Dissertation on

METHOTREXATE INDUCED PULMONARY TOXICITY IN PSORIASIS PATIENTS

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CERTIFICATE

This is to certify that the dissertation on "**METHOTREXATE INDUCED PULMONARY TOXICITY IN PSORIASIS PATIENTS** " is a record of research work done by **DR.G.ALLWYN VIJAY** in partial fulfillment for M.D.BRANCH- XVII (T.B. AND RESPIRATORY DISEASES) EXAMINATION of The Tamilnadu Dr.M.G.R.Medical University to be held in March 2010. The period of study is from March 2009 to September 2009.

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DECLARATION

I hereby declare that the dissertation entitled "**METHOTREXATE INDUCED PULMONARY TOXICITY IN PSORIASIS PATIENTS**" submitted for the Degree of Doctor of Medicine in M.D., DEGREE EXAMINATION, Branch-XVII, TUBERCULOSIS & RESPIRATORY DISEASES is my original work and the dissertation has not formed the basis for the award of any degree, diploma, associate ship, fellowship or similar other titles. It had not been submitted to any other university or Institution for the award of any degree or diploma.

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CONTENTS

INTRODUCTION

Methotrexate is an anti-metabolite widely used in malignancy, rheumatoid arthritis and refractory cases of psoriasis[1]. The value of low dose methotrexate is well established[2-4]. Most patients are able to tolerate low dose methotrexate with generally sustained efficacy[5]. The main pulmonary side effect of methotrexate is interstitial pneumonitis. Its incidence has been found to be about 7 to 8%, in studies in which methotrexate at antineoplastic doses was used, in combination with other cytotoxic agents[6]. There are evidences of pulmonary function defects in patients on long term low dose methotrexate in rheumatoid arthritis patients. Acute methotrexate induced pneumonitis has also been reported after low-dose therapy (<20 mg/wk) for rheumatoid arthritis[7-12]. Pulmonary function test of methotrexate pneumonitis patients show restrictive pattern with impairment in diffusion capacity of carbon monoxide. It is known that in patients receiving other cytotoxic drugs such as bleomycin, abnormalities in pulmonary function can be detected before the patients become symptomatic[13,15].

Because methotrexate is frequently used in patients suffering from conditions such as RA, dermatomyositis or sarcoidosis, which can be associated with interstitial lung disease, determining the exact role of methotrexate in the development of pulmonary complications in these

patients seems to be difficult. Therefore, we conducted a cross-sectional 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[16].

AIM OF THE STUDY

To know the incidence of pulmonary toxicity and derangements in pulmonary function in psoriasis patients taking Methotrexate on long term basis through DLco, spirometry and radiological evaluation.

REVIEW OF LITERATURE

PSORIASIS:

Psoriasis is a non-infectious, chronic inflammatory disease of the skin, characterised by well-defined erythematous plaques with silvery scales, with a predilection for the extensor surfaces and scalp, and a chronic fluctuating course. The prevalence is approximately 2% in European populations. Accurate figures for many other parts of the world are not available but there seems to be consistent evidence that the prevalence of psoriasis is lower in people of African origin and lower still in some Asian communities such as the Japanese. Psoriasis may start at any age but is unusual before the age of 5; the oldest recorded onset was in a patient aged 107. There appear to be two epidemiological patterns of psoriasis: The first shows an onset in the teenage and early adult years; an increased prevalence of HLA Cw6. In a second grouping, disease onset is in the fifties or sixties, a family history is less common and the HLA group Cw6 is not so prominent. Some authors refer to these two groups of patients as type 1 and type 2 psoriatics. The clinical course of psoriasis is very variable. As a general rule clinical impressions suggest that the earlier the age of onset and the more severe the initial presentation, the more severe the lifetime course of the disease.

Aetiology : There are two key pathophysiological aspects to the abnormalities in psoriatic plaques: First, the keratinocytes hyperproliferate with a grossly increased mitotic index and an abnormal pattern of differentiation involving the retention of nuclei in the stratum corneum (in normal skin the dead stratum corneum cells do not have nuclei). Second, there is a large inflammatory cell infiltrate comprising polymorphs, T cells and other inflammatory cells. It is uncertain which of these characteristics is primary. Traditionally, psoriasis was viewed primarily as a disorder of cell turnover but in recent years there has been increased support for the hypothesis that the hyperproliferation may be secondary to the inflammatory infiltrate and that the increase in keratinocyte proliferation is a consequence of inflammatory cell mediators or signalling.There is a large familial component to psoriasis. Formal estimates from twin studies suggest a hereditability of around 80%. In monozygotic twins perhaps one-third of pairs will be concordant for psoriasis. Put another way, two-thirds of monozygotic twins will not be concordant despite an apparently identical or near-identical genetic background. The mode of inheritance of psoriasis does not fit a clear Mendelian pattern and, like atopic dermatitis, is therefore described as genetically complex. Empirical estimates suggest that if one parent has psoriasis, then the chance of a child being affected is in the order of 15-20%. If both parents have psoriasis, the probability of a child being affected is 0.5. Both these estimates are increased if one sibling already has the disease. Genome scanning linkage and association studies have indicated various chromosomal areas of susceptibility including the HLA region. Disordered cell proliferation in psoriasis is reflected by the increase in the number of mitoses visible in the psoriatic plaque. The transit time-that is, the time it takes for keratinocytes in the

basal layer to leave the epidermis-is shortened in psoriasis from perhaps 28 to 5 days. Whilst it used to be thought that the cell cycle was actually reduced in psoriasis, more recent data suggest that it is just that the proportion of cycling cells (rather than cells that are in G_0) is increased.

There are some data suggesting that the non-plaque skin also shows an elevated rate of proliferation, although any increase above background rate is modest. These data have not been confirmed in all studies. The nails of patients with psoriasis, even when clinically unaffected, do, however, grow more quickly than those of controls. The importance of keratinocyte hyperproliferation initially received support from the demonstration that cytostatic drugs such as methotrexate were clinically useful. However, more recent data suggest that methotrexate

may exert its effects primarily through an influence on the immune system.

The evidence implicating a key role for an immune pathogenesis relates to:

The association with certain HLA groups (HLA Cw6)

The success of certain immunosuppressive drugs (such as ciclosporin) in improving the clinical state of the disease

Reports of the development of psoriasis in recipients of bone marrow transplants from donors with a history of psoriasis.

