Reviewer's report

Title: Comparison of the efficacy and safety of two starting dosages of prednisolone in early active rheumatoid arthritis (CORRA): study protocol for an investigator-initiated, randomized, double-blind, placebo-controlled trial

Version: 2
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Reviewer: Kent Johnson

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What is noted below seem important enough to be considered "major".

This is a very nicely designed trial, especially being blinded, using a reasonable non-inferiority margin and therefore a sufficiently large sample size, incorporating both its two difference hypotheses and its single non-inferiority hypothesis in a proper hierarchical analysis design, and providing a resampling routine to deal with missing data in the statistical analysis. The aim is to show that aggressive or mild steroid use in the first 12-weeks will translate into an x-ray benefit at 1-year.

Patients should be stated as methotrexate naïve. The enrolment criteria seem OK otherwise.

Even if the hierarchical testing proves successful, I think there is substantial concern that confusion nevertheless will surround the interpretation of any conclusion. There are two reasons for this:

1-The design wherein the controlled intervention, steroids or placebo steroids, is only 12-weeks in duration yet the primary analysis time point is week 52 provides for a large potential for confounding therapy in the intervening weeks 13 to 52. Any of the following could be the explanation for a positive result, the Sharp Score ANCOVA, rather than the result being due to the hypothesis – early steroid use reduces one year radiographic progression: (i) sufficiently imbalanced methotrexate use, (ii) sufficiently imbalanced weeks 13-52 steroid use, (iii) sufficiently imbalanced progression to biologics. The only way to deal with this potential interpretation difficulty is without severely constraining treatment options in weeks 13-52 is to pre-specify that “trial success” will only be declared if the primary 1-yr Sharp Score ANCOVA is accompanied by the absence of significant interactions with methotrexate use, post week 12 steroid, and switching to biologics. These provisos will change the type 1 error calculations however.

2-The design has other plausible stand-alone endpoints such as percent remission, percent low disease activity, physical function, and patient global. Should “trial success” only be declared if none of these are found to perform sufficiently poorly, or are the investigators content with having these results be given a purely descriptive role?

These considerations are not as critical as when a new drug is seeking a specific
claim in rheumatoid arthritis, and the descriptive value of a large, well conducted trial is great. However, one wants a balance of the within-trial design rigor to maximize internal validity to ensure that success will, in fact, translate into yielding “information concerning the optimal glucocorticoid dosage schedule in the treatment of patients with early rheumatoid arthritis.” (Quote from the Discussion section of the Abstract). The above items of potential confusion threaten this outcome.

The paper would be substantially improved with discussion of the above items in the text.

In some places there is an awkwardness to the rhetoric that may have resulted from translation. Editing by someone with English as their native language may be helpful.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

'I declare that I have no competing interests'