POSSIBLE ASSOCIATION OF LOW DOSE METHOTREXATE THERAPY FOR RHEUMATOID ARTHRITIS WITH CHRONIC PULMONARY FIBROSIS

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KEY WORDS: COMPLICATIONS OF METHOTREXATE THERAPY FOR RA, CHRONIC PULMONARY FIBROSIS.

ABSTRACT

Hypothesis: *Low dose methotrexate (MTX) treatment is used extensively as a second-line therapy in RA. Two forms of interstitial lung diseases are related to low dose MTX therapy, the first is acute methotrexate pneumonitis which is a life-threatening complication that occurs in less than 10% of RA patients treated with MTX. The other interstitial lung affection is chronic pulmonary fibrosis (PF).*

Aim of work: *To evaluate whether chronic PF can be a significant complication in RA patient treated with low dose methotrexate (MTX).*

Subjects: *The study was performed on 40 RA patients who fulfilled the American College of Rheumatology classification criteria for RA, The patients were classified into two separate groups. The first group consisted of 20 RA patients who were being treated with low dose MTX at the time of initial assessment, while the other group comprised another 20 RA patients who were not being treated with MTX, but treated with second-line therapy other than MTX.*

Methods: *Pulmonary function tests were performed for all patients at the time of initial assessment using the standard protocol. All patients underwent HRCT chest scanning. Supine views were taken in serial slices 10 mm apart and 1 mm in width. According to the study design, the patients were followed over 18 months from the time of the initial assessment. Clinically, the patients were assessed regularly at time intervals*

of 3 months particularly for development of any chest illness together with the patient compliance of drug therapy and its effect on disease. Follow up chest radiographs and HRCT were performed at the end point. The age of the patients and disease duration in the MTX group were 52.1+ 2.9 years and 8.9 ± .2 years respectively while in the other group they were 50.8 ± 2.1 years and 9.2 ± 5.1 years respectively.

Results: *Pulmonary function results at baseline assessment expressed no significant differences between the two groups with p value > 0.05. On initial HRCT chest scanning, 3 patients were found to have PF interstitial lung disease pattern, two of them were being treated with MTX. There was no significant difference in the dose and duration of MTX treatment between the two RA patients treated with MTX and has PF on initial evaluation and those who were being treated with the drug and had no evidence of PF on HRCT on chest scanning at the initial evaluation.*

Change in pulmonary function tests from the time of initial assessment to the end of the study was not clinically or statistically significant in both groups (p value > 0.05). Furthermore, there was no clinical or pulmonary function evidence that MTX had any deteriorating effect on PF detected in two patients on initial assessment even when compared with the patients who were not being treated with it.

Conclusion: *This study showed no clinical, physiological or radiological evidence that low dose MTX treatment used successfully in treatment of RA is associated with chronic fibrotic lung disease.*

INTRODUCTION

Rheumatoid arthritis *(RA)* is a chronic inflammatory disease characterized by hyperplasia of the synovium with excess inflammatory cells leading to progressive destruction of the joints together with extraarticular autoimmune manifestations in which several cytokines as many interleukins and tumor necrosis factor-α are involved in almost all aspects of articular inflammation and destruction[1].

Two main classes of drugs are used in the treatment of RA, non-steroidal anti-inflammatory drugs *(NSAIDs)* and disease modifying antirheumatic drugs *(DMARDs).* In the last group, combination therapy is increasingly used in the treatment of RA, and most of the studies have shown that some combinations are superior to monotherapy[2]. By

introducing DMARDs earlier in the disease course, it is possible to prevent damage and disability that otherwise would occur and to stabilize joint function as near to normal as possible. So these agents could improve patient survival and increase the number of years that patient enjoys a better quality of life[3].

Low dose methotrexate *(MTX)* treatment is used extensively as a second-line therapy in RA. This antimetabolite agent is an inhibitor of folic acid synthesis that inhibits rapidly proliferating cells in the S phase and suppresses cell mediated and humoral immunity as well as inflammation via inhibition of pro-inflammatory cytokines[4].