The precise molecular mechanisms operating in psoriasis are, however, poorly understood. A large number of theories have been advanced over the last 30 or 40 years claiming that one particular mediator may be a key or rate-limiting factor in psoriasis. The majority of these explanations have not stood the test of time, nor have they provided useful therapeutic insight.

Psoriasis is a chronic disease characterised by variation in both temporal and spatial extent. Most of this variation cannot be explained. At any one time perhaps 10% of people who have received the diagnosis of psoriasis have no lesions and perhaps 15% may report remissions of up to 5 years or more.

METHOTREXATE

Methotrexate is a folate antagonist used as a chemotherapeutic agent as well as in the treatment of non-neoplastic inflammatory diseases. When used in high doses for the treatment of cancers, the incidence of pulmonary toxicity is estimated at 7 percent. Toxicity does not appear to have dose dependency but may be related to frequency of administration. In one study, daily or weekly treatment carried more risk of pulmonary injury than treatment every 2 to 4 weeks. Synergistic toxicity has been reported with combination therapy using cyclophosphamide. Tapering of corticosteroid therapy or adrenalectomy may also increase the risk of Methotrexate induced toxicity[17]. The mechanism of methotrexate-induced lung injury is unknown. Clinically, toxicity presents with several syndromes. The most common of these is the development of a symptom complex characterized by fever, dyspnea, cough, malaise, and myalgias, usually within weeks after initiation of therapy. Chest radiograph usually shows diffuse interstitial infiltrates. Occasionally, chest radiograph may show unilateral or bilateral effusions, a nodular appearance, or may even be normal. Additionally, hilar and mediastinal adenopathy have been observed. Skin rash is present in up to 17 percent of patients and peripheral blood eosinophilia in up to 40 percent of patients. Bronchoalveolar lavage in this setting may show a lymphocytic alveolitis, suggestive of

a hypersensitivity reaction. However, illness may resolve even with continuation of the drug, and rechallenge does not necessarily result in relapse. These findings suggest that hypersensitivity may not be the true mechanism of injury. This presentation of methotrexate-induced pulmonary toxicity parallels the hypersensitivity-type syndrome that is sometimes observed with bleomycin. As some patients may go on to develop chronic pneumonitis and pulmonary fibrosis, the drug is generally withdrawn when toxicity occurs. Pulmonary toxicity from methotrexate may also present as a more insidious sub acute syndrome of interstitial lung disease. Symptoms including cough, fever, dyspnea, headache, and malaise typically occur within 4 months after the initiation of treatment. Radio graphically and clinically this syndrome more closely resembles the type of chronic pneumonitis seen with other cytotoxic drugs and has been described as complicating all routes of Methotrexate administration (oral, intravenous, intrathecal). In contrast to many other chemotherapeutic agents, the pneumonitis caused by methotrexate appears in general to be responsive to corticosteroids. Pathological findings in the lung parallel those seen with lung injury due to other cytotoxic drugs, with interstitial and alveolar inflammation and fibrosis. Additionally, eosinophilic infiltration of the interstitium as well as granulomatous inflammation may be observed. These latter findings are again suggestive of a potential hypersensitivity-type mechanism of inflammation. Methotrexate-induced lung injury may also appear as an acute syndrome with pleuritis and pleural effusion. Respiratory distress progressing to noncardiogenic pulmonary edema has been described

after intrathecal administration of the drug and may be neurogenic in origin[18].

In patients with rheumatoid arthritis, polymyositis,and other collagen vascular diseases, the potential for a variety of pulmonary manifestations related to the underlying disease can make the diagnosis of methotrexate-induced pneumonitis challenging. The diagnostic criteria of Searles andMckendry are frequently employed in an effort to determine whether pulmonary involvement is related to methotrexate. Though they have not been validated in a prospective cohort, these criteria are commonly used to assist with this diagnosis. In a multicenter case-control study of methotrexate-induced lung toxicity in patients with rheumatoid arthritis, Alarcon and colleagues identified risk factors associated with the development of pneumonitis, including age greater than 60 years (associated with a six fold increase in risk of pneumonitis compared with those less than 50 years of age), prior history of rheumatoid pleuro-pulmonary disease, diabetes, previous use of disease-modifying antirheumatic drugs, and hypoalbuminemia. The prognosis with methotrexate associated lung toxicity is generally felt to be favourable. As noted, symptoms and radiographic abnormalities may resolve even with continuation of treatment. The use of corticosteroids is generally recommended though prospective trials of this intervention are not available. The overall mortality rate with methotrexate induced pneumonitis is approximately 10 percent.

SEARLES AND MCKENDRY CRITERIA[19]:

Diagnostic criteria:

Acute onset of breathlessness.

Fever (>38 C).

Tachypnoea (> or = 28 breaths / minute) with non productive cough.

Radiographic infiltrates of interstitial or alveolar infiltrates.

WBCs < or =15,000.

Negative blood or sputum culture for pathogenic organisms.

Pulmonary function tests showing restrictive pattern with low diffusion

capacity.

PaO2 < 55mmhg in room air.

Biopsy, histopathology consistent with bronchiolitis or interstitial pneumonitis with giant cells and without evidence of pathogenic organism.

Presence of Methotrexate pneumonitis:

Definite : at least 6

Probable :at least 5

Possible : at least 4

MODIFIED SEARLES AND MCKENDRY CRITERIA:

MAJOR CRITERIA:

1. Hypersensitivity pneumonitis by histopathology without evidence of pathogenic organism.

2. Radiological evidence of pulmonary interstitial or alveolar infiltrates.

3. Blood cultures (if febrile) and initial sputum cultures (if sputum is produced) negative for pathogenic organisms.

MINOR CRITERIA:

1. Shortness of breath < 8 weeks.

2. Non productive cough

3. O_2 saturation < 90% at the time of initial evaluation on room air.

4. DLco < or = 70% predicted for the age.

5.leukocyte count < or = 15000/mm^3.

A definite case had to meet major criterion 1 (pathologic evidence) or criteria 2 (radiologic evidence or an abnormal chest radiograph) and 3(negative cultures) plus three of the five minor criteria (shortness of breath, non productive cough, O_2 saturation ≤ 90%, DLCO [diffusing capacity of the lung for carbon monoxide] ≤ 70%, and leukocyte count ≤ 15 000 cells/mm^3). Patients were said to have met major criterion 3 if they were afebrile and did not produce sputum, even if no blood or

sputum cultures were done. In some patients, bronchoalveolar lavage fluid was

cultured to rule out infectious causes of disease. Probable case-patients had to meet major criteria 2 and 3 plus two of the five minor criteria. No other case-patients were considered to have methotrexate-induced lung injury.

