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*Original Research Article*

# Is chronic interstitial lung disease a complication of long-term methotrexate use? 10 years study investigates

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***Abstract:*** Methotrexate use is known to be associated with acute pneumonitis, an acute hypersensitivity reaction. Historically there have been concerns that methotrexate may be a cause for chronic pulmonary fibrosis. We wanted to study the effect of long-term methotrexate use on the incidence of chronic interstitial lung disease (ILD). All patients commenced on methotrexate in our unit between 2004–2007 were evaluated retrospectively from our hospital trust records after 10 years of follow up. The incidence of pulmonary fibrosis was based on clinical presentation with symptoms of dyspnoea and confirmation by means of pulmonary function tests and detection of pulmonary fibrosis on high resolution computed tomography of the chest. Data for 129 patients were analyzed. 64/129 (50%) patients completed 10 years of methotrexate treatment at follow up. Methotrexate was used for various indications, most commonly rheumatoid arthritis (106). Four male patients developed chronic ILD. All cases were in patients with Rheumatoid Arthritis and the incidence in Rheumatoid Arthritis subgroup was 4/106 (3.8%). There was no association of symptomatic ILD to the duration or dose of methotrexate therapy. All cases of ILD were in male patients with rheumatoid arthritis, they had usual interstitial pneumonia pattern ILD typical of Rheumatoid Arthritis associated ILD and the incidence rate was comparable to previous studies on rheumatoid arthritis associated with interstitial lung disease (4%-7%). This adds to previous publications from shorter-term studies showing a lack of evidence that MTX could be causing chronic ILD.

***Keywords:*** Methotrexate; chronic pulmonary fibrosis; interstitial lung disease; rheumatoid arthritis

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## Key message:

1] Ten years study of methotrexate use finds no suggestion that MTX causes chronic ILD.

2] Incidence of symptomatic RA-ILD is 3.8% over 10 years of follow up.

## 1. Introduction

Methotrexate (MTX) is an immunosuppressant that counteracts the action of folic acid. With the growing use of methotrexate, methotrexate related pulmonary complications were reported for its use in childhood leukaemia, rheumatoid arthritis, psoriasis, and other



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cancers.

The non-infective lung complications in these reports can be divided into acute and chronic. Methotrexate pneumonitis is an acute complication. It is usually associated with non-specific features such as fever, dry cough, hypoxia, and negative cultures. Imaging demonstrates interstitial infiltrates. On chest high resolution computed tomography of the (HRCT) the infiltrates are throughout the lung fields with a ground glass appearance. These findings are not exclusive to methotrexate and are also seen in other drug hypersensitivity reactions. Several authors have proposed criteria to help define these complications[1,2].

3 case report publications published pre 1990, with a total of five patients, have suggested a link between methotrexate and chronic pulmonary fibrosis (PF). The reports have insufficient clinical details to confirm methotrexate as a cause of chronic ILD and to exclude other causes of the lung disease[3-5]. Longitudinal cohort studies have refuted that methotrexate causes chronic pulmonary fibrosis. Dawson *et al*. conducted a study where HRCT and serial pulmonary function tests were performed over a 2-year period on rheumatoid patients receiving low dose methotrexate. This study shows no association between methotrexate and the development of ILD[6]. Pulmonary function-based studies have also been reassuring[7,8]. Moreover, studies on methotrexate use in Wegener's granulomatous vasculitis[9] and sarcoidosis[10], both with predominant lung manifestation showed no concern.

Distinguishing between different types of interstitial lung disease and its aetiology is challenging and specialised. To complicate matters, it is a known extra-articular manifestation of rheumatoid arthritis. The incidence of ILD in rheumatoid arthritis is 4%-7%[11]. Appearance on chest HRCT is discriminatory and is essential in assessing patients with ILD[12].

Two meta-analyses of 1630[13] and 8584[14] patients in randomized controlled trials found no evidence of non-infective respiratory disease being associated with MTX. Whilst being powerful in terms of patient numbers, and also for being useful for studying the effects on the lung in a variety of conditions (with or without known association with lung disease), those studies were limited by short follow up periods of only 1 to 2 years. Despite the published evidence, some clinicians still have conceptual concerns that methotrexate use can cause chronic PF as chronic hypersensitivity pneumonitis can present with a UIP pattern ILD[15]. We wanted to add to the published literature by studying the effect of 10 years of methotrexate use on the incidence of chronic ILD.

# 2. Methods

All patients consecutively commenced on methotrexate in St Helens and Knowsley Trust Hospitals rheumatology unit from 2004-2007 inclusive were evaluated retrospectively from our NHS trust database. Data collection was from methotrexate proforma completed by educating nursing staff, electronic case notes and radiological images. American Rheumatism Association 1987 revised criteria were used to define patients with RA. Treatment decisions were made prior to the data evaluation. Data evaluation was undertaken to allow for a 10-year follow up.