Two forms of interstitial lung disease are related to low dose MTX therapy, the first is acute methotrexate pneumonitis which is a life-threatening complication which occurs in about < 10% of RA patients treated with MTX[5]. The other interstitial lung affection is chronic pulmonary fibrosis *(PF)* which is reported in patients treated with MTX for psoriasis despite absence of any recognized association between interstitial lung disease and this dermatologic disorder[6].

Aim of study

The aim of this study was to evaluate whether chronic PF can be a significant complication in RA patient treated with low dose MTX protocol. It depends particularly on evaluation of the included patients with high resolution computer tomography *(HRCT)* which has been proved to be a very useful non-invasive diagnostic tool for interstitial lung disease[7].

SUBJECTS AND METHODS

Subjects:

This study included 40 RA patients fulfilling the American College of Rheumatology classification criteria for RA[8]. The patients were classified into two separate groups. The first group *(group I)* was consisted of 20 RA patients who were being treated with low dose MTX at the time of initial assessment; the MTX mean dose and duration of use were 10 $\pm$ 2.5 mg and 28 $\pm$ 18.8 months respectively, while the other group *(group II)* comprised another 20 RA patients who were not being treated with MTX. Treatment was with second-line therapy other than MTX; NSAIDs, corticosteroids or simple analgesics. All the patients were selected from the Outpatient Department of Dr. Erfan General Hospitals, Jeddah, Kingdom of Saudi Arabia, in the period from January2001 to June 2002.

Exclusion criteria were pregnancy or planning for such, smoking and presence of history of interstitial lung disease as extrinsic allergic alveolitis, pneumoconiosis, asbestosis or Caplan's syndrome.

Methods:

The included patients were subjected to detailed clinical assessment. This included thorough history particularly any previous chest illnesses or risk factors related to these illnesses as medications, occupations and domestic animal exposure. Also detailed history of the current RA was taken particularly, the duration of RA, presence of extraarticular complications, criteria of disease activity and history of previous and current medications. A detailed clinical examination was performed and included chest radiographs.

Pulmonary function tests were performed for all patients at the time of initial assessment using the standard protocol *(Respirometer 22 [Sensor medics-USA]).* They consisted of forced expiratory volume in 1 sec. *(FEV_1),* forced vital capacity *(FVC),* and diffusion capacity for carbon monoxide *(DLCO).* The highest of the three reproducible values was used and expressed as the percentage of the predicted values for age, height and gender according to standardized tables[9]. For DLCO, the standard for normal pulmonary function was defined as diffusion capacity for CO greater than 75% of the predicted value.

All patients underwent HRCT chest scanning *(Hi-speed-Ge-Milwaukee.USA)* in the supine position taken in serial slices 10 mm apart and 1 mm in width. Interpretation of HRCT regarding pulmonary fibrosis was according to these criteria; ground-glass appearance was defined as a patchy or diffuse increase in lung density that didn't obscure pulmonary vasculature[10]. A reticular pattern was defined as the presence of intersecting lines forming anything from a fine network to frank honeycombing that was thought to be typical of usual interstitial pneumonia[11]. Other HRCT features denoting pulmonary parenchymal affection of RA were primarily looked for prior to therapy including rheumatoid necrobiotic nodules, BOOP, bronchiectasis and pleural effusion/thickening being not related to MTX pulmonary parenchymal affection.

The included patients according to the study design were followed over 18 months from the time of the initial assessment. Clinically, the patients were assessed regularly at time intervals of 3 months particularly for development of any chest illness together with assessment of the patient compliance of drug therapy and its effect on disease course. Also, follow up chest radiographs and HRCT were performed at the end point of the study.

