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REVIEW ARTICLE

EFFECT AND SAFETY OF LOW DOSE OF MYCOPHENOLATE MOFETIL AND N-ACETYL CYSTEINE IN INTERSTITIAL LUNG DISEASE (ILD)

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ABSTRACT

Background: In Interstitial lung disease (ILD), Glucocorticoids and immune-modulatory agents are mainstays of therapy. Only few studies with dose of 2-3 gm. /day have been performed for evaluation of role of Mycophenolate mofetil and N-acetyl-cysteine in ILD(IPF).

Aims & objectives: In this study our objective were to examine the safety and efficacy of low dose Mycophenolate Mofetil (MMF) and N-Acetyl cysteine and to determine its impact on lung function in patients with ILD(IPF) based on the ILD subtypes.

Methods: We retrospectively identified patients, who met the ATS/ERS 2010 criteria for ILD and received low dose of MMF 360 mg/ twice a day and N-Acetyl cysteine 600 mg tdsfor 12 months. All of them had routine laboratory, pulmonary function and radiological investigation (high resolution computed tomography-HRCT) data available and were enrolled in the study. Forced vital capacity (FVC), total lung capacity (TLC), diffusion capacity of the lung for carbon monoxide (DLCO), 6-minute walking distance (6MWD), HRCT scans and routine laboratory data at treatment onset were compared with respective values 6 and 12 months after treatment onset.

Result:thirty two were treated with low dose MMF and N-Acetyl-cysteine for ILD (IPF). The most commonreason for initiating low dose MMF& N-Acetyl cysteine was an adverse effect of high dose of MMF and adverse effect of prior immunomodulatory agent. There were significant alterations in FVC, TLC, DLco and 6MWD pre and 6 and 12 months post treatment. No case of clinically significant infection leucopenia or elevated liver enzyme were recorded. Low dose MMF and N-acetyl-cysteine, well tolerated and allows reduction or discontinuation of steroids without worsening of symptoms or objective progressive of disease. MMF in combination with N-Acetyl cysteine is less toxic and its targeted anti fibrotic properties make it potentially more effective than other immunosuppressive.

Conclusion; Low dose MMF 360 mg and N-Acetyl-cysteine 600 mg appears to be safe and well tolerated and show significant alterations in FVC, TLC, and DLCo in patients with ILD (IPF) and allows reduction or discontinuation of steroids without worsening of symptoms. Larger-scale studies are needed to further evaluate the efficacy of low dose of MMF and N-Acetyl cysteine in this patient population

INTRODUCTION

Interstitial lung disease, is aheterogeneous chronic, progressive, irreversible, and usually lethal lungdisease of unknown cause (Schwarz, 2003). ILD and can lead to significant morbidity and mortality (Marigliano B Soriano, 2013). ILD occurs in middle-agedand elderly adults (median age at diagnosis 66 years, range 55–75 years), is limited to the lungs, and isassociated with a histopathological or radiological patterntypical of usual interstitial pneumonia (Schwarz, 2003; Marigliano B Soriano, 2013 and Kocheril, 2005).

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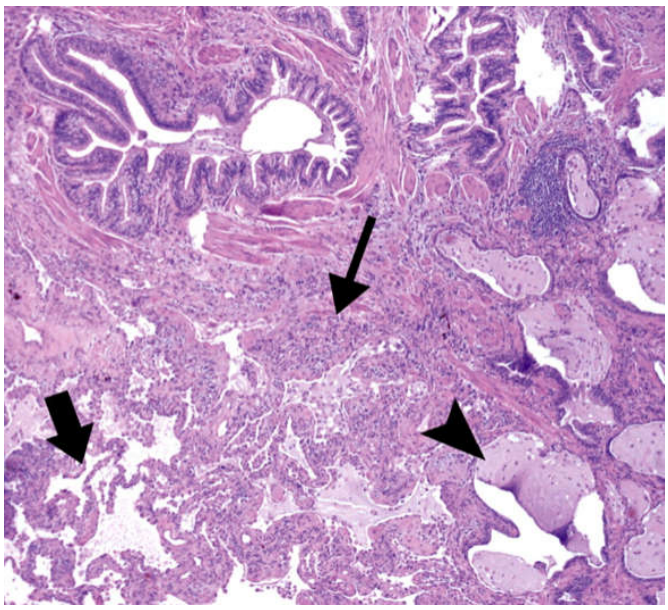
CTD-ILD is most common type of frequently encountered ILD (Strange, 2004). Mycophenolate Mofetil (MMF), an inhibitor of inosine monophosphate dehydrogenase, influences T and B lymphocytes proliferation by altering the synthesis of guanosine nucleotides and inhibits transforming growth factors β (TGF- β), leading to immunosuppressive and anti-fibrotic effects (Allison, 1993 and Chan, 2000). N-Acetyl cysteine reduces the lung oxidative stress (Eur Respir J, 2004) and have potent mucolytic action (Eur Respire J, 2003). The majority of studies included patients from European and North American origin (Schneider, 2012), currently, there is no data and studies done on Indian patients. The main histo-pathological features of usual interstitialpneumonia, best seen at low magnification, is a heterogeneousappearance with areas of sub-pleural and

