practice.

Disclosure statement: A.K. has received grants/research support from Amgen, Abbott, BMS, Roche, Janssen and UCB. J.S. has undertaken clinical trials or and provided expert advice or and engaged in symposium presentations for and/or received grant support from Abbott, Astra-Zeneca, BMS, Celgene, Glaxo, Janssen, Medimmune, MSD, Novartis-Sandoz, Novo-Nordisk, Pfizer, Roche and UCB. The other author has declared no conflicts of interest.

**References**


