Letters to the Editor

Comment on: Efficacy and safety of various repeat treatment dosing regimens of rituximab in patients with active rheumatoid arthritis: results of a Phase III randomized study (MIRROR)

Sir, We read with interest the recent article by Rubbert-Roth et al. [1]. The MIRROR trial provided an opportunity to answer an important clinical question: is there a difference in efficacy between lower doses and higher doses of rituximab in the treatment of RA?

Bias is widespread in the medical literature and we note several issues in the published report of this study that are of concern and potentially misleading.

(i) Although the design of this study is stated to be a randomized, double-blinded controlled trial, the process was reported as flawed by the authors, resulting in a biased study and incorrect treatment allocation to some of the participants [1]. A more detailed and clear explanation of exactly what happened and how this affected the treatment allocation, blinding process and results is needed.

(ii) The whole purpose of the complex process of blinding and randomization involved in such a study design is to reduce or eliminate both covert and overt bias in so far as is possible. Therefore, the analyses that adjusted for baseline factors as reported raises serious concerns about the design, process, analysis and results, as the analyses should be straightforward with such a design.

(iii) Figure 2 reports that some patients received placebo. Nowhere in the ‘Methods’ section is there a statement about a placebo being administered in this trial.

(iv) Although the authors used an as-treated analysis instead of an intention-to-treat analysis, we believe this is not acceptable and those who were incorrectly assigned should have been excluded from the analysis. An intention-to-treat analysis is favoured by such a study design because of the biases introduced in an as-treated analysis. As treated is the preferred analysis for a cohort study [2, 3]. Using an unadjusted P-value when performing multiple analyses of the same study to conclude that results are statistically significant is incorrect and does not reflect best practice.

(v) Although the authors conclude that some analyses suggest that the higher dose is more efficacious, the clear message from the data presented (despite the flaws) is that a lower dose is as effective. This study was not designed to show superiority. When other similar outcome assessments show no difference, this is likely a chance finding.

(vi) As one of their two rheumatology key messages, the authors state that ‘some efficacy outcomes suggest improved outcomes for RTX 2 × 1000 vs 2 × 500 mg’. For the above reasons, we disagree with the authors that this is the key message to be learnt from the study results.

In summary, we have several concerns about this report. We believe in the interest of fair and honest reporting that this article should be amended. Additional details should be provided on exactly what happened during the treatment allocation process, whether a placebo was
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actually used and how more appropriate analyses affected the results of this study.

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Richard Conway1 and John J. Carey1
1Department of Rheumatology, Galway University Hospitals, Galway, Ireland.

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Correspondence to: Richard Conway, Department of Rheumatology, Galway University Hospitals, Merlin Park, Galway, Ireland. E-mail: drrichardconway@gmail.com

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Comment on: Efficacy and safety of various repeat treatment dosing regimens of rituximab in patients with active rheumatoid arthritis: results of a Phase III randomized study (MIRROR): reply

Sir, We would like to thank Conway et al. [1] for their interest in our article [2] and their comments, which raise important aspects of the reporting of clinical trials.

The mis-randomizations resulted from the Interactive Voice Response System (IVRS) vendor failing to update the medication list following a protocol amendment, which consequently resulted in the medication list not being synchronized with the randomization schedule. In practice, this caused the IVRS to allocate a medication pack containing a different regimen to that specified in the randomization schedule, and resulted in 60 patients (16% of the study population) being administered a rituximab regimen that was inconsistent with their randomized schedule. The blinding process itself, however, was unaffected and neither the sponsor, investigators nor patients were aware of the rituximab regimen being administered to patients.

As a result of these mis-randomizations, a number of analysis populations were considered, including intent-to-treat (ITT)-as randomized, ITT-as treated, ITT-misrandomizations excluded and a formal per-protocol (excluding mis-randomizations and other major protocol violators). The primary analysis [American College of Rheumatology (ACR) 20 at Week 48] was performed on all these populations and showed consistent outcomes with no difference between the treatment arms being observed in any analysis population. Given that the majority of mis-randomized patients still resulted in patients receiving a protocol-defined regimen (A–C) we decided to use the ITT-as treated population for the remaining efficacy analyses for several reasons. These included maximizing available patient data and, therefore, power, as well as permitting efficacy and safety profiles to be reported in the same patient populations.

With regard to the statistical analyses and, specifically, randomization based on predefined strata with subsequent adjusted P-values, these are in compliance with both International Conference on Harmonization (ICH) statistical principles and Committee for Medicinal Products for Human Use (CHMP) guidance on adjusting for baseline covariates [3, 4]. Indeed, this approach is common practice in statistical analyses of clinical trials. Multiplicity adjustments were not planned for secondary and exploratory analyses and all P-values for efficacy endpoint comparisons of rituximab were exploratory or descriptive.

With respect to the reference to placebo in Fig. 2 [2], an early protocol design included treatment Arm C as a single course of rituximab (2 × 1000 mg) for the entire 48-week period. To maintain the blinding, this required placebo infusions at Week 24. However, a subsequent protocol amendment was made so that this regimen more closely reflected that in other studies where re-treatment with 2 × 1000 mg was given at Week 24. This protocol amendment was not accepted in the UK and, therefore, some patients continued to receive the original Arm C placebo regimen. The results for this group of patients are not reported in our article as this treatment regimen was inconsistent with the final study design and the patient numbers were too small for interpretation (n = 6 in total).

The study was designed to show superiority of dose escalation (Arm B) compared with consistent dosing with 2 × 500 mg (Arm A), and as stated in the discussion, no statistical difference between the dose regimens was found for the primary endpoint (ACR20). Nevertheless, rituximab was observed to be effective, with ACR scores consistent with previously published data [5, 6]. In addition, some predefined exploratory analyses did suggest improved responses in Arm C (2 × 1000 mg), including European League Against Rheumatism (EULAR) response rates, DAS remission rates, ACR50 rates and Disease Activity Score (DAS) over time. These observations of somewhat better efficacy with the rituximab 1000 mg regimen are also consistent with published data [5], as well as more recent findings indicating improved effects on prevention of joint damage with this dose regimen [7]. Further, clinical responses have also been suggested to be associated with a more profound degree of B-cell depletion, which in turn, may be more readily achieved.

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