PSORIASIS AND METHOTREXATE

Pulmonary disease in the course of psoriasis is rare. Possible aetiologies include microbial infection, a drug-induced reaction and capillary leak syndrome[20]. An infectious origin for the pulmonary involvement in patients seems improbable because of the absence of micro organisms in the repeated blood samples and alveolar lavage. The absence of improvement under broad-spectrum antibiotics and the rapid improvement with corticosteroids also make this aetiology unlikely. The hypothesis of a drug-induced reaction is plausible. Methotrexate and acitretin, two drugs frequently used in psoriasis, may both be responsible for interstitial pneumonitis, along with gold salts classically used in the treatment of psoriatic arthritis. Low-dose methotrexate is responsible for immunoallergic interstitial pneumonitis in up to 3% of patients treated for rheumatoid arthritis[21-22]. This complication is less frequent in patients treated for psoriasis than for rheumatoid arthritis, perhaps because the latter predisposes the lungs to drug-induced damage[22-26]. The pathogenesis of psoriasis-associated aseptic pneumonitis is unknown[27]. However, it has recently been shown in an animal model that T-helper (Th) 1 lymphocytes, which are known to be activated in psoriasis, could induce alveolitis[28] and that tumour necrosis factor, a major Th1 cytokine produced in psoriasis[29], could promote lung invasion by lymphocytes by up regulating cytokines involved in cell adhesion[30]. Although methotrexate pneumonitis is not considered a dose-related phenomenon, the incidence of this adverse effect during low dose and long term methotrexate therapy needs further Investigations. Five clinical pulmonary syndromes have been associated with methotrexate treatment. Non-cardiogenic pulmonary edema and pleuritis 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. Acute interstitial pneumonitis is the most common pulmonary toxicity and is characterized by shortness of breath, non-productive cough, 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. Some of them, such as psoriasis, are not associated with the development of interstitial pulmonary fibrosis as part of the underlying disease process. In a recent case-control study the strongest risk factors for lung injury identified in patients with rheumatoid arthritis (RA) receiving methotrexate were older age, rheumatoid pleuropulmonary disease, previous use of disease-modifying antirheumatic drugs, low serum albumin, and the presence of diabetes.

DIFFUSION:

By the time inspired gas reaches the alveoli, movement of gas molecules Is determined almost entirely by diffusion; This is so efficient that alveolar gas can be considered uniform without the existence of any intra-alveolar gas concentration gradients. Gas transfer across the alveolar wall into the pulmonary capillary involves passage of molecules through the epithelial cell, basement membranes, the interstitium and the endothelial cell and thence through plasma and the red cell membrane to the interior of the red cell. The rate of gas transfer in the lung depends on:

1surface area available for transfer;

2 thickness of the alveolar–capillary membrane;

3 solubility and molecular weight of the gas concerned

CO2 has a similar molecular weight to O2 but diffuses about 20 times more rapidly because of its high solubility. The diffusing capacity (*D*L) for a gas within the lung can be expressed by the following equation:

$$D_L = V_{GAS}/P_1 - P_2 \quad \ldots\ldots\ldots\ldots\ldots\ldots(1)$$

where *V*gas is the volume of gas transferred in unit time and *P*1 and *P*2 are the pressures of gas in alveoli and capillary blood respectively. Thus the diffusing capacity for carbon monoxide (CO) is defined as:

$$\mathbf{D}_{LCO} = V_{CO}/ P_1 - P_2 \quad \ldots\ldots\ldots\ldots\ldots\ldots(2)$$

and since the *P*CO in capillary blood is usually so small that it can be neglected, Eqn 2 can be simplified to:

$$\mathbf{D}_{LCO} = V_{CO}/P_{Aco} \quad \ldots\ldots\ldots\ldots\ldots\ldots(3)$$

It is now agreed that the normal alveolar membrane causes no appreciable impediment to O2 diffusion from alveoli to blood. Theoretically, diffusion may be influenced by intra-alveolar oedema or exudate, interstitial oedema, exudate or fibrosis, thickening of the alveolar wall, thickening of the capillary membrane or increase of the intracapillary path for O2 due to capillary dilatation. Pulmonary diffusing capacity measures the impediment produced by all the factors involved in transfer of O2 to the erythrocyte; for the whole lung the V_A/Q ratio is probably the most important factor. In high V_A/Q areas, ventilation is wasted and little or no gas is exchanged in spite of an intact transfer surface leading to a decrease in *D*LCO for the lungs as a whole. There are no methods at present available that can distinguish between V_A/Q abnormality and impaired diffusion but the general consensus of opinion

is that V_A/Q disturbances are more important than thickening of the alveolar membrane. A significant part of the diffusion pathway lies between the capillary endothelium and the red cell. An additional factor that influences diffusion of O2 is the rate of the chemical reaction that combines O2 with haemoglobin within the red cell. The diffusing capacity can thus be considered as having two components, the first reflecting transfer from the alveolus to the interior of the red cell and the second concerned with the combination of O2 with haemoglobin. These two components can be expressed as the

inverse of their effective diffusing capacities in the following equation:

$1/D_L = 1/D_m + 1/QV_c$ .....(4)

where *D*m is the membrane component of resistance to diffusion, Q describes the rate of reaction of O2 with haemoglobin and *V*c is the volume of capillary blood. Q*V*c is thus the effective diffusion capacity for the rate of reaction of O2 with haemoglobin. These two separate components of the resistance to diffusion can be measured by special methods and are approximately equal. Significance of changes in *D*LCO From Eqn 4 it follows that changes in capillary blood volume can influence *D*L, which in consequence is decreased in anaemia and

increased in polycythemia, left-to-right cardiac shunts, exercise and the supine position. A low value for *D*L may also indicate:

1 small lungs or lesions reducing lung volumes, e.g. pneumonectomy;

2 obstructive lung disease with non-uniform V_A/Q distribution;

3 emphysema with decrease of total gas-exchanging area;

4 interstitial lung disease with altered ventilation, perfusion and probably diffusion in many areas.

