

## Methotrexate pulmonary toxicity, what's after?

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### ABSTRACT

Methotrexate is a potent drug in rheumatoid arthritis; however it has variety of side effects. This review will illustrate its pulmonary toxicity. In cases of suspected methotrexate lung injury the clinician has to decide if methotrexate treatment has to be discontinued and which is the best therapeutic approach. The use of additional tests, such as pulmonary function tests, high-resolution computed tomography scan, bronchoalveolar lavage fluid and surgical lung biopsy to support the diagnosis. The present review will provide as well therapeutic decisions after discontinuation of methotrexate in cases of pulmonary toxicity.

**Key words:** methotrexate, pneumonitis, fibrosis, toxicity, rheumatoid arthritis.

**Abbreviations:** Rheumatoid arthritis (RA), interstitial lung disease (ILD), cyclic citrullinated peptide (CCP), rheumatoid factor (RF), pulmonary function tests (PFT), Bronchioalveolar Lavage (BAL), tumor necrosis factor (TNF), usual interstitial pneumonia (UIP), bronchiolitis obliterans with patchyorganizing pneumonia (BOOP).

### 1. INTRODUCTION

Rheumatoid arthritis (RA) is not only a joint disease; it is a systemic disease with extra-articular manifestations including pulmonary involvement (Cortet et al. 1997). Methotrexate is used in RA treatment (Jasvinder et al. 2012) and can cause pulmonary toxicity manifestations that can be difficult to distinguish if the abnormalities secondary to RA or methotrexate for which the approach of each condition is different (Craig et al. 1987). This paper will focus on methotrexate lung injury diagnosis and management.

### 2. DISCUSSION

RA is a common systemic disease with a prevalence ranging from 0.5% to 2%. Pulmonary involvement is a well known extra-articular manifestation of RA (Cortet et al. 1997), and many factors are associated with RA related interstitial lung disease (ILD) such as anti-cyclic citrullinated peptide (CCP) antibody, Male gender, smoking and rheumatoid factor (RF), (Kelly et al. 2014), methotrexate is recommended for RA treatment (Jasvinder et al. 2012), despite being an excellent drug in RA, it has a variety of side effects e.g: haematopoietic causing cytopenia

and hepatotoxic, transient elevation of liver enzymes, nausea, vomiting and respiratory complications (Zachariae et al. 1990; Gispen et al. 1987).

Methotrexate pulmonary toxicity in RA is a confusing dilemma, as RA itself can involve the lung other than methotrexate side effect. Pulmonary manifestations in RA varying from pleural effusions, pleural thickening, mottling, reticulation, and chronic fibrosis, Caplan syndrome (Aronoff et al. 1955). Pathologically, five different groups based on histologic patterns were identified: pulmonary rheumatoid nodules, usual interstitial pneumonia (UIP), bronchiolitis obliterans with patchy organizing pneumonia (BOOP), lymphoid hyperplasia, and cellular interstitial infiltrates (Yousem et al. 1985).

Unfortunately, no specific markers exist to differentiate drug-induced lung disease from other pathologic processes., Methotrexate as well affects the lungs The major clinical syndromes ascribed to it include hypersensitivity pneumonitis and chronic alveolitis/fibrosis (Craig et al. 1987), so American College of Rheumatology recommends baseline chest radiograph, Monitoring for toxicity should be done every 4 to 8 weeks. Systems review and physical examination should include monitoring for symptoms or signs of pulmonary toxicity (shortness of breath, cough, rales), (Simms et al. 1996). There are certain risk factors can predict methotrxate lung toxicity e.g: older age, diabetes, rheumatoid pleuropulmonary involvement, previous use of disease-modifying antirheumatic drugs, hypoalbuminemia and the presence of preexisting lung disease (Graciela et al. 1997; Golden et al. 1995) but unfortunately methotrexate induced lung disease can't be predicted usually as it can occur with very low dose as low as 7.5mg weekly and in a very short duration as short as 1 week (Cannon et al. 1997) and with different methods of administration, oral, intravenous, intramuscular and intrathecal administrations (Cannon et al. 1983).

Methotrxate induced lung disease usually present with shortness of breath, cough, and fever. Most often a sub-acute process, in which symptoms are commonly present for several weeks before diagnosis (Kremer et al. 1997). A Diagnostic criterion was proposed by Searles, McKendry for methotrexate pneumonitis (Clearkin et al. 1997).

- \* acute onset dyspnoea
- \* fever over 38°C
- \* tachypnoea > 28 breaths/min
- \* radiological evidence of pulmonary interstitial or alveolar infiltrates
- \* white cell count < 15 x 10<sup>9</sup>/l
- \* negative blood and sputum cultures
- \* pulmonary function tests (PFT) demonstrating a restrictive defect and reduced diffusion capacity
- \* admission PaO<sub>2</sub> < 7.5 kPa on air
- \* biopsy evidence of bronchiolitis or interstitial pneumonitis with giant cells, without evidence of infection

Definite diagnosis: > 6 criteria met

Probable diagnosis: 5 criteria met

Possible diagnosis: 4 criteria met

Bronchoalveolar Lavage (BAL) may be helpful in the evaluation of patients suspected of having methotrexate induced lung injury and will show presence of large numbers of lymphocytes. This further supports the hypothesis that immune mediated mechanisms may play a part in the pathogenesis of methotrexate induced lung injury in some patients (Akoun et al. 1987).

However, it is yet difficult to differentiate if biopsy was not obtained as radiology & PFT in RA may have similar findings to that with methotrexate lung injury (Remy-Jardin et al. 1994; Hyun-Kyung Lee et al. 2005). Withdrawal of methotrexate and supportive care are the mainstays of therapy. In cases in which active inflammation causes significant derangement of gas exchange, corticosteroids are warranted (Craig et al. 1987). A patient who recovers from methotrexate lung injury should not be re-treated with it (Kremer et al. 1997).

The next big dilemma to the rheumatologist comes now, how can we treat our patients after stopping such potent drug? As an alternative leflunomide can be used instead of methotrexate if not tolerated or contraindicated (Smolen et al. 2010), but Unfortunately, reports of ILD associated with leflunomide use are likely the result of channeling of high-risk patients to leflunomide treatment, particularly those with a history of methotrexate use or preexisting ILD unlike Patients with no history of ILD and no previous methotrexate use show no excess risk of developing ILD with leflunomide treatment (Suisa et al. 2006).

The next step in managing RA is to start a biological agent, anti-tumor necrosis factor (TNF), rituximab, abatacept or Tocilizumab, preferably anti-TNF agent (Smolen et al. 2010).

However, anti-TNF not yet a safe drug to be used in a patient with underlying lung disease and data are really conflicting, as anti-TNF biologics may improve pulmonary fibrosis in the setting of RA-ILD (Vassallo et al. 2002; Bargagli et al. 2004). Unfortunately, they can worsen lung disease in RA patients and this phenomenon has been reported with different anti-TNF agents (Kramer et al. 2002; Schoe et al. 2006; Lindsay et al. 2006) which can be fatal (Ostor et al. 2004). And finally fortunately, there are safe biologics to be used as ILD is not associated with rituximab, abatacept or Tocilizumab (Powers et al. 2014).

### 3. CONCLUSION

Methotrexate induced lung injury is a great Dilemma to the rheumatologist, first issue is to make such a diagnosis, is it methotrexate induced?. As the abnormalities may be secondary to RA itself rather than being attributed to the drug and second issue is after making such diagnosis and stopping methotrexate, what another potent agent will be used instead of it for controlling RA in the setting of ILD?

### DISCLOSURE STATEMENT

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