The incidence of PF was based on clinical presentation with dyspnoea and confirmed by chest x-ray and chest HRCT. Confirmation of ILD type was provided by a second opinion with an ILD radiology expert.

Case records were interrogated for clinical features, corticosteroids, DMARDs, and biologic treatments and respiratory diagnoses including recent chest imaging reports.

Mann-Whitney U test was used to compare quantitative data and Chi-squared was used to compare frequencies. Statistical analysis was performed using SPSS 25.0 (IBM, Armonk, NY, USA).

# 3. Results

Data for 129 patients were analyzed, in which 86 patients (67%) were female and 64 (50%) patients completed 10 years of Methotrexate treatment at follow up. Methotrexate was used for various indications; RA (106), inflammatory arthritis (IA) (7), psoriatic arthritis (6), mixed connective tissue disease (2), spondyloarthropathy (2), for one patient with each of the following conditions: PMR, monoarthritis, giant cell arteritis, reactive arthritis, sarcoidosis, polymyositis and

scleritis. Twenty eight were current cigarette smokers. All except one patient's initial dose of methotrexate was 10 mg orally weekly. Folic acid 5 mg three times weekly was co-prescribed with this as standard.

Fifty-nine out of 106 (56%) patients with RA were started on methotrexate within 1 year of diagnosis and 46/106 (44%), this was delayed by 1 year or more. One patient had a polymyalgic presentation of RA, MTX was introduced prior to the diagnosis of RA being made. Seventy four (70%) were known to be seropositive for Rheumatoid factor or AntiCCP antibodies and 59 had erosive disease when commencing MTX. Twenty-three patients were transferred to subcutaneous MTX during follow up, 14 were on regular prednisolone, Twenty-one (16%) patients progressed to biologic therapy, ten patients continued with Methotrexate treatment alongside biologics.

Four patients developed symptomatic chronic interstitial lung disease. All cases were in patients with Rheumatoid Arthritis and the incidence in Rheumatoid Arthritis subgroup was 4/106 (3.8%). All patients with symptomatic ILD were male, which was statistically significant ($p = 0.01$). All patients had usual interstital pneumonia pattern ILD. Mean duration of RA at the time of onset of pulmonary fibrosis (PF) was 7.7 years (2-15). The mean duration of methotrexate use before the onset of ILD was noted was 6 years (2-10). The mean time period of methotrexate use before the onset of ILD was noted was 4.2 years (2-8). There is no association of ILD diagnosis and methotrexate exposure from analysis of methotrexate treatment duration, average or final dose of methotrexate therapy. This is shown in **Table 2**.

| | **ILD Patients (4)** | **No ILD (125)** | **P-value** |
|---|---|---|---|
| **Mean final dose MTX/week (range in brackets)** | 18.12 mg (10-25mg) | 14.7 mg (2.5-30mg) | P=0.27 |
| **Mean Average dose MTX/week(range in brackets)** | 13.8mg (10-16.25mg) | 12.4 mg (6.25-22.5mg) | P=0.32 |
| **Average duration of MTX therapy (range in brackets)** | 6 yrs (2-10 yrs.) | 8 yrs (0-13 yrs.) | P=0.25 |
| **<5 yrs duration of MTX** | 2 | 39 | See below |
| **>5 yrs duration of MTX** | 2 | 86 | P=0.38 |
| **10 yrs. MTX** | 1 | 63 | P=0.41 |

**Table 1.** MTX use and PF

| | | | | |
|---|---|---|---|---|
| **Age** | 73 | 63 | 61 | 68 |
| **MTX duration (years)** | 2 | 3 | 10 | 9 |
| **Time to commence MTX after RA diagnosis (years)** | <1 | 7 | 3 | 7 |
| **Reasons for stopping MTX** | CVA/Death | Physician choice | N/A-Continued | Physician choice |
| **Initial dose (mg/week)** | 10 | 10 | 10 | 7.5 |
| **Final dose (mg/week)** | 10 | 20 | 17.5 | 25 |
| **Diagnosis** | RA | RA | RA | RA |
| **RF** | 0 | 1 | 1 | 1 |
| **Ant-CCP** | 0 | 1 | 1 | NK |
| **Other Medications** | | Rituximab | | Prednisolone |
| **Outcome** | Died(CVA) | Died(Resp) | Alive | Died(Cancer) |
| **Other co-morbidities** | COPD | Severe COPD | | Transitional Cell Cancer ureter |
| **Smoker** | X | Smoker | X | Never |

**Table 2.** The details of the patients who developed symptomatic ILD

Interestingly a majority of patients (75%) who developed ILDs had started the methotrexate treatment at least a year after the diagnosis of RA. Due to the small number of cases, this does not reach statistical significance ($p = 0.22$) to conclude if early commencement of methotrexate may have led to a better outcome.

One of the patients with ILD is still alive today and remains on methotrexate. One died predominantly due to complications of COPD, his methotrexate was withdrawn 3 years prior to death. No benefit was reported from the patients who had their methotrexate stopped. Two patients died due to unrelated causes.