*D*L is of particular value in defining abnormality and response to treatment in the interstitial lung diseases, which include fibrosing alveolitis, sarcoidosis, asbestosis, farmer's lung, collagen diseases of the lung and polyarteritis nodosa. In some conditions, e.g. sarcoidosis, changes in *D*L may be a more sensitive indicator of response to treatment than radiological changes. *D*L has also been used (after adjustment for the ventilated lung volume to give the KCO) as a measure of fresh pulmonary haemorrhage in Goodpasture's syndrome, where increases in KCO are attributed to uptake of CO by sequestered haemoglobin in the lung. Ideally, the gas used for estimations of *D*L should be O2, and the relevant equation is:

$\mathbf{D}_{LO2} = V_{O2}/P_{AO2} - P_{C02}$ .....(5)

where *P*cO2 is mean pulmonary capillary pressure. Such measurements are possible although because of the difficulty in measuring *P*cO2 it is more usual in routine practice to measure *D*LCO. CO has a great affinity for haemoglobin (240 times that of O2). At low alveolar pressures of CO only a small proportion of haemoglobin is saturated with CO during passage through the pulmonary capillaries, so that the *P*CO in the blood is small relative to the *P*CO in the alveoli. The relatively large difference between *P*ACO and *P*cCO makes the CO method for measuring diffusion capacity more accurate and reproducible than the O2 method. In essence the techniques employed require measurement of the uptake of CO (V_{CO}) and *P*ACO by means of an infrared analyser,

*P*cCO is assumed to be zero and the values are entered into Eqn 3. Simultaneous measurement of alveolar volume by He dilution also allows determination of the transfer coefficient (*D*LCO/*V*A, or *K*CO), which may be a more appropriate indicator of the effectiveness of gas exchange when lung volume has been lost because of either disease or surgery. Although steady-state measurements of *D*LCO are possible, they are less reproducible than the single-breath method that is currently the procedure of choice.

COLLINS AUTOMATED SYSTEM FOR

MEASURING DLCO

ATS RECOMMENDATION FOR PERFORMING DLCO:

Equipment:

1. Volume accuracy same as for spirometry(±3% over 8L range, all gases)
2. Documented analyzer linearity from 0 to full span ± 1%
3. Circuit resistance less than 1.5cm H_2O at 6 L/sec flow
4. Demand valve sensitivity less than 10 cm H_2O to generate 6L/sec flow
5. Timing mechanism accurate to ±1% over 10 sec; checked quarterly
6. Documented instrument dead space(Inspiratory/Expiratory) less than 0.1L
7. Check for leaks and volume accuracy(3L calibration) daily
8. Validate system by testing healthy non smokers (Biologic control) quarterly

Technique:

1. Subject should refrain from smoking for 24 hours before the test
2. Subject should be instructed carefully before the procedure
3. Subject should inspire rapidly;2.5 sec or less for healthy subjects, 4 sec or less in obstruction
4. Subject should achieve an inspired volume greater than 90% of VC
5. Subject should achieve breath hold for 9-11 sec, relaxing against closed glottis or closed valve (No valsalva or mullers manoeuvre)
6. V_D wash out should be 0.75 L-1.0L(0.5 L if VC less than 2.0 L)
7. Alveolar sample volume should be 0.5-1.0 L collected in less than 4 sec
8. Visual inspection of V_D washout and alveolar sampling should be used for system that continuously analyzes expired gas
9. Test gas should contain 21% O_2 at sea level; supplemented O_2 should be

discontinued before testing if possible

10. Four minutes should elapse between repeat tests

Calculations:

1. Average at least two acceptable tests; duplicate determinations should be within 10% or 3ml/min/mm of Hg
2. Use Jones method of timing of breath hold
3. Alveolar volume should be determined by single breath dilution of tracer gas
4. Adjust for V_D volumes (Instrument and patient)
5. Determine inspired gas conditions(ATPS or ATPD)
6. Correct for CO_2 and H_2O absorption
7. Report D_L/V_A in ml CO (STPD)/min/mm Hg per L(BTPS)
8. Correct for Haemoglobin concentration
9. Adjust for COHb
10. Adjust for altitude
11. Use reference equations appropriate to the laboratory method and patient population

Acceptable test criteria for diffusing capacity of the lung for carbon monoxide:

Use of proper quality-controlled equipment, V_I (Inspired Volume) of >85% of largest VC in <4 sec, A stable calculated breath hold for 10±2 s. There should be no evidence of leaks, or Valsalva or Mueller maneuvers, Expiration in <4 s (and sample collection time <3 s), with appropriate clearance of V_D (Dead space volume) and proper sampling/analysis of alveolar gas.

Pulmonary Function Tests in DPLD

1.Severity and pattern of disease

Simple lung function testing using lung volumes and gas transfer factor gives a reasonable measure of the extent of disease.

2. Monitoring the course of the disease

VC and DLCO are the most appropriate and simplest indicators of change in DPLD. DLCO predict survival in some studies. In Wells et al[20] study, increased mortality is associated with reduced DLCO, FVC and TLC. The one index that appears to be a good predictor of the subsequent clinical course is DLCO.

RADIOLOGIC IMAGING IN DPLD

Patients with suspected DPLD will have a chest radiograph as the initial imaging investigation. In most cases, this is abnormal and occasionally the radiographic appearances are sufficiently characteristic to enable a specific diagnosis to be made when taken in conjunction with the clinical and laboratory findings. Chest radiograph is an essential test for the assessment of DPLD, however a normal Chest Radiograph cannot exclude the diagnosis. If available, previous x-rays or reports of x-rays should be obtained and compared with the recent x-rays. In appropriate clinical settings, HRCT may be sufficiently characteristic to preclude the need for biopsy[7].

PULMONARY HRCT

HRCT scanning is capable of imaging the lung with excellent spatial resolution and providing anatomical detail similar to that seen by gross pathological examination. Images are usually obtained in the supine and prone position. In normal patients, dependent lung opacity is often seen in the posterior, subpleural regions of the lung. In certain diffuse lung diseases, such as non specific interstitial pneumonia (NSIP), images can be identical to those seen in normal patients. Prone images will differentiate between

these two possibilities, since normal dependent density in the posterior lung will disappear on prone images, whereas true lung disease-related density will persist. Dynamic expiratory images are also obtained to screen for air trapping.

1. Detection of DPLD

HRCT scanning is able to detect DPLD not visible on the chest radiograph. The relative sensitivities of the two techniques for the detection of DPLD are 94% and 80%, respectively.

2. Characterisation of disease and extent of disease

The diagnostic accuracy of HRCT scanning is further increased by concurrent clinical evaluation[49].Unlike chest radiography, HRCT scans provide cross sectional images and the extent of disease is therefore much more readily appreciated than on the chest radiograph. HRCT scanning may also elucidate patients with complex lung function abnormalities—for example, co-existing fibrosing alveolitis and emphysema.

