

Let's re-examine these MTX points once again

Duran *et al* may have missed my point. If so, this is my fault in that I must not have made it clearly enough. I detected a clear implication of industry bias in the thrust and premise of their findings. To support this position, they extrapolate from studies which purport to illustrate the wisdom of the implications of their review. They correctly point out that one of the references I quoted in the editorial¹ on methotrexate (MTX) folate single-nucleotide polymorphisms (SNPs) leading to different outcomes employed higher doses of MTX and there was little difference in reported toxicity between 15 and 25 mg of the drug when administered parenterally.²

I am sure that Duran *et al* would agree that one can support, or undermine, virtually any premise by selectively focusing on elements of the published literature which buttress and resonate with a particular position. The publication by Schiff *et al*³ which they have used to support their premise that SQ MTX at higher doses is associated with 'no increase in toxicity', was sponsored by a company that manufactures a parenteral form of MTX for the market.

It thus seems that they are selectively quoting a (very good) pharmaceutical-sponsored investigation when it supports their position, but imply bias in design elements in the other pharmaceutical sponsored research that they have analysed in their publication.⁴

Perhaps Duran *et al*⁵ had not recognised the clear irony in their letter by focusing on ref. 4 to support their bias?

Yes, there are studies, some of which I have co-authored, showing that parenteral MTX is associated with improved bio-availability and therefore superior efficacy, but there has never been a study showing that patients would uniformly and predominantly benefit from an increase of 20 to 25 mg of parenterally administered weekly MTX without experiencing more toxicity, over efficacy. This is not a technicality. It is a fact. And, yes, it is possible to point to studies that imply that their particular position does indeed represent what is likely to be true. The key words here are 'imply', and 'likely'.

I think that I would have been happier with the publication by Duran *et al* if they had framed their findings more carefully. That is, it is indeed possible that an ideal dose of MTX, when administered parenterally, was not used in the publications they quote, but before we take an additional step of assigning a negative bias to a large number of previously published trials, we

need to tap into the better parts of our nature by assigning a judicial perspective that could have been improved upon. Duran *et al* have performed a service by focusing on the dose and route of administration issues of MTX in the literature they quote. However, the authors display a 'guilty until proven innocent' mentality in their approach to the analysis of these trials. There is a degree of sanctimony here, which is both unnecessary and distasteful.

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