No cases of methotrexate pneumonitis occurred. No acute exacerbations of ILD were reported.

# 4. Discussion

In this 10-year study of 129 patients, half the patients remained on MTX for 10 years and only 4 patients developed symptomatic ILD. All cases of ILD were in male patients with RA. Development of symptomatic ILD was associated with being male but it was not related to dose or duration of MTX therapy. All ILD cases were UIP pattern ILD and the incidence in RA patients was 3.8%.

That we had patients where methotrexate was being used for conditions not associated with ILD gives further evidence that MTX does not cause chronic ILD, as these patients did not develop ILD. That the ILD is UIP, the type most commonly found in RA[16] is also supporting that the ILD we found is due to the underlying RA and not methotrexate. That no clinical benefit was reported from stopping the methotrexate in the patients with ILD is additional evidence that methotrexate was not the cause of the ILD, as would be anticipated if it was a chronic hypersensitivity pulmonary reaction. Additionally there is the continued benefit, in terms of survival, in the patient remaining on MTX.

Three studies have looked at the incidence of ILD in patients with RA. Bongartz *et al*.[11] followed a population-matched incidence cohort of patients from 1955 to 1995, 582 patients with RA and 603 patients without RA were followed up for a mean period of 16.2 years. They found 128 patients had MTX at some time and 46/582 RA patients developed ILD (7.7%), 23/582 (4.0%) had definite ILD. In the control group, 0.9% developed ILD. The 10-, 20- and 30-year cumulative incidence rates for all ILD in RA patients was found to be 3.5%, 6.3%, and 7.7%, respectively (adjusted for the competing risk of death), conveying a lifetime risk of close to 10%. The median survival of RA patients after diagnosis was 2.6 years. Koduri *et al*.[17] followed 1460 patients with early RA who were recruited into the Early RA Study (ERAS), from 1986 to 1998. Half of the 52 patients with ILD had ILD at baseline (12) or within 3 years and the annualized incidence was 4.1/1000 and the 15-year cumulative incidence was 62.9/1000. The most commonly used DMARD was sulphasalazine (70%) and MTX (42%). Median survival once diagnosed with ILD was 3 years. They found no adverse association between RA-ILD and MTX. Kiely *et al*. investigated ILD specifically in this and the Early RA network (ERAN) cohort. Recruitment was from 1986 to 2012 with 2701 patients with up to 25 years follow up, they had a large control group of 1114 patients not exposed to with methotrexate. Prevalence of ILD was 3.7%. Again no association was found between ILD and MTX use and like ourselves there was a suggestion (but without statistical significance) that MTX may delay presentation of RA-ILD.

We used symptomatic ILD as our outcome measure for ILD in an outpatient population, which allows our study to be comparable with their studies. We had specialist ILD radiology review and detailed clinical details available for our cases of ILD. Treatment of RA was different between our study and earlier studies, with methotrexate initiated earlier in our study. However, the incidence of ILD is remarkably consistent across all the studies, which supports the conclusion that the ILD is related to the RA disease and not DMARD therapy.

The majority of patients (75%) who developed ILD, had a delay in initiation of methotrexate treatment by at least 1 year from the time of diagnosis. Rojas-Serrano[18] *et al*. found MTX given as a treatment for 52/78 RA-ILD with was strongly statistically associated with improved survival outcome which would be in keeping with our hypothesis that the early introduction of MTX may be beneficial in delaying presentation of RA-ILD.

As with retrospective case studies our study has some limitations. A small number of ILD cases means we are unable to identify continuous variables as statistically significant clinical risk factors or possible confounding factors. However, this low number of symptomatic cases is also demonstrating the low incidence of symptomatic ILD in a population where methotrexate is being frequently used for a long period of time. We didn't have a suitably sized control group, we had anticipated patients who didn't continue with MTX treatment to provide that group but only seven patients took MTX for less than a year. It is now Rheumatologists first line treatment of choice and in our unit is tolerated well in the long term. The main time that Rheumatologists do not prescribe methotrexate in patients with RA is if they have severe lung disease that would suggest they wouldn't have the reserve to survive methotrexate pneumonitis; or when patients are so symptomatic with their pre-existing respiratory disease they couldn't distinguish it from an acute pneumonitis reaction. As such we cannot identify a suitable control group that has not been exposed to methotrexate. We looked to combine a group of patients with relatively low methotrexate exposure and to be adequately powered, this gave us a 5-year MTX treatment cut off. We found patients who took MTX for more or less than 5 years had no clinical or statistical association between duration of their MTX therapy and with the development of symptomatic ILD.

# 5. Conclusion

This study confirms the finding from previous high-quality shorter-term studies that there is no evidence suggesting long term use of methotrexate causes chronic ILD.

Clinicians should be reassured they can continue prescribing MTX to patients who are found to have RA-ILD once infection if present, has been treated and MTX-P excluded; as the ILD is due to their underlying RA and not their methotrexate therapy.

## Conflict of interest

The authors declare no conflict of interest.

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