3. Impact on lung biopsy samples

HRCT scanning has a high degree of accuracy in many forms of DPLD. The percentage of first choice diagnoses made with a high level of confidence in two studies was 82% and 93%.Fibrosing alveolitis may be confidently distinguished from other forms of DPLD with an accuracy of 88%. Using Bayesian analysis, Grenier *et al* concluded that the combination of clinical, radiographic, and HRCT findings enabled a correct diagnosis with a high level of confidence in 61–80% of patients with DPLD. Based on the findings it is evident that HRCT scanning can prevent the need for a histological diagnosis. For patients in whom lung biopsy samples are required, HRCT scanning is better able to differentiate between the need for transbronchial biopsy or

open lung biopsy samples. It is also able to determine the most appropriate areas from which the biopsy samples should be taken.

4. Assessment of disease activity

There is evidence that a predominant ground glass pattern and is more likely to represent active inflammatory disease and to respond to appropriate therapy Reticular and honeycomb patterns on HRCT scans correlate well with histological evidence of fibrosis.

5. Prediction of response to treatment

Because of its ability to differentiate between cellular and fibrotic disease with reasonable accuracy, HRCT scanning can be used to predict response to treatment and is significantly more accurate than chest radiography in this respect.

HRCT PATTERNS

1. Reticular opacities: Thickening of the interstitial connective tissue network of the lung will result in reticular opacities of varying morphology. This thickening can result from fluid/cellular infiltration or deposition of fibrous tissue.
2. Nodules: There are several ways to classify nodules: well defined vs. poorly defined; upper vs. lower lobe distribution; and relationship to the secondary pulmonary lobule. The last is the most useful characteristic, since it provides a focused differential diagnosis and is reflective of the underlying disease pathophysiology. There are three possible HRCT distributions of nodules: perilymphatic, random, and centrilobular.
3. Honeycombing: Honeycomb lung remodelling (honeycombing) reflects the end stage of a number of diseases that cause parenchymal destruction. It presents a

characteristic HRCT pattern, with subpleural, thick-walled cysts that share walls and, when advanced, are often stacked in multiple layers. Other signs of fibrosis (traction bronchiectasis and reticulation) typically accompany it. Honeycombing is highly suggestive of a pathologic diagnosis of usual interstitial pneumonia (UIP), although it can be attributable to other diseases

4. Traction bronchiectasis: Bronchial dilatation occurring as a consequence of interstitial fibrosis is referred to as traction bronchiectasis.The bronchi often appear irregular (corkscrewed) and are not associated with radiologic evidence of bronchial inflammation (gross bronchial wall thickening or mucous impaction). Other signs of lung fibrosis (honeycombing or irregular reticulation) often accompany traction bronchiectasis. While traction bronchiectasis is quite specific for fibrosis, the differential diagnosis is broader than that of honeycombing. In patients with known collagen vascular disease, bibasilar, peripheral, traction bronchiectasis accompanied by ground-glass attenuation can be considered diagnostic of NSIP.

5. Ground glass opacity:GGO is increased lung opacity that does not obscure the associated vessels and represents abnormalities below the resolution of HRCT. GGO has been associated with active or reversible lung disease. However, ground-glass opacity can also be seen in cases in which fibrosis is the predominant abnormality. Ground-glass attenuation can only be considered as reflecting the presence of potentially reversible disease if there are no associated findings of fibrosis in the same area. The differential diagnosis of ground glass opacity should be based upon the host immune status and duration of symptoms.

The presence of connective tissue diseases, environmental inhalants, and drug use also should be considered when increased diffuse lung opacity is present.

Pulmonary Function Tests

Full pulmonary function tests (PFT) should be performed in all cases of suspected DPLD. They aid in the diagnosis, assessment of disease severity, response to treatment and prognosis. PFT measurements should include forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, vital capacity (VC) and diffusion capacity of carbon monoxide.

Lung function tests are usually restrictive with small lung volumes seen as reduced VC in DPLD. The FEV_1/FVC ratio is either maintained or often increased. DLCO is typically reduced in DPLD to greater extent than the lung volumes. Coexistence of DPLD with obstructive airway disease (e.g. emphysema), can confuse the results with a mixed pattern of restriction observed as reduced lung volumes and obstruction manifesting as a reduced FEV_1/FVC ratio. DPLD are usually thought to be characterised by restrictive lung function, by which is meant a reduction in lung volumes with preserved ratio of forced expiratory volume in one second.

Diagnosis and assessment of diffuse parenchymal lung disease can be done with FEV_1, forced vital capacity (FVC), FEV_1/FVC ratio, and VC together with a reduction in carbon monoxide transfer factor (DLCO). However, in early disease lung volumes and transfer factor may be within the normal range. Lung function tests are conventionally used to give a global index of functional impairment. Vital capacity (VC), total lung capacity (TLC), and DLCO are most commonly used while in the UK, exercise testing is used relatively little. Several studies have correlated lung function and

exercise test parameters with the degree of pathological abnormality on lung biopsy samples using the latter as the gold standard. Watters et al developed a composite clinical radiographic physiological (CRP) score using seven variables: dyspnoea, chest radiograph, FEV_1 and FVC, TLC, DLCO/VA, resting A–a gradient, and exercise oxygen saturation.

XRAY CHEST PA VIEW of a patient with methotrexate induced pulmonary toxicity.

HRCT CHEST of the same patient whose x-ray is given above

HRCT CHEST of another patient with traction bronchiectasis

MATERIALS AND METHODS

POPULATION STUDIED

This is a cross sectional study done by Institute of Thoracic Medicine, Chetpet and Government general hospital, Chennai during the period from march 2009 to september2009.The study patients were from Department of Dermatology, Government General Hospital , Chennai.

INCLUSION CRITERIA:

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

EXCLUSION CRITERIA:

Not able to perform PFT

Patients treated for pulmonary tuberculosis in the past

Patients known to have restrictive lung diseases due to other known causes like collagen vascular diseases.

METHOD :

All eligible Psoriasis patients who are on methotrexate therapy for more than 3 months (cumulative dosage exceeding 150mg) 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.

ATS RECOMMENDATION FOR PERFORMING SPIROMETRY

Procedures for recording spirometry were done as per ATS recommendation that include; Checking the spirometer calibration, Explanation of the test to subject, Preparation of the subject including asking about smoking, recent illness, medication use and measurement of weight and height. The subject were then instructed and demonstrated about the test including correct posture with head slightly elevated, rapid and complete inhalation and exhalation with maximal force.

