actually used and how more appropriate analyses affected the results of this study.

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References

Letters to the Editor

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-mis-randomizations 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 × 1000mg 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 regimens 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.
with the higher dose [8]. Given the consistent nature of these observations, from both within this study and within the published literature, it is appropriate to conclude that there is evidence of improved outcomes with the rituximab 2 × 1000 mg regimen.

Finally, with regard to the key messages, the data clearly confirm that all regimens of rituximab used in this study were efficacious. That some endpoints suggested better outcomes with the rituximab 2 × 1000 mg regimen is supported by the analyses conducted, is consistent with published data and may have a plausible biological rationale. They are, therefore, considered important observations that may maximize the potential benefit from treatment with rituximab.

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