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EDITORIAL

Can we finally exonerate methotrexate as a factor in causing or exacerbating fibrotic interstitial lung disease in patients with rheumatoid arthritis?

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Methotrexate (MTX) is the recommended first-line disease-modifying antirheumatic drug (DMARD) for most patients with rheumatoid arthritis (RA) [1, 2], either alone or in combination with biological therapy to reduce biologic-associated immunogenicity and improve drug survival. Clinically apparent interstitial lung disease (ILD) occurs in 7–10% of patients with RA and 33–61% have subclinical ILD [3–5]. These estimates vary depending on thresholds for investigation, diagnostic methodology and definition of controls. ILD in patients with RA is poorly understood despite being recognised as prevalent, with considerable impact on prognosis, survival and therapeutic approach. Median survival after RA-associated ILD (RA-ILD) diagnosis is only 3–7 years, which is markedly reduced compared with RA patients without ILD and the general population [3, 6, 7]. Growing evidence suggests that RA disease control is of paramount importance, as increased systemic disease activity is associated with increased mortality in patients with RA-ILD [8], therefore making the decision whether to continue or stop an effective drug (MTX) even more important. Discussions continue amongst Rheumatologists, Pulmonologists and Radiologists as to whether MTX is culpable in causing or worsening fibrotic ILD (fILD), despite accumulating evidence to assuage concerns. Here, we describe the current clinical challenge, propose suggestions to guide clinical decision-making within the current state of evidence and discuss future directions to address unresolved questions.

The clinical challenge and reasons for the controversy

In clinical practice, if ILD is diagnosed in a patient receiving MTX, there is often confusion and debate as to whether MTX was responsible for or hastened initiation or progression of ILD and whether it should be withdrawn or continued. Historically, there has been a strongly held view to consider MTX culpable, due to the antecedent temporal association of clinical ILD with MTX treatment even though it is also widely accepted that ILD is an extra-articular manifestation of RA and may occur in MTX-naïve patients. Although guidelines recommend the use of MTX in some fibrotic ILDs e.g. pulmonary sarcoidosis [9], there is considerable reticence around its use with rheumatic-associated ILD.

A recent international survey regarding RA-ILD of Rheumatologists ($n = 354$) and Pulmonologists ($n = 262$) from six continents demonstrated highly variable perceptions of prevalence and mortality, risk factors and medications to avoid in patients with ILD [10]. A sizeable proportion of Rheumatologists (18%) and Pulmonologists (25%) considered MTX use a risk factor for ILD development in patients with RA and the majority would avoid MTX in patients with existing ILD — 61% and 57% respectively [10].

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Questions remain difficult to answer, because chest radiographs, requested pre-MTX as a baseline comparator in case of clinical deterioration and development of MTX-induced pneumonitis, are usually insufficiently sensitive to detect ILD. Without baseline high-resolution computed tomography (HRCT) chest scans (and/or lung function tests) to evaluate for sub-clinical ILD, prior to starting MTX therapy, it is difficult to interpret the rate of progression on subsequent imaging, when respiratory symptoms develop and ILD is diagnosed (Fig. 1). In the absence of large, longitudinal studies with serial assessments in DMARD-naïve patients, the natural history, rate of progression and the expected event rate of RA-ILD is unknown. Confusion may also arise due to conflation between disease-related ILD and drug-related adverse events, e.g., infection or the rare (< 1%), but recognised (and clinically relevant), life-threatening complication of MTX-induced pneumonitis. Methotrexate-pneumonitis usually presents within the first year of treatment with MTX, although late-onset, insidious cases have been reported [11].

The evidence

A systematic literature review to evaluate whether MTX caused progression of fibrotic ILD, found $n = 13$ studies supportive of this claim (albeit with poor quality of evidence and serious to critical risk of bias), and $n = 16$ studies to show that MTX does not cause f-ILD, with high-quality evidence and low to moderate risk of bias [12]. Three studies demonstrated that MTX may improve outcomes in patients with RA-ILD, slowing the rate of progression [12]. Although the authors aimed to interrogate a causal relationship between MTX and fibrotic ILD, most epidemiological studies are caveated by the difficulty in differentiating between cause and association, and therefore assertions regarding 'cause' should be interpreted with caution. In any case, the evidence presented robustly reassures against MTX inducing or exacerbating fibrotic ILD.