After assuming the correct posture nose clip was attached and mouthpiece was placed in mouth with close lips around the mouthpiece. Patient was instructed to inhale completely and rapidly with a pause of one second at Total Lung Capacity and then to exhale maximally until no more air can be expelled while maintaining an upright posture. Repeated instructions were given. Minimum of three manoeuvres were repeated; no more than eight are usually required.

The variables recorded included FVC, FEV_1 and FEV_1 /FVC ratio. Three technically satisfactory measurements were obtained in which FVC was reproducible within 300 ml. The subject's FVC was defined as the maximal FVC which was determined before the DLCO test, as recommended by the ATS.

ATS RECOMMENDATION FOR PERFORMING DLCO

DLCO measurements were performed in compliance with the American Thoracic Society (ATS) guidelines. DLCO was measured using a single-breath technique. The DLCO was routinely adjusted for haemoglobin if the value was outside the normal range. Measurements of DLCO were made with a Collins automated system using a gas mixture that contained 0.3% Methane tracer gas and 0.3% carbon monoxide. The breath

holding time was 10 seconds and the washout volume was 0.75 L. Each subject's height and weight were measured.

The participants were seated, wearing nose clips, and performed at least two DLCO manoeuvers separated by more than 4 minutes. The mean DLCO value from two manoeuvers that matched within 3 ml/min/mm Hg was reported.

Before the test was performed, each subject was instructed about all of the required manoeuvers. After the subject had adapted to the mouthpiece of the test apparatus, four or five tidal volumes were recorded to determine a regular end expiratory baseline. The subject was then asked to exhale as far as possible, to the point till maximal exhalation had been reached (residual volume RV); making a rapid, maximal inhalation within 2 to 2.5 seconds to VC continuing to hold the breath for 10 seconds while relaxing against a closed glottis and exhaling rapidly. If after two attempts an acceptable measurement could not be made, the procedure was then abandoned.

The values were interpreted as follows:

DLCO and DLCOHb : Normal(>80% predicted) Mild diffusion defect (65-80%), Moderate diffusion defect(45-65%) and severe diffusion defect(<45%).

FVC:Normal(>80% predicted), Mild Reduction(60-80%), Moderate Reduction(40-60%), Severe Reduction(<40%).

RESULTS

In this study 154 patients from the outpatient department of psoriasis clinic of dermatology department of government general hospital, Chennai who were receiving methotrexate for psoriasis were screened. Out of which 30 patients who were eligible as per inclusion criteria were included in the study. Out Of these patients 7 were smokers, 2 were diabetic,2 were hypertensive out of which 1 was known patient of rheumatic heart

disease on treatment and 4 were known bronchial asthma patients. None of these patients with co-morbidity had methotrexate induced fibrosis.

AGE AND SEX DISTRIBUTION:

AGE AND SEX DISTRIBUTION

In this study, there were 15 males and 15 females.

Their age distribution was:

	20-35 years	**35-50 years**	**51 to 65 years**	**>65 years**
males	2	5	6	2
females	4	9	2	0

COMORBID CONDITIONS:

RADIOLOGICAL LESION VS PFT:

RADIOLOGICAL LESION VS SPIROMETRY:

	Restriction	Obstruction	Early obstruction	normal	Total
With radiological lesion	3	0	0	0	3
Without radiological lesion	10	3	5	9	27
Total	13	3	5	9	30

There were 21 patients with spirometric abnormalities.3 patients with radiological lesions had restrictive pulmonary function defect.10 patients without radiological lesions

had restrictive pulmonary function defect.3 patients had obstruction.5 patients had early obstruction as suggested by decrease in mid mean expiratory flow, normal fev_1 and normal chest x-ray.

There were 11 (36.6%) patients with restrictive ventilatory defect without radiological abnormalities, 7 (23.3%) patients with diffusion defects without radiological abnormalities. There were 5 (16.6%) of patients with small airway disease as evidenced by decrease in mean mid expiratory flow without other ventilatory defects and normal x-ray chest.

There were 3 patients with restrictive ventilatory defect and no diffusion defect and 2 patients with diffusion defect and no restrictive ventilatory defect. 2 patients had diffusion defect, small airway disease (decreased mmef) radiological lesions but no restrictive ventilatory defect.

CUMULATIVE DOSE VS PFT:

Diffusion defect and restrictive ventilatory defect occurred with least cumulative dose of 150mgs. Small airway disease occurred with a least cumulative dose of 860mgs.Least cumulative dose at which methotrexate induced pulmonary toxicity (10%) occurred was 2250 mgs.3 (10%) patients had received above this cut off cumulative dose without developing radiological lesions or pulmonary function defects. Hence in this study pulmonary toxicity seems to be independent of cumulative dose and is not dose dependant

CUMULATIVE DOSE AND PULMONARY FUNCTION

EOSINOPHILS VS PFT:

Ventilatory defects / Eosinophils%	**restriction**	**Diffusion defect**	**early obstruction**	**normal**
< 7%	9	8	2	8
>7%	4	2	3	3
Total	13	10	5	11

There was no relevance between pulmonary function defects and eosinophil count.

SYMPTOMS VS PFT:

SYMPTOMS VS SPIROMETRY:

	restriction	**obstruction**	**Early obstruction**	**Total (no:21)**
Symptoms > 1 month	4	2	2	8
Symptoms <1 month	9	1	3	13
Total	13	3	5	21

All 3 patients with pulmonary fibrosis presented with respiratory symptoms more than 1 month. There were 5 patients with symptoms, no pulmonary fibrosis and diffusion defect. There were 2 patients without symptoms, no pulmonary fibrosis and

diffusion defect. There were 2 patients with symptoms, restrictive pattern and no pulmonary fibrosis. There were 8 patients without symptoms, restrictive pattern and no pulmonary fibrosis. There were 2 patients with symptoms, early obstruction and no pulmonary fibrosis. There were 3 patients without symptoms, early obstruction and no pulmonary fibrosis.

SYMPTOMS VS DIFFUSION DEFECT:

	Diffusion defect	**Normal diffusion**	**Total**
Symptoms > 1 month	5	3	8
Symptoms < 1month	5	17	22
Total	10	20	30

PSORIATIC ARTHRITIS AND PULMONARY IMPAIRMENT:

There were 5 patients with psoriatic arthritis in this study.1 patient had pulmonary fibrosis.2 patients had diffusion defect and 2 patients had restrictive pattern in spirometry.

