

Reply to:

Methotrexate and not much harm to the lungs

by H. Yazici

Sirs,

We would like to thank Professor Yazici for his comments on our recent article and we agree with his sentiments and judgement.

While the population under study clearly differs between randomised controlled trials (RCTs) and observational studies (OS), the best available evidence suggests that the quality of the study is more important than the design when testing cause and effect hypotheses (1, 2). Similar treatment effects are seen in multiple illnesses when comparing high quality RCTs to high quality OS (1-4). Counter-intuitively the effect size may be more homogenous in OS (2), possibly due to the selection bias of RCTs.

Physicians may believe RCTS represent a superior form of evidence, but robust data to support this postulate are lacking (1, 2). Limitations of RCTs include short-duration, lack of power to assess rare outcomes and questionable external validity. A systematic review of observational studies of at least 2 years duration (5) also found lung disease attributable to

methotrexate to be very rare, which addresses many of the concerns outlined in his letter.

Thus we agree no single meta-analysis or study will address all the potential concerns and confounders, but we believe our study's strength lies in the complementary nature of the material presented from short-duration RCTS, to the existing evidence from longer duration observational studies, offering robust evidence that methotrexate rarely causes interstitial lung disease, if it does at all.

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