

Response to: 'When binary and continuous responses disagree' by Dr Ouyang

We thank Dr Ouyang for his comment on our work.¹

We fully agree that patients stop treatment based, in part, on a lack of satisfactory clinical response. Thus, examining disease activity during follow-up, for instance at 1 year, will be influenced by attrition bias. If patients mostly stop the drug due to inefficacy, comparing only the patients who remain on treatment may lead to the tautological finding that for the people remaining on treatment, the drug is effective.

Another potential explanation for the dissociation between drug retention and other measures of effectiveness could be related to the fact that patients treated with tocilizumab had more previous therapies than patients treated with tumour necrosis factor (TNF) inhibitors.² It is therefore plausible that the lack of other treatment alternatives may influence patients and physicians to keep a less effective treatment.

In addition to ineffectiveness, patients stop their treatment for many other reasons, which are unfortunately not always well documented. In our study, half of the patients in each group stopped for 'other reasons' than effectiveness or adverse events, which may include a combination of reasons. We thus cannot assert the exact motive of drug discontinuation for most patients, which prevented us to draw any conclusion regarding differences between groups. Moreover, one treatment could be more effective than the other, and even if we were to consider only patients who remained under therapy, we could still detect some differences in degree of efficacy.

Though the LUNDEX³ is a solution to account in part for attrition bias, we agree with Dr Ouyang that it is incomplete because it supposes that all patients stopped for ineffectiveness, which may underestimate true effectiveness, and because it does not take into account difference in baseline characteristics. In addition, it does not allow directly statistical hypothesis testing to determine whether a difference is significant or not. In our opinion, new methods and recommendations are thus dearly needed for comparative effectiveness research. Points to consider on this particular subject are currently being developed by a European League Against Rheumatism task force, in which we are actively taking part. We hope that the results of this initiative will help researchers to navigate between the different methods available and improve the quality of future studies.

Regarding Disease Activity Score 28 joints (DAS28) evolution, we found that DAS28 decreased more with tocilizumab as

monotherapy and in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARD) than with TNF inhibitors, but this was statistically significant only for tocilizumab in combination with csDMARDs compared with TNF inhibitors in combination with csDMARDs (coefficient 0.44, $p=0.04$). As discussed in our article, this is consistent with tocilizumab's greater effect on acute-phase reactants.

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