METHOTREXATE INDUCED PULMONARY FIBROSIS:

There were 3(10%) cases of methotrexate induced pulmonary toxicity according to modified searles and mckendry criteria. All of them (100%) had pulmonary diffusion defects.2 (66%) had restrictive ventilatory defects only. There were 2 males and 1 female patient. 2 males were above 50 years with psoriasis vulgaris and female was 20 years with pustular psoriasis. All 3 patients had dry cough and dyspnoea for more than 1 month. 2 patients (66%) had bilateral diffuse interstitial fibrosis. 1(33%) patient had

bilateral lower lobe traction bronchiectasis.

	Patient 1	Patient 2	Patient3
Age	60	20	56
Sex	male	Female	Male
Psoriasis type	Psoriasis vulgaris	Pustular psoriasis	Psoriasis vulgaris
Fever	no	no	No
cough	yes	yes	No
Expectoration	No	no	No
Dyspnoea	yes	yes	Yes
Duration of symptoms	4 months	4 months	4 months
Total count	8000/cmm	14600/cmm	7600/cmm
Eosinophils	2%	4%	2%
X-ray chest	B/L Interstitial pattern	B/L lower zone reticular shadows	B/L Interstitial pattern
HRCT Chest	B/L Interstitial fibrosis	B/L Lower lobe traction bronchiectasis	B/L Interstitial fibrosis
PFT	Severe restriction	Moderate restriction	Normal
Diffusion capacity	Severe	Mild	Mild
Arthritis	No	No	Yes
Cumulative dose	9360	8340	2250
Dose / week	30mg	15mg	7.5mg

DISCUSSION

In this study 9 patients showed normal radiology and pulmonary function test.21 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

There were 3 (10%) patients with radiological evidence of methotrexate induced pulmonary fibrosis.

There were 10 (33%) patients with restrictive pulmonary function defect without radiological evidence of methotrexate induced pulmonary fibrosis.

There were 7 (23%) patients with diffusion defect in this study without radiological evidence of methotrexate induced pulmonary fibrosis. Of these 7 patients, 5 patients had spirometric defect in the form of restriction.

There were 14 (47%) patients with symptoms, no radiological abnormality and no spirometric abnormalities. Of the above 14 patients, 2 patients (6.6%) had diffusion defect.

Prevalence of pulmonary function abnormalities in this study matches similar studies elsewhere.

DLco could be an early predictor of pulmonary function impairment in psoriasis Patients on long term methotrexate.

BIBLIOGRAPHY

1. Jolivet J, Cowan KH, Curt GA, et al. The pharmacology and clinical use of methotrexate. N Engl J Med 1983; 309:1094-1104

2. Weinblatt ME, Coblyn JS, Fox DA, et al. Efficacy of low dose methotrexate in rheumatoid arthritis. N Engl J Med 1985;312:818-22

3. Williams HJ, Willkens BF, Samuelson CO, et al. Comparison of low-dose oral pulse methotrexate and placebo in the treatment of rheumatoid arthritis. Arthritis Bheum 1985; 28:721-29

4. Weinstein A, Marlowe S, Korn J, et al. Low dose methotrexate treatment of rheumatoid arthritis. Am J Med 1985; 79:331-37

5. Kremer JM, Phelps CT. Long-term prospective study of the use of methotrexate in the treatment of rheumatoid arthritis: update after a mean of 90 months. Arthritis Bheum 1992; 35:138-45

6. Sostman HD, Matthay RA, Putman CE. Methotrexate-induced pneumonitis. Medicine 1976; 55:371-88

7. Engelbrecht JA, Calhoon SL, Scherrer JJ. Methotrexate pneumonitis after low-dose therapy for rheumatoid arthritis. Arthritis Rheum 1983; 26:1275-78

8. Cannon GW, Ward JR, Clegg DO, et al. Acute lung disease associated with low-dose pulse methotrexate therapy in patients with rheumatoid arthritis. Arthritis

Rheum 1983; 26:1269-73

9. St Clair EW, Bice JR, Snyderman B. Pneumonitis complicating low-dose methotrexate therapy in rheumatoid arthritis. Arch Itern Med 1985; 145:2035-38

10. Louie S, Iillington GA. Low dose methotrexate pneumonitis in rheumatoid arthritis. Thorax 1986; 41:703-04

11. Cook NJ, Carroll GJ. Successful reintroduction of methotrexateafter pneumonitis in two patients with rheumatoid arthritis. Ann Rheum Dis 1992; 51:272-74

12. Hargreaves MB, Mowat AG, Benson MK. Acute pneumonitis associated with low dose methotrexate treatment for rheumatoid arthritis: report of five cases and review of published reports.

13. Barrera P, Laan BFJM, van Riel PLCM, et al. Methotrexate-related pulmonary complications in rheumatoid arthritis. Ann Rheum Dis 1994; 53:434-39

14. Irifune K, Yokoyama A, Kohno N et al. T-helper cells induce alveolitis but do not lead to pulmonary fibrosis in mice. Eur Respir J 2003; 21: 11-18.

15. Clinical and experimental rheumatology 2001;19:727-730

16. Alarcon GS, Kremer JM, Macaluso M, et al: Risk factors for methotrexate-induced lung injury in patients with rheumatoid arthritis. A multicenter, case-control study. Methotrexate-Lung Study Group. *Ann Intern Med* 127:356–364, 1997.

18. Sostman HD, Matthay RA, Putman CE, et al: Methotrexate induced pneumonitis. *Medicine (Baltimore)* 55:371–388, 1976.

19. Searles G, McKendry RJ: Methotrexate pneumonitis in rheumatoid arthritis: Potential risk factors. Four case reports and a review of the literature. *J Rheumatol* 14:1164–1171, 1987.

20. Kelly CA. Rheumatoid arthritis: classical rheumatoid lung disease. Clin Rheumatol 2993;7:1-13.

21. Kremer JM, Alarcon GS, Weinblatt ME, Kaymakcian MV, Macaluso M, Cannon GW, et al. Clinical, laboratory, radiographic, and histopathologic features of methotrexate-associated lung injury in patients with rheumatoid arthritis: a multicenter study with literature review. Arthritis Rheum 1997;40:1829–37.

22. Roth PE, Grosshans E, Bergoend H. Psoriasis: development and fatal complications. Ann Dermatol Venereol1991; 118: 97-105.

23. Cottin V, Tebib J, Massonnet B et al. Pulmonary function in patients receiving long-term low-dose methotrexate.Chest 1996; 109: 933-8.