RESULTS

All patients' data are expressed in mean ± SD. The age of the patients and disease duration in the MTX group were 52.1± 2.9 years and 8.9 ± 4.2 years respectively while in the other group were 50.8 ± 2.1 years and 9.2 ± 5.1 years respectively. C-reactive protein *(CRP)* was 25.8 ± 22 mg/L in the MTX group and 26.9 ± 23.8 mg/L in the other group. Rheumatoid factor *(RF)* was positive in 90% *(n=36)* patients of both groups. There was 32 female *(80%)* and 8 male *(20%)* distributed in the two groups included in the study. All the results are given in table *(1).*

Table (1): Patients' characteristics of both groups.

Patient characteristic	Group I	Group II
Age (years)	52.1± 2.9	50.8 ± 2.1
Disease duration	8.9 ± 4.2	9.2 ± 5.1
CRP (mg/L)	25.8 ± 22	26.9 ± 23.8
RF (no of +ve patients)	17	19

Pulmonary function results as assessed at the baseline are given in table *(2).* FEV_1 *(liters),* FVC *(liters)* and DLCO *(% of the predicted value)* were 2.18 ± 0.68, 2.9 ± 0.88 and 69.8 ± 20.4 respectively in the MTX group while were 2.02 ± 0.72 , 2.7 ± 0.81 and 68.1 ± 20.8 respectively in the other group. These results expressed no significant differences between the two groups with p value > 0.05.

Table (2): Pulmonary function tests results for both groups at the initial assessment.

Pulmonary function test	Group I	Group II
FEV_1 (lifters)	2.18±0.68	2.02±0.72
FVC (lifters)	2.9±0.88	2.7±0.81
DLCO (%of the predicted value)	69.8±20.4	68.1±20.8

On initial HRCT chest scanning, 3 patients were found to have PF *(Figs.1, 2& 3)* interstitial lung disease pattern, two of them were being treated with MTX. There was no significant difference in the dose and duration of MTX treatment between the two RA patients treated with MTX and has PF on initial evaluation and those who were being treated with the drug and had no evidence of PF on HRCT chest scanning at the initial evaluation.

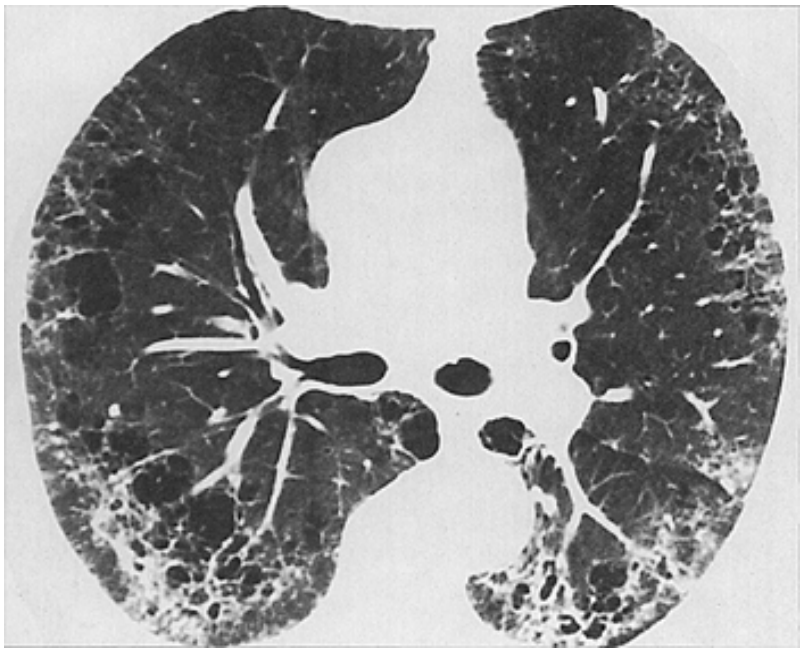

Fig. (1): HRCT scan of the chest shows; pulmonary fibrosis. Typical distribution of the fibrotic zone in the pleural space in a honeycombed pattern. This scan shows cystic tissue transformations of varying size with development of emphysema. The form of the accompanying subpleural emphysema varies as a result of traction.

