When patients with rheumatoid arthritis fail tumour necrosis factor inhibitors: what is the next step?

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EDITOR'S CHOICE

The advent of biological agents in general and tumour necrosis factor (TNF) inhibitors in particular has dramatically changed the outcomes and outlooks for patients with rheumatoid arthritis (RA).[1] Not only have they expanded the treatment options in quantitative terms, but their combination with methotrexate (MTX) or other disease-modifying antirheumatic drugs (DMARDs) has also led to a quantitative revolution in the therapeutic response of patients with RA: never before have we experienced so profound effects with American College of Rheumatology (ACR) 50% improvement responses being achieved by 40–60% of the patients, ACR70 responses by 20–40%, and remission having become an achievable goal.[2] The efficacy of these therapies relates to all characteristics of RA: disease activity, joint damage and physical function. Alas, these results also reveal that up to 60% of patients with RA do not reach a degree of 50% improvement and, while most patients treated in clinical care who fail these therapies are primary non-responders, some experience reactivation of their disease after an initial major improvement.[3]

In general, TNF inhibitors are used in patients with RA in whom at least one DMARD, usually MTX, has shown insufficient efficacy.[4] Currently, three TNF blockers are available: adalimumab, etanercept and infliximab. While these agents have not been compared head to head, meta-analyses have suggested similar efficacy.[5] However, the overall responsiveness appears to be higher in patients with early disease who had undergone fewer prior DMARD therapies than in those with longstanding disease and many preceding treatment courses.[2] Although not derived from a direct comparison of these two types of patient populations, this has been a consistent finding when considering results of respective trials across all three TNF inhibitors.

Where TNF inhibitors have failed, three treatment options are currently available: the co-stimulation blocker abatacept,[6] the B cell depleting antibody rituximab[7] and the application of another TNF inhibitor.[3 8 9] The first two choices are sensible since the molecules targeted by abatacept and rituximab are different from those targeted by the TNF blockers, and the mechanisms of action therefore appear to be different even if a common final pathways may be affected. The latter choice sounds counterintuitive since one targets a molecule whose inhibition has previously failed, although one reason for loss of efficacy and thus secondary failure of a TNF blocker may be the development of neutralising antibodies against the respective compound, which may not be counteractive to the effectiveness of another TNF inhibiting agent.[10] However, while informative, the data reporting such effects have been primarily based on empirical grounds including clinical experience, small case series and open label or registry data rather than randomised, double-blind, controlled clinical trials.

In this issue of *Annals of Rheumatic Diseases*, yet another option is presented: tocilizumab ***(see page 1516)***.[11] Tocilizumab is a humanised antibody directed to the interleukin (IL)6 receptor (R), which inhibits the binding of IL6 and thus IL6-induced cell activation. It has previously been shown to be active as monotherapy and in combination with MTX[12–14] and appears to also interfere with joint damage.[15] The data revealed by Emery *et al* now expand these findings to a population of patients who had previously experienced therapy with a TNF inhibitor. However, the response rate attained appears to be lower than that in patients who had active disease despite MTX and had not yet experienced a TNF inhibitor.[13] This is in line with the data obtained with rituximab and abatacept in similar patient populations[6 7 16 17] (table 1). Indeed, when considering what was mentioned before for the comparison of longstanding disease with multiple past therapies versus MTX-naïve patients with early disease, one has to appreciate that an increasing proportion of RA patients become refractory to synthetic or biological DMARD therapy with increasing treatment course numbers, in accordance with previous observational data.[18]

On another notion, since IL6 is activated by TNF[19] it may seem illogical that an agent that inhibits a pathway downstream of TNF is efficacious if TNF blockade has failed. However, the logical may not rule biological events. Not only do the data presented by Emery *et al* prove that inhibition of IL6-mediated pathways is efficacious in patients who previously failed TNF blockade, but also other TNF inhibitors appear to be effective in patients who have been previously exposed to TNF blockers according to a recent double-blind, randomised, placebo controlled trial of golimumab.[20]

Table 1 American College of Rheumatology 70% improvement (ACR70) responses obtained with active medication plus methotrexate or placebo plus methotrexate at 6 months in the indicated clinical trials

Agents	MTX-IR	Anti-TNF-IR	Reference(s)
Abatacept/placebo	20/7	10/2	Genovese *et al*, Kremer *et al*[6 21]
Rituximab/placebo	20/5	12/1	Cohen *et al*, Emery *et al*[7 22]
Tocilizumab/placebo	22/2	12/1	Emery *at al*, Smolen *et al*[11 13]
Adalimumab/placebo	21/3	ND	Keystone *et al*[23]
Etanercept/placebo	15/0	ND	Weinblatt *et al*[24]
Infliximab/placebo	18*/2	ND	Lipsky *et al*[25]

*Mean value of all active therapy arms.
IR, insufficient response; MTX, methotrexate; ND, not determined; TNF, tumour necrosis factor.

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Thus, the current study expands the armament against RA, although it does not help us to decide which therapy should come next after TNF inhibitors have been unsuccessfully employed: we just lack predictive markers, be they biological or clinical ones. Decisions will, therefore, be driven by patient preference of modes of application, physicians' experience and risks of the individual compounds. Whether tocilizumab will have a different safety profile than TNF inhibitors may not be discernible from the published clinical trials, but may have to await long-term extension trials and registry data. However, we already know based on the randomised studies that infection, haematological and hepatic toxicity and lipid abnormalities have been observed with tocilizumab.

Nevertheless, there is reason to be excited: once tocilizumab becomes licensed in other countries as it is currently in Japan, we will have further expanded the therapeutic options that in turn will allow an increase in the proportion of RA patients who achieve a good clinical outcome. And with more drugs to come, the time is not too distant when we will attain a state of remission in the vast majority of our patients.

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