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Methotrexate Induced Pulmonary Toxicity in Psoriasis Patients

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ABSTRACT

The episodes of auto-immune diseases is increasing in alarming rate these days. Despite of accurate and advance diagnostic facilities management of diseases is out of control and remained chronic diseases. The management of disease requires long-term treatment with harmful agents, such as Methotrexate or other immuno-suppressive drugs. The net side effects produced from Methotrexate are based on the duration of treatment and cumulative concentration of the drug. The major pulmonary adverse effect of methotrexate is interstitial pneumonitis. There are several evidences of pulmonary function defects in patients receiving methotraxate at low level but for longer period of disease. The present study was undertaken to analyse the findings found on chest x-rays, high resolution computed tomography (HRCT) and pulmonary function tests (PFT) in a cohort of patients without previous recognized interstitial lung disease. The studied patients were receiving methotrexate as a treatment for psoriatic arthritis, a condition not associated with pleuropulmonary disease. The incidence of pulmonary toxicity in psoriasis patients taking Methotrexate on long term basis. This is a cross sectional study done in Department of Pulmunory Medicine of our Institute during the period from March 2022-2023. Fivety patients chosen for our study were clinically diagnosed with Psoriasis and were on methotrexate therapy for >3 months (cumulative dosage exceeding 150 mg). All the patients were subjected to detailed history taking, clinical examination, complete haemogram, liver function test, renal function test, spirometry, diffusion capacity of carbon monoxide and radiological examination including x-ray chest and HRCT Chest (read by 2 independent readers).The data were tabulated and analysed. we conclude that the frequency of development of advanced pulmunory toxicity on methotrexate therapy for psoriasis is small in low-risk subjects and methotrexate alone is not responsible for the progressive lungs disease. Methotrexate therapy, psoriasis, lungs disease.

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Key Words
Methotrexate therapy, psoriasis, lungs disease

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INTRODUCTION

Methotrexate (MTX) is an antimetabolite which competitively inhibits dihydrofolic acid reductase; inhibits purine and thymidylic acid synthesis, which in turn interferes with DNA synthesis, repair and cellular replication. MTX is a good treatment option for neoplastic, rheumatic and dermatological diseases[1-3]. However, rarely, may cause side effects, such as agranulocytosis and bone marrow suppression, mucosal tissue inflammation and necrotic changes, liver cell necrosis and hepatic cirrhosis, pulmonary fibrosis and severe renal dysfunction. In various countries different official guidlines are present for the safe prescription of methotrexate but there is no consensus statement on this issue. While selecting methotraxate as a treatment option there comes many questions regarding the dosage, risk of liver damage, how to monitor for hepatotoxicity and when to do liver biopsy[4-6].

There are mainly five clinical syndromes related with the treatment of psoriasis with methotraxate. Non-cardiogenic pulmonary edema[7] and pleuritis[8,9] are uncommon and have been reported in patients receiving methotrexate for malignancies at high doses. Pulmonary nodulosis has been described in a rheumatoid arthritis patient[10]. Acute interstitial pneumonitis is the most common pulmonary toxicity and is characterized by shortness of breath, non-productive cough, dyspnoea, fever and fatigue with radiographic bilateral interstitial and/or alveolar infiltrates. Interstitial fibrosis has been reported in patients receiving methotrexate for rheumatic and non-rheumatic conditions[11,12]. Some of them, such as psoriasis, are not associated with the development of interstitial pulmonary fibrosis as a part of the underlying disease process.

Since methotrexate is generally used in patients suffering from conditions such as psoriosis, which can be associated with interstitial lung disease. However the exact mechanism of methotraxate action in development of pulmonary complications in these patients is not well established yet and a matter of further research. Therefore we conducted a transversal study to analyse the findings found on chest x-rays, high resolution computed tomography (HRCT) and pulmonary function tests (PFT) in a cohort of patients without previous recognized interstitial lung disease who were taking methotrexate as a treatment for psoriatic arthritis a condition not associated with pleuropulmonary disease.

MATERIALS AND METHODS

This is a cross sectional study done in Department of Dermatology with the collaboration of Pulmonary Medicine at Al-Falah school of medical science and research centre Faridabad. Fivety patients chosen for our study were clinically diagnosed with Psoriasis and were on methotrexate therapy for more than 3 months (cumulative dosage exceeding 150 mg). All the patients were subjected to detailed history taking, clinical examination, complete haemogram, liver function test, renal function test, spirometry, diffusion capacity of carbon monoxide and radiological examination including x-ray chest and HRCT Chest (read by 2 independent readers). The data were tabulated and analysed.

Inclusion criteria:

- Psoriasis patients have taken more than 3 months of methotrexate with respiratory complaints
- Age group above 14 years
- Patients who were willing for the study and gave informed consent for the study
- Both sexes

Exclusion criteria:

- Patients have previous history of pulmonary tuberculosis
- Patients suffering from other pulmonary disorder due to other known causes like collagen vascular diseases

RESULTS

Of the total registered cases who were receiving methotrexate for psoriasis were screened. Out of total 50 COPD patients studied 32 were males and 18 were females, the male: female ratio being approximately 1.9:1. Their ages ranged from 35-85 years with an average of 58 years. The maximum number of patients having COPD syndrome belonged to the age group of 56-65 years. (Table 1).

