Choice of second biologic in rheumatoid arthritis patients with inadequate response to initial anti-TNF

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The recently published Rotation or Change (ROC) trial (1) addresses an ongoing uncertainty in rheumatoid arthritis (RA) management. In the trial, Dr Gottenberg *et al*. report that patients with inadequate response to an initial TNF-antagonist had better outcomes in some disease activity measures if changed to a non-TNF-biologic compared with those rotated to a second TNF-antagonist. This study evaluates a common dilemma in RA management and has potential to trigger wide-spread changes in clinical practice. However, we are concerned that several important limitations, especially in the choice of outcomes, may have substantially biased the study's findings.

A critical limitation of the trial is that the key reported outcome measures intrinsically rely upon erythrocyte sedimentation rate (ESR). Nearly half of the patients randomised to the "non-TNF-biologic" trial arm received tocilizumab, a medication that can directly decrease serum inflammatory markers (including ESR) independently from effects on clinical RA activity due to its mechanism of action. Several authors have demonstrated DAS28-ESR scores may not be ideal for assessments of RA activity during treatment with tocilizumab (2-5). This concern is especially noteworthy since, in the ROC trial, tocilizumab had approximately twice the odds of favorable EULAR response compared to either rituximab or abatacept (which do not substantially directly effect ESR). Furthermore, improvement in Health Assessment Questionnaire (HAQ) scores, which do not rely on serum inflammatory markers, did not differ between treatment arms.

The trial authors interpreted non-significant differences in CRP changes between the two arms (p=0.06) as evidence that tocilizumab's direct effect on serum inflammatory markers did not have an undue influence on study findings. However, the authors also report a highly significant difference in the change in ESR between arms (p<0.001). The calculation of an alternative validated outcome measure that does not include inflammatory markers (*e.g*. CDAI), presentation of individual components of the DAS28-ESR, or a subgroup analysis excluding patients who received tocilizumab could help support the authors' conclusions.

Additionally, although treatment failure rates differed between treatment arms, lack of blinding due to the trial's pragmatic design makes this result less reliable. It is conceivable that knowledge of randomisation may have influenced decisions to switch to a third-agent (a scenario counted as treatment failure).

While the ROC trial is an important contribution in evaluating a notably understudied essential clinical question, further analysis and interpretation of this study is warranted before concrete changes to RA guidelines are considered based on its findings.

P.C. GANDIGA, *MD, FACP*
M.D. GEORGE, *MD, MSCE*
J.F. BAKER, *MD, MSCE*

Division of Rheumatology, University of Pennsylvania, Philadelphia, PA, USA.

Address correspondence to: Dr Prateek C. Gandiga, Division of Rheumatology, University of Pennsylvania, 3400 Spruce Street, White Building, 5th Floor, Philadelphia, PA 19104, USA.
E-mail: prateek.gandiga@uphs.upenn.edu

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