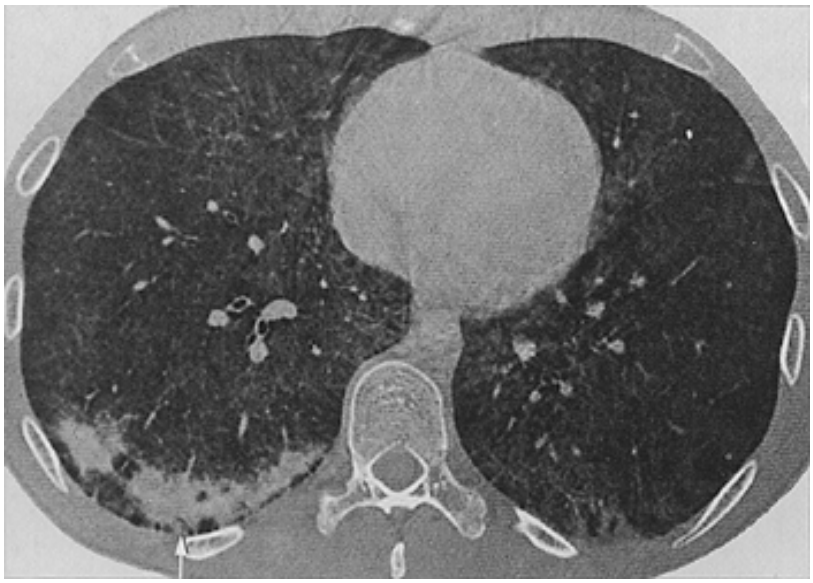

Fig. (2): HRCT scan of the chest shows; pulmonary fibrosis, more compact fibrotic infiltrates (arrow) are found.

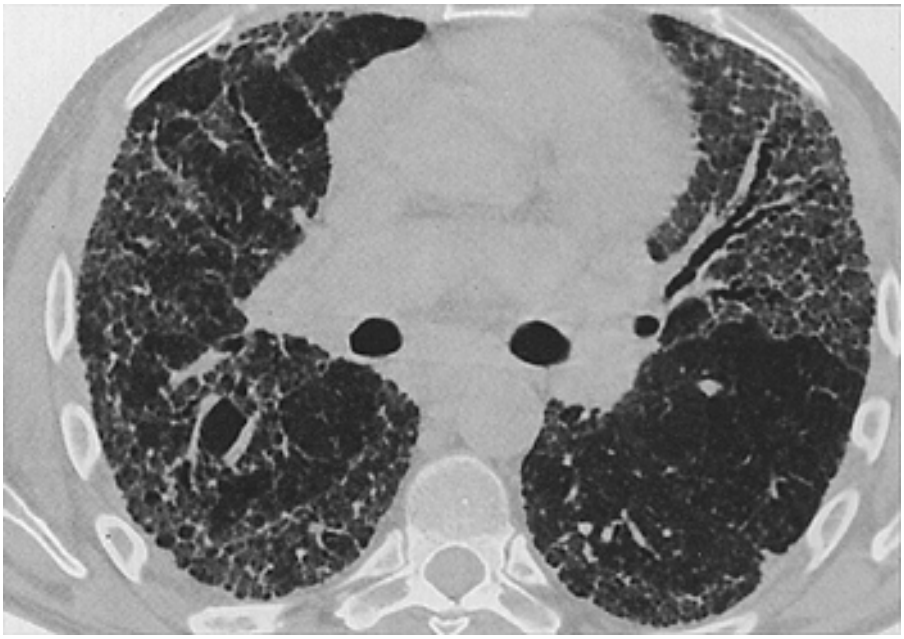

Fig. (3): HRCT scan of the chest shows; pulmonary fibrosis with generalized pattern involvement.

Table (3): Change in pulmonary function tests in both groups.