A case–control study with a discovery and international replication cohort, examined the association of antecedent MTX exposure with ILD in 410 patients with RA-ILD and 673 patients with RA without ILD [13]. Analysis of

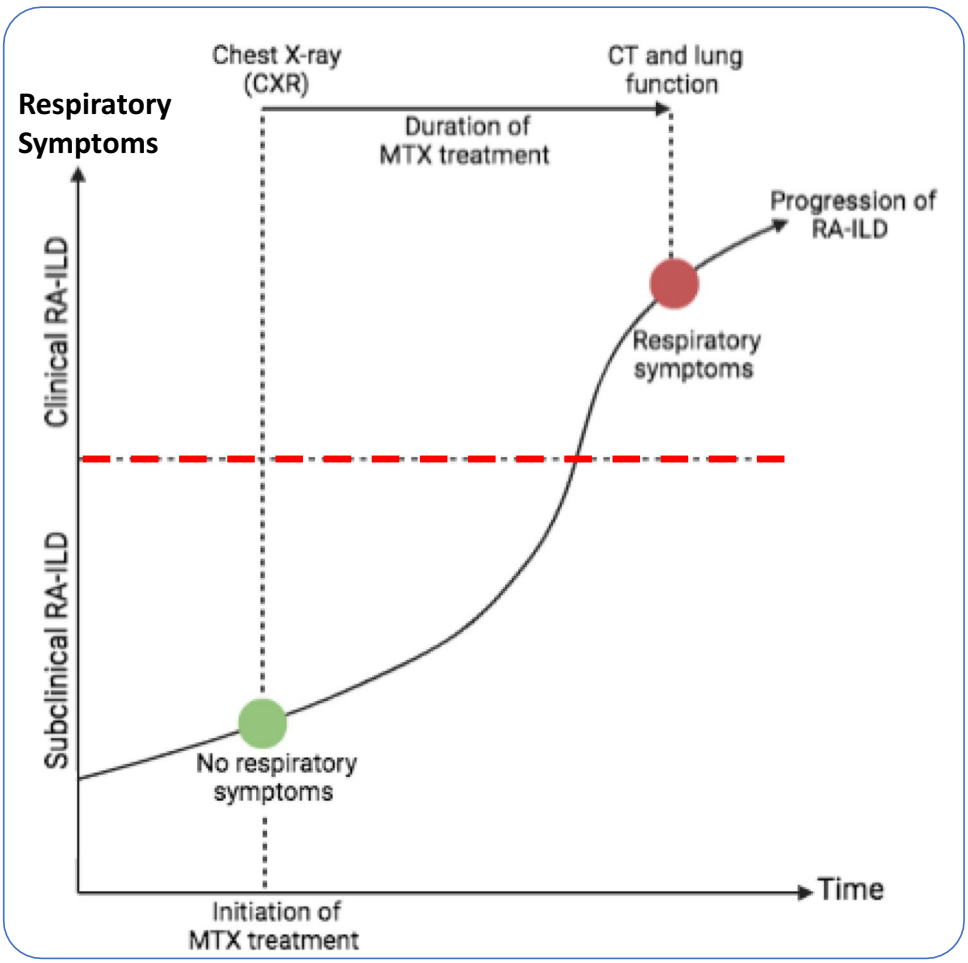

Fig. 1 Clinical course of an individual patient with RA diagnosed with ILD. Y axis shows respiratory symptoms, with a red dotted line indicating threshold for clinical and sub-clinical (asymptomatic) RA-ILD. X-axis indicates time. Patients usually start at the green dot with no respiratory symptoms. A CXR is performed pre-MTX, as a baseline comparator in the event of pneumonitis. When respiratory pathology progresses beyond the red-dotted threshold and respiratory symptoms develop (red dot), a CT chest and lung function test are performed. Historically, ILD diagnosis at the red dot may have been attributed to MTX, due to the temporal treatment period and the absence of a baseline comparator assessments (CT chest/lung function) or a reliable expected event rate of ILD

