Bias? Not so fast

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Duran *et al*[1] present the results of a literature search performed on a very large number of publications comparing methotrexate (MTX) with a biologic agent. Their literature review eventually yielded 13 published trials for their analysis. The authors were particularly interested in the dose, and route of administration, of MTX. As the efficacy of the new agent studied was being compared with MTX, it is reasonable to determine if the dose of the latter drug was adequate. If it was not, there could indeed have been a bias in the study design, which favoured the new agent. As these trials were all sponsored by the pharmaceutical manufacturers of the new drug, there would certainly be a motive for bias. As any reader of detective novels knows, there must be both a motive and an opportunity to commit the crime being investigated. Following this line of investigative reasoning, pharmaceutical manufacturers have both.

However, a review of the authors' findings raises some troubling questions regarding their methodology and the implications of their findings. First, the recommendations for the maximal dosage of MTX are from a consensus document published in 2009.[2] The recommendations for the total dose of MTX of '25–30 mg' were derived from a Delphi procedure and therefore represent expert opinion, rather than actual findings from a carefully conducted trial. It is of interest that there were no recognisable names in the group who may have been associated with prior research on MTX, or its dosing, but that critique is perhaps a bit unfair. After all, if they are academic experts who considered the problem carefully, their opinions should be respected. But it should be acknowledged this is not what we would call clinical science.

In considering the opinions of the expert panel, it is apparent that some important elements are missing. These missing elements are relevant to the authors' premise that the dose of MTX recommended[2] is indeed optimal. First, how strong is the evidence that there is a considerable difference in clinical response between a mean dose of 20 and 25 mg of weekly MTX? I am unaware of any trials in which patients receiving the former dose were pushed to the higher dose and achieved significant further clinical improvement without experiencing some possible clinical or laboratory toxicity, which may have accompanied the dose increase. There are indeed many patients who can tolerate the higher dose of MTX without toxicity, but there are many who cannot. That is, there is significant interindividual variability in folate pathway single nucleotide polymorphisms, which is well documented.[3 4] To adopt a 'one size fits all' approach to achieving a particular targeted weekly dose of MTX makes no sense, unless one is studying individuals with identical folate genetics. Of course, this is not realistic in human trials, and is absurd to even consider.

Thus, investigators have no way of determining in advance whether or not a patient would be able to tolerate an increase in the dosage of MTX from 19 to 25 mg without experiencing either stomatitis, transaminitis, lethargy, gastrointestinal distress or brain fog. (And for the purposes of the model, we will of course assume complete bioavailability through parenteral administration as the dose of MTX is increased). To be clear, I am unaware of any studies documenting that an increase of MTX, given by the appropriate route of parenteral administration, from a mean of 19–20 to 25 mg does more good than harm. Where do the two theoretical lines of efficacy and toxicity cross? Why not push to 30 or 35 mg? (And we should also consider that a patient withdrawn from a randomised controlled trial for a reason of toxicity is considered a non-responder when analysed using non-responder imputation methodology, which is considered de rigueur for a conservative analysis of outcomes). Thus, it is possible that pushing the dose could achieve the opposite biostatistical effect from the one that is proposed by the authors.

The point is that the balance between maximal efficacy and toxicity is highly variable and likely to be quite different in diverse genetic populations. For instance, anecdotal evidence would indicate that Asians are not able to tolerate higher doses of MTX.

Finally, let's assume that the 2009 consensus document is correct in that optimal MTX responses can be achieved at 25 mg/week, administered parenterally, without significantly increasing toxicity. It is interesting that 7 of the 13 studies included in the authors' review were from 2010 or before. Thus these studies would have had no opportunity to consider the opinions of the expert panel and incorporate higher doses of MTX in their design or implementation. It would have been obviously anachronistic for the authors who led these trials to consider recommendations that had not been published prior to their conduct.

It is thus simply unfair to suggest any preplanned bias, which appears to be part of the authors' implicit message. In fact, the dosages and route of administration employed by these trials reflect the common empirical practice in vogue at the time those trials were conducted.

In summary, there is no evidence of which I am aware that increasing the dose of parenterally administered MTX from 20 to 25 mg is associated with a balance that favours efficacy over toxicity, even with the appropriate use of folate and folinic acid supplementation. The recommendations the authors refer to are opinions, not scientifically derived.[2] They may indeed be correct. But, they could also be wrong.

It is presently unclear where the typical efficacy safety lines cross in different populations. It could very well be that, with decades of empiric experience with the use of weekly MTX, the state of the art has evolved to achieve a maximal routine dose that has achieved a close to ideal balance between clinical efficacy and toxicity. But, only a carefully conducted clinical investigation can establish what that dose may be in genetically disparate populations.

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