para-septal fibrosis and honeycombing (i.e., cystic fibroticairspaces lined by bronchiolar epithelium and often filledby mucin and variable numbers of inflammatory cells) alternating with areas of less affected or normal parenchyma (spatial heterogeneity). Small areas of active fibrosis (fibroblast foci) are present in the background of collagendeposition, and they reflect the temporal heterogeneity ofthe process and indicate current ongoing disease (Schneider, 2008). Inflammation is usually mild and consists of a patchylymphoplasmacytic interstitial infiltrate (Figure 1).

Histologic features of UIP

Photomicrograph (original magnification, ×40; hematoxylin-eosin stain) shows patchy fibrosis with remodeling of the lung architecture. Interstitial chronic inflammation is mild, with only a few lymphoid aggregates (thin arrow). Cystically dilated airspaces that produce a honeycomb pattern (arrowhead) and areas of relatively unaffected lung (thick arrow) are present



Mueller-Mang C et al. Radiographics 2007;27:595-615

Thepresence of a usual-interstitial-pneumonia pattern onhigh-resolution CT is characterized by reticular opacities, often associated with traction bronchiectasis, with little orno ground-glass opacifications. Honeycombing,manifested as sub-pleural, clustered cystic airspaces withwell-defined walls (typically 3–10 mm in diameter), iscommon and is critical for making a definite diagnosis, BAL cellular differential showing neutrophils or eosinophil's, or cellular interstitial infiltrates in surgical lung biopsy specimens are treated more aggressively – and respond more favorably than patients with a fibrotic pulmonary phenotype (Tausche, 2001). Patients with IPF usually seek medical attentionbecause they suffer chronic and progressive exertiondyspnea and cough. Bibasilar inspiratory crackles areheard on chest auscultation and frequently fingerclubbing is found. The natural history of IPF has beencharacterized as a steady or slowly progressive lungdisorder, and most patients follow this pattern. However, recent findings indicate that IPF is a heterogeneousdisease and new clinical phenotypes with distinct patternsof survival are being described. The pathogenic mechanismsare unclear, but a growing body of evidenceindicates that the disease is the result of an abnormalbehavior of the alveolar epithelial cells that provoke the migration, proliferation, and activation of mesenchymal cells, with the formation of fibroblast and myofibroblast foci. Activated myofibroblasts secrete exaggerated amounts of extracellular matrix molecules with the subsequent destruction of the lung architecture. In an effort to limit a patient's exposure to the adverse effects of glucocorticoids, certain immunomodulatory agents (e.g. CYC or azathioprine [AZA]) have been incorporated into ILD (IPF) treatment regimens as steroid-sparing agents. However, like glucocorticoids, these agents carry their own potential toxicities and side effects. Recently, mycophenolate mofetil (MMF), an inhibitor of proliferating lymphocytes via its effects on the purine synthesis pathway. Treating ILD (IPF) patients with MMF and N-Acetyl cysteine. Our primary objective was toevaluate the safety and tolerability of using MMF and N-Acetyl cysteine ina heterogeneous sample of patients with variousILD (IPF). A secondary objective of this study wasto examine the impact of MMF and N-Acetyl cysteine on pulmonary physiology in these patients.

Methods

This was a single centerretrospective, open- label, randomized, parallel study conducted in the Department of Pharmacology , Department of Medicine , SIMS Hapur, U.P. the study was done for on avg 371 days fromDecember 2016 to June 2017 a total no of 32 patients were enrolled in the therapy.We identified all the patients with IPF(ILD) who were either a