24. Salaffi F, Manganelli P, Carotti M et al. Methotrexate-induced pneumonitis in patients with rheumatoid arthritis and psoriatic arthritis: report of five cases and review of the literature. Clin Rheumatol 1997; 16: 296-304.

25. McKenna KE, Burrows D. Pulmonary toxicity with psoriasis receiving methotrexate therapy. Clin Exp Dermatol2000; 25: 24-7.

26. Imokawa S, Colby TV, Leslie KO, Helmers RA. Methotrexate pneumonitis: review of the literature and histopathological findings in nine patients. Eur Respir J 2000; 15: 373-81.

27. Alarcon GS, Kremer JM, Macaluso M et al. Risk factors for methotrexate-induced lung injury in patients with rheumatoid arthritis. Ann Intern Med 1997; 127: 356-64.

28. Ameen M, Taylor DA, Williams IP et al. Pneumonitis complicating methotrexate therapy for psoriasis. J Eur Acad Dermatol Venereol 2001; 15: 247-9.

29. Morand JJ, Sallaberry M, Guennoc B et al. Syndrome de fuite capillaire : problématiques étiopathogéniques et thérapeutiques. Nouv Dermatol 2000; 19: 701-7.

30. Nickoloff BJ. The immunologic and genetic basis of psoriasis. Arch Dermatol 1999; 135: 1104-10.

31. Guo RF, Ward PA. Mediators and regulation of neutrophil accumulation in inflammatory responses in lung: insights of the IgG immune complex model. Free Radic Biol Med 2002; 33: 303-10.

32. Van Barneveld PWC, Van Der Mark TW, Sleijfer DT, et al. Predictive factors for bleomycin-induced pneumonitis. Am Bev Respir Dis 1984; 130:1078-81

33. Forster RE. Rate of gas uptake by red cells.In: Fenn WO, Rahn H, eds. *Handbook of Physiology*.Washington, DC: American Physiological Society, 1964: 839.

34. Said SI, Thompson WT, Patterson JL,Brummer DL. Shunting effect of extreme impairment of pulmonary diffusion. *Bull Johns Hopkins Hosp* 1960; 107: 255.

35. Finley TN, Swenson EW, Comroe JH. The cause of arterial hypoxaemia at rest in patients with ‘alveolar capillary block syndrome’. *J Clin Invest* 1962; 41: 618.

36. McHardy GJR. Diffusing capacity and pulmonary gas exchange. *Br J Dis Chest* 1972; 66: 1.

37. Roughton FJW, Forster RE. Relative importance of diffusion and chemical Reaction rates in determining rate of exchange of gases in the human lung, with special reference to the diffusing capacity of pulmonary membrane and volume of blood in the lung capillaries. *J Appl Physiol* 1957; 11: 290.

38. Greening AP, Hughes JMB. Serial estimation of carbon monoxide diffusing capacity in intrapulmonary haemorrhage. *Clin Sci* 1981; 60: 507.

39. Armstrong BW, Hurt HH, Palumbo L *et al.* Normal pulmonary DO2: a 10 year follow up and an analysis of its errors. *J Appl Physiol* 1967; 23: 902.

40. Comroe JH, Forster RE, Dubois AB, Briscoe WA, Carlsen E. *The Lung: Clinical Physiology and Pulmonary Function Tests*, 2nd edn. Chicago: Year Book Publishers, 1962.

41. Darling RC, Cournand A, Richards DW. Studies on the intrapulmonary Mixture of gases. III. An open circuit method for measuring residual air. *J Clin Invest* 1940; 19: 609.

42. Prime FJ. Respiratory function tests for a clinician. *Tubercle* 1973; 3: 1.

43. Bates DV, Macklem PT, Christie RV. *Respiratory Function in Disease*. Philadelphia: WB.

44. Series ‘‘ATS/ERS task force: standardisation of lung function testing’’ Eur Respir J 2005; 26: 319–338.

45. American thoracic society: Single breath carbon monoxide diffusion capacity (Transfer factor) : Recommendations for a standard technique- 1995 update, Am J Respir update, Am J Respir crit care Med 152:2185-2198,1995.

46. British Thoracic Society. The diagnosis, assessment and treatment of diffuse

parenchymal lung disease in adults: introduction.Thorax 1999; 54(suppl):S1–S28.

47. Hansel Armstrong, Idiopathic interstitial pneumonia and immunologic disease of lungs; 564-588.

48. Papiris SA, Maniati M, Constantopoulos SH, et al. Lung involvement in primary Sjögren's syndrome is mainly related to the small airway disease. Ann Rheum Dis 1999;58:61–4.

49. Brett Elicker, Carlos Alberto de Castro Pereira HRCT patterns of diffuse interstitial lung disease with clinical and pathological correlation J Bras Pneumol. 2008;34(9):715-744.

50. Principles of internal medicine , Harrison's, 17th edi,

ABBREVIATIONS

ATS	American Thoracic Society
CVD	Collagen Vascular Disease
DIP	Diffuse Interstitial Pneumonia
DLCO	Diffusing Capacity for Carbon Monoxide
DLCO/VA	Diffusing capacity for carbon monoxide per unit of alveolar volume
DPLD	Diffuse Parenchymal Lung Disease
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GGO	Ground Glass Opacity
H_2O	Water
Hb	Haemoglobin
HRCT	High Resolution Computerised Tomography
ILD	Interstitial lung diseases
KCO	Transfer coefficient of the lung (DLCO/VA)
LIP	Lymphocytic Interstitial Pneumonitis
MCTD	Mixed Connective Tissue Disease
NSIP	Non-Specific Interstitial Pneumonitis
O_2	oxygen
PaO_2	partial pressure of oxygen

PFT	Pulmonary Function Test
Q	perfusion
RA	Rheumatoid Arthritis
Th_1	T helper cells 1
TLC	Total lung capacity
VA	Alveolar Volume
VD	Dead space volume
WBCs	white blood cells
WK	Week

PATIENT PROFORMA

Name : Age/Sex : Address :

Clinical Diagnosis : Psoriasis

Methotrexate :

Started on :

Dosage :

Cumalative Dose :

Comorbid Illness :

Other Significant H/o :

Smoker / Non Smoker :

Blood Investigation :

Bid Hb TC DC ESR RBS UREA CREATININE

Na+ K+ S.Bilirubin(T) SGOT SGPT SAP Protein(T) Albumin

ECG

CXR HRCT

SPIROMETRY

DLCO