

Methotrexate and not much harm to the lungs

Sirs,

Through a meta-analysis of randomised controlled trials (RCTs) of methotrexate *versus* placebo or another active agent, Conway and colleagues propose that pulmonary harm caused by methotrexate exists but is quite unusual, with a significant but small relative risk of 1.1 (1). Being a practicing rheumatologist, I wholeheartedly agree. However, this does not deter me from pointing out an important limitation, not mentioned by the authors.

As in all forms of research, validity is an important issue in RCTs. External validity, concerns whether the results of an RCT – however flawless the internal validity – are applicable to patients with different demographic, socioeconomic or clinical characteristics. For example, will a drug shown to be useful among a group of patients with mild rheumatoid arthritis still prove to be useful among patients with more severe disease?

Judging the validity of a RCT concerning the harm data is particularly important, for 3 main reasons:

1. RCTs, at least for logistic and financial

reasons, are conducted among a limited number of individuals; a serious adverse event that is reproducibly associated with a certain drug among 1/500 patients will have a little chance of being observed in a trial among 500 patients.

2. RCTs have relatively short duration, and an important adverse event which appears only after a year's use might not be detected in a RCT of 6 months' duration.

3. Finally, the issue related to harm data from RCTs has to do with patient recruitment into such trials. RCTs have the well known limitation of excluding unreliable, incommunicable, side effect prone, multi drug user and co-morbidity burdened patients. The potential to cause interstitial lung disease would lead to exclusion of such patients from a trial in which a patient might receive methotrexate.

Therefore, the meta-analysis of Conway *et al.* overcomes the problem of small numbers, but cannot overcome the problems of short duration and patient selection. This problem is endogenous to RCTs and meta-analyses of any RCT data (2). Therefore, observational data from the time-honoured medical records of everyday practice are needed to provide optimal information concerning the incidence of side effects of any medication.

I want to agree with what is said not only with my heart but also with my cerebrum that pulmonary problems with methotrexate are unusual and I want to point out what I consider is an important caveat.

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