Editorial

Should rheumatoid arthritis patients preferentially be treated with tocilizumab after rituximab failure?

A randomized controlled clinical trial investigating the underlying disease process would be of help

Over the past decades the role of different key players in the pathophysiology of RA, such as cytokines and T- and B-cells, has been gradually clarified. This has led to the development of a multitude of sophisticated targeted therapies, so-called biologic DMARDs (bDMARDs), many of which have proven to be very efficacious and are marketed today. The first wave of bDMARDs were TNF-α inhibitors (TNFi) and next came the IL-6 receptor, T-cell and B-cell antagonists. All of these bDMARDs have primarily been tested in RA patients refractory to conventional DMARDs, the logical target population given their cost and safety profile [1, 2]. Rituximab (RTX; a B-cell antagonist) is mostly used in a second line after TNFi, and like all of the second generation bDMARDs, such as abatacept (ABA) (a T-cell antagonist) and tocilizumab (TCZ; an IL-6 receptor antagonist), it has been extensively studied also in the TNFi refractory population [1, 2]. There is, however, a lack of knowledge on the safety and efficacy of bDMARDs in RA patients refractory to second generation bDMARDs, including RTX. Moreover, until now there are no effective predictors of response to RA treatment and despite available guidelines [3, 4], rheumatologists find it difficult to choose between bDMARDs with different mechanisms of action for their individual patients in the first line, but even more after bDMARD failure. In this issue of Rheumatology, Walker et al. present a study showing that RA patients after RTX failure responded better to TCZ compared with TNFi or ABA, as measured by DAS28-ESR, Clinical Disease Activity Index (CDAI) and EULAR good-response criteria [5]. The effect on the health assessment questionnaire disability index (HAQ-DI) and drug retention rates, however, did not differ between the different bDMARDs tested after RTX, probably illustrating that patients and their doctors still do not like to switch treatment too rapidly, certainly in refractory RA [5]. This is a very valuable new information that could change our treatment paradigm, but before we all start prescribing TCZ to our RA patients after RTX proved unsuccessful we have to weigh the evidence very carefully.

There have been studies in this population before, but they mainly focused on safety issues [6, 7] or had a small sample size [8]. Data for this study were derived from the European Collaborative Registries for the Evaluation of RTX in Rheumatoid Arthritis (Cererra), an investigator-led, industry-sponsored, multinational prospective longitudinal observational database [5]. Observational trials have the advantage of providing data reflecting daily practice, including normal patients in standard circumstances, but they are also by definition prone to methodological weaknesses such as selection bias (reasons why patients enter the trial, or not, are often unclear; sometimes certain patients are systematically left out), confounding by indication (treatment allocation is free, but by definition subjective and often untransparent; certain treatments are preferentially given by certain doctors to certain types of patients), missing data, imprecise timing of patient evaluation, and others [9]. Attempts can be made to correct for these inherent weaknesses or at least to clarify to what extent we can trust the interpretation of the data. In this study, the authors have tried to solve this by providing as much information as possible on the patients they included. Study participants were comparable to the global population they were selected from, showing this was a representative sample. Moreover, patient characteristics did not differ significantly between the treatment groups, nor their use of additional medication throughout the study. Nevertheless, patients treated with TCZ were more often young men with a high number of previous bDMARDs and less frequent glucocorticoid use, but the differences between treatment groups were retained after statistical adjustment for these parameters. Patient selection could have been affected by the specific response kinetics of RTX, with a peak-effect only after 2–3 months and an unpredictable long-lasting effect, hampering evaluation of efficacy. The authors have tried to solve this by including only patients within 6 months following the last RTX infusion. The study protocol contained a risk of imprecise data collection, since baseline data could be obtained up to 21 days after starting the new biologic, but luckily in 88% they were collected on the day the new treatment was started. Further, the timing of the 6 months follow-up visit had a margin of 3 months, leading to a median of 24.6 weeks (interquartile range, 20.1–28.1), fortunately without differences between treatment groups.

Thus, despite potential pitfalls, the conclusions of this study seem reasonable. It is, however, always difficult to translate results at the group level to individual treatment choices. None of the candidate response predictors (reason for switching and number of previous bDMARDs) in this study were helpful. The reason might be related to the small sample size, but ultimately a personalized treatment approach should of course be based on a better understanding of the disease process at the...
individual patient level. This kind of information can obviously not be obtained from an observational trial. The present target population has, however, previously been studied more in depth by Das et al., showing that in RTX non-responders TCZ worked better than ABA and that, compared with responders, RTX non-responders showed higher baseline IL-6 levels and persistent serum IL-6 elevation, despite synovial B-cell depletion [10].

In conclusion, the findings of this observational study [5] are certainly appealing, but it is too early to conclude that TCZ is the treatment of choice in RA patients after unsuccessful treatment with RTX, pending confirmation in randomized controlled trials. A better understanding of the specific disease processes at the individual patient level is needed before optimal bDMARD sequencing in RA can be achieved and rheumatology finally enters the era of precision medicine.

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**References**