Pulmonary function test	Group I		Group II	
	Mean	SD	Mean	SD
FEV_1 (liters)	- 0.10	±0.3	-0.91	±0.29
FVC (liters)	- 0.05	±0.39	- 0.042	±0.34
DLCO	- 2.61	±11.48	- 2.58	±10.77

The patients were regularly followed on clinical basis according to the study design mentioned before. No patients developed clinical features suggestive of acute MTX pneumonitis. Two patients missed the regular follow up, one from each group. Also, two patients who were not being treated with MTX changed to MTX line of therapy due to ineffectiveness of other lines. On the other hand, one patient from the MTX group stopped the drug due to development of a non-progressive dry cough which thought to be due to isolated airway irritation caused by MTX[12].

Moreover, the change in pulmonary function tests from the time of initial assessment to the end of the study was not clinically or statistically significant in both groups *(p value > 0.05).* The change in pulmonary function tests are given in table *(3).* Further more, there was no clinical or

pulmonary function evidence that MTX had any deteriorating effect on PF detected in two patients on initial assessment even when compared with the patients were not being treated with it. On subsequent HRCT scanning, no patients developed any PF patterns apart from one patient from the MTX group developed subpleural changes of a predominantly reticular pattern which was not found on initial scanning.

DISCUSSION

Rheumatoid arthritis is a chronic inflammatory autoimmune disease characterized by progressive erosions and cartilage destruction. The current therapeutic strategy uses increasingly aggressive regimens early in the course of the disease to improve the outcome. Among multiple lines of treatment for RA, low dose MTX is increasingly used nowadays. The aim of this study was to investigate whether low dose MTX therapy could be associated with chronic or subacute pulmonary side effects.

Despite that acute life threatening MTX pneumonitis is thought to occur in a percentage of RA patients treated with MTX, it is interesting to note that no cases of this lethal complication developed in patients included in this study. But this may be explained on the basis that most of the study patients had been taking MTX for more than 6 months and it is known that most cases of this acute complication developed in the first 6 months of therapy[13], however absence of any acute cases in this study is concomitant with the study of *Dayton et al. (1995)*[14], who reported no cases of acute MTX pneumonitis during 5 years follow up of 31 RA patients, also going with study done by *Beyeler et al. (1996)*[15], who reported only one case among 100 RA patients treated with MTX.

The study showed only three patients with PF on HRCT at initial assessment, two of them were receiving MTX. The PF patients did not differ significantly, clinically or statistically from the other RA patients treated with MTX in the dose and duration of the MTX used. Thus there is no evidence that MTX caused this PF pattern on HRCT scan of these two patients. Interstitial lung changes related to RA are frequent and independent of disease duration. They are more frequent and severe in rheumatoid factor-positive patients and in patients with more severe joint involvement candidate for MTX therapy. On further pulmonary function test over a follow up period of 18 months; there was no significant change in pulmonary function tests in patients maintained on MTX when compared with those RA patients who were not taking MTX. Furthermore, there was no accelerated deterioration in pulmonary function in patients with PF detected on initial scan when compared with rest of the study patients in both groups.

In previous studies that investigate pulmonary function changes in RA patients on MTX, the authors concluded that, although there was some deterioration in parameters of pulmonary function, this did not reflect any clinical significance in these patients on MTX[16]. In consideration with this study results which showed no significant changes in pulmonary function in MTX users when compared to non users, so it would seem likely that the changes described previously were related to aging process and pulmonary affection associated with RA rather than MTX therapy.

The other reports which demonstrated chronic PF due to MTX in psoriatic patients could represent coincidental finding, particularly that many other studies have not detect any deterioration of pulmonary function in psoriatic patients treated with MTX[17]. Furthermore, MTX has been reported that it successfully controls RA-associated pulmonary fibrosis in four patients[18].

Conclusion:

This study showed no clinical, physiological or radiological evidence that low dose MTX treatment used successfully in treatment of RA is associated with chronic fibrotic lung disease. However further long-term follow up of these patients is of great value in further evaluation of this subject.

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احتمال أن يكون الميزوتركسات المستخدم في علاج التهاب المفاصل الرثيانى قد يصاحبه حدوث تليف رئوي مزمن ؟(دراسة مستقبلية)

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المقدمة و الهدف من البحث:

ان عقار الميزوتركسات بالجرعات المنخفضه و الذى يستخدم بكثره كخط علاج ثان فى حالات التهاب المفاصل الرثيانى المزمن و قد أشيع حدوث نوعين من أمراض الرئه مع استخدام عقار الميزوتركسات بالجرعات المنخفضه، الاول هو الالتهاب الرئوى الحاد و هذا يعتبر من الاثار الجانبيه المميته و الذى قد تحدث فى أقل من 10% من المرضى المصابون بالتهاب المفاصل الرثيانى المزمن و الذين يستخدمون عقار الميزوتركسات بالجرعات المنخفضه فى العلاج، أما النوع الثانى من أمراض الرئه هو حدوث تليف رئوى مزمن.

لذلك كان الهدف من هذا البحث هو تقييم مدى حدوث التليف الرئوى المزمن بين المرضى المصابون بمرض التهاب المفاصل الرثيانى المزمن والذين يستخدمون عقار الميزوتركسات بالجرعات المنخفضه فى العلاج.

مواد وطرق البحث:

هذه الدراسه اشتملت على 40 مريضا يعانون من مرض التهاب المفاصل الرثيانى المزمن و قد تم اختيارهم على حسب المواصفات المقترحه من كلية الروماتيزم الامريكيه (ACR) و تم تقسيمهم الى مجموعتين؛ تحتوى كل مجموعه على 20 مريضا وكان متوسط أعمار المرضى فى المجموعتين هو 52.1 عاما وكان متوسط معاناتهم من المرض هو 9.2 عام.

علما بأن أفراد المجموعه الاولى كانوا يستخدمون عقار الميزوتركسات بالجرعات المنخفضه فى العلاج ، بينما أفراد المجموعه الثانيه كانوا يستخدمون عقارا آخر غير الميزوتركسات فى العلاج وذلك عند التقيم الاولى فى بداية الدراسه.

وقد تم عمل فحص وظائف الرئتين و كذلك عمل أشعه مقطعيه للصدر لجميع المرضى عند بداية الدراسه. تم متابعة جميع المرضى لمدة ثمانية عشر شهرا ابتداء من يناير 2001 و حتى يونيه 2002 مع العلم أنه كان يتم مناظرة جميع الحالات بصفه دوريه كل ثلاثة أشهر اكلينيكيا . ثم تم تكرار عمل أشعه مقطعيه للصدر لجميع المرضى عند نهايه الدراسه.

نتائج البحث:

لم تظهر دراسة وظائف الرئتين أى فروق ذات دلاله احصائيه واضحه بين أفراد المجموعتين عند بداية الدراسه ($P>0.05$) .أما دراسة نتائج الاشعه المقطعيه للصدر عند بداية الدراسه فقد أظهرت وجود ثلاث حالات لديهم تليف رئوى اثنان منهم يستخدمون عقار الميزوتركسات بالجرعات المنخفضه. وكذلك عند دراسة نتائج فحص وظائف الرئتين و الاشعه

المقطعيه للصدر عند نهاية الدراسه لم تظهر أى فروق ذات دلاله احصائيه واضحه بين أفراد المجموعتين. و كذلك لم نجد أى دليل أكلينيكى أو أشعاعى أو فسيولوجى أن عقار الميزوتركسات أدى الى حدوث تدهور أو زياده فى التليف الرئوى الذى أكتشف عند بداية الدراسه لدى اثنان من المرضى الذين كانوا يستخدمون عقار الميزوتركسات بالجرعات المنخفضه فى العلاج.

الاستنتاج:

أظهرت هذه الدراسه عدم وجود دليل اكلينيكى أو فسيولوجى أو اشعاعى أن استخدام عقار الميزوتركسات بالجرعات المنخفضه فى علاج مرض التهاب المفاصل الرثيانى يؤدى الى حدوث تليف مزمن بالرئتين.