the discovery cohort revealed a strong inverse relationship between MTX exposure and RA-ILD (adjusted OR 0.46, 95% CI 0.24–0.90; $p = 0.022$), which was confirmed in the replication samples (pooled adjusted OR 0.39, 95% CI 0.19–0.79; $p = 0.009$). Using both the derivation and validation samples, the combined adjusted OR was 0.43 (95% CI 0.26–0.69; $p = 0.0006$). ILD diagnosis in RA-ILD was significantly delayed in MTX ever- compared to never-users (11.4 ± 10.4 years and 4.0 ± 7.4 years, respectively; $p < 0.001$). This study suggested that MTX use is not associated with an increased risk of RA-ILD in patients with RA and that ILD was detected later in MTX-treated patients [13]. Important caveats include that study was retrospective and that MTX prescription was less likely in patients with insidious ILD or respiratory symptoms. In a multi-centre prospective study of two early RA inception cohorts of 92 eligible ILD cases, 39 occurred in 1578 (2.5%) MTX exposed and 53 in 1114 (4.8%) non-MTX exposed cases [14]. RA-ILD cases only developing after any conventional synthetic DMARDs ($n = 67$) showed MTX exposure not to be associated with incident RA-ILD (OR 0.85, 95% CI 0.49 to 1.49, $p = 0.578$).

In general, there is a growing body of literature providing reassurance regarding respiratory adverse events and MTX. A systematic literature review studied the relative risk of pulmonary adverse events in patients treated with MTX and found 7 studies, with 504 respiratory adverse events in 1630 participants [15]. MTX was not associated with an increased risk of adverse respiratory events (relative risk 1.03, 95% confidence interval 0.90 to 1.17), respiratory infections (1.02, 0.88 to 1.19), or non-infectious respiratory events (1.07, 0.58 to 1.96) [15]. No pulmonary deaths occurred in this study.

It is important to note that clinicians must not forget the clinically relevant and recognised, albeit rare, event of MTX-pneumonitis. For example, pre-specified analysis of pulmonary adverse events, in the randomised placebo-controlled Cardiovascular Inflammation Reduction Trial (CIRT) ($n = 2391$), there were 7 cases of possible pneumonitis (0.3%) in the low-dose MTX group (target dose 15–20 mg/week), compared with 1 (< 0.1%) in the placebo group [16].

The impact:

The impact of the decision of whether to start, switch or stop a drug for an individual patient, as well as at the population level, is not insignificant. Inappropriate cessation of MTX (attributed to ILD cause/exacerbation), may result in depriving a patient of an effective drug that may be beneficial for both articular inflammation, as well as potentially protective against progressive lung disease. Indeed, a recent study in 227 patients with RA-ILD demonstrate the importance of RA disease control, as moderate-severe disease activity was associated with significantly increased risk of mortality [8]. Divergent views and/or poor communication between specialties, as to whether MTX is responsible for causing or exacerbating fibrotic ILD, may adversely affect the therapeutic alliance between the doctor-patient, as mixed messages may lead to distrust and poor adherence to prescribed medications, extending beyond MTX.

Suggested management approach

We would suggest that the management of all patients with RA and suspected or established ILD should be discussed in an ILD multidisciplinary team (MDT), ideally attended by Respiratory physicians, Rheumatologists and Radiologists. There is growing evidence to support that MTX does not cause fibrotic ILD and may even provide some protection against ILD development/propagation. MTX is a critical drug in controlling RA disease activity and given accumulating observations that RA systemic disease control is important in limiting progression of ILD, it is important to preserve effective drugs.

In a patient with pre-existing lung disease, we would recommend an assessment of respiratory reserve before starting MTX, to determine whether a patient could cope with potential decompensation in the (albeit rare) event of pneumonitis occurrence, given that pre-existing lung disease is a risk factor for the development of MTX-pneumonitis [17, 18]. A careful risk:benefit analysis with shared decision-making regarding MTX initiation in patients with moderate-severe ILD is warranted, with evaluation of symptoms, exercise tolerance, lung physiology and extent of change on HRCT chest scanning. It is difficult to set fixed thresholds for clinical decision-making algorithms and each patient's management should be based on a MDT discussion.

Summary and future directions

As MTX is the most commonly prescribed DMARD for RA and given that ILD (clinical/subclinical) in RA is not uncommon, the question surrounding the potentially contributary role of MTX in ILD, frequently arises in clinical practice and is an important question to address robustly. Despite the growing body of evidence to refute the role of MTX in fibrotic ILD, the issue remains live and there seems to be subconscious resistance to detach from the dogma of assigning blame to MTX. Whilst the temptation may be to revert to hard-wired heuristics relying on anecdotal experience and historical eminence-based routine, we all have a responsibility to challenge assumptions, and practice evidence-based medicine. A concerted educational effort to ensure consistent messaging within- and cross- speciality (Pulmonology, Rheumatology, Radiology and others) is

required to finally retire the age-old debate and exonerate methotrexate, to allow us to move forward to focusing on creating the evidence-base to guide prescribing.

Declarations

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