The age wise sex distribution data is summarized in Table 2. Highest incidence of cases was between 21 and 30 years age group with 30% followed by 31 and 40 years with 21%. Least incidence was observed in the age group above 60 years with 5% cases. Males were more prominent in age group 21-30 years whereas

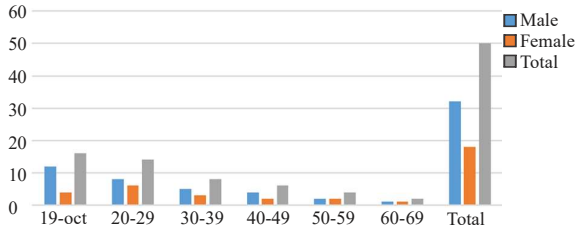

Fig. 1: Demographic data of patients

Table 1: Demographic data of patients

Patients Detail	Number of cases	Percentage
Male	32	64
Female	18	36
Average duration of COPD	7.6 years	-

Table 2: Distribution of biochemical parameters among the test population

	Male	Female
Variables	COPD (32)	COPD (18)
Age	53.6±6.2	48.1±3.2
BMI	21.1±1.4	19.2±2.1
Psoriasis type	Psoriasis vulgaris, pustular psoriasis, psoriasis vulgaris	
T. cholesterol (mmol L)	3.9±0.9	3.6±0.4
Triglycerides (mmol L)	1.6±0.03	1.4±0.06
Fever	Yes	Yes
Cough	Yes	Yes
Expectoration	No	No
Dyspnoea	Yes	Yes
Duration of symptoms	4 months	4 months
Total count	8000 cmm	14600 cmm
Eosinophils	2%	4%
X-ray chest	B L Interstitial pattern	B L lower zone reticular shadows
HRCT chest	B L Interstitial fibrosis	B L lower lobe traction bronchiectasis

females were more affected in age group 31-40 years. The average age, BMI, the W/H ratio the total serum cholesterol and the serum triglycerides levels were higher in the male patients as compared to the females patients Table 2.

DISCUSSION

MTX is a drug of antifolate category which is used as a mainstay of treatment for psoriasis and rheumatoid arthritis because of its efficacy and long track record of safety[13]. The most common minor adverse events associated with lowdose MTX use are stomatitis, headaches, nausea, fatigue and anorexia[14,15]. While hepatotoxicity has historically been the most feared side effect, pancytopenia is now emphasized as the most serious adverse event. It has been observed in approximately 1.5% of patients taking low-dose MTX[16]. Psoriatic plaque erosion is a rare cutaneous manifestation of low-dose MTX toxicity with unknown prevalence and has been hypothesized that a painful erosion of psoriatic plaque is an early cutaneous sign of pancytopenia[17]. The most common risk factors for psoriatic plaque erosion are being the initiation or reinstatement of MTX after a drug hiatus, an increase in the MTX dose, renal impairment and the use of NSAIDs or aspirin. Age >55, folate deficiency, low serum albumin level and drug-drug interactions are also common risk factors.

In this study 9 patients showed normal radiology and pulmonary function test. Tweventy one patients had pulmonary function abnormalities. In this study there were 13 (43%) patients with restrictive pulmonary function defect. Belzenegui et al reported 2 cases with mild restriction among 27 patients in a similar study. There were 10 (33%) patients with diffusion defect in this study. Belzenegui *et al.* reported 2 cases among 27 patients in a similar study. There were 5 (16%) patients with small airway disease as suggested by decrease in mean mid expiratory flow. Belzenegui et al reported 5 cases among 27 patients in a similar study. There were 3 (3%) patients with radiological lesions, 1 had bronchiectasis and 2 had interstitial fibrosis. Patients with Co-morbidities like bronchial asthma (n = 3), rheumatic heart diseases (n = 1), hypertension (n = 1) diabetes mellitus (n = 1) and habits like smoking (n = 7) did not have radiological features of methotrexate induced pulmonary fibrosis. There was no case of acute pneumonitis during the study period. Average duration of respiratory symptoms in suspected patients was more than 1 month. The study is comparable with the previous studies with prevalence rate for methotrexate induced pulmonary fibrosis nearing 2% of 154 patients receiving methotrexate from dermatology outpatient department. Diffusion capacity was an useful aid in all 3 patients with methotrexate induced pulmonary toxicity.

CONCLUSIONS

Hence, we conclude that the frequency of development of advanced pulmunory toxicity on methotrexate therapy for psoriasis is small in low-risk subjects and methotrexate alone is not responsible for the progressive lungs disease. Psoriatic patients are inherently predisposed to develop restrictive pulmonary function defect and more so in the presence of risk factors and hence all patients should be screened for risk factors and the presence of restrictive pulmonary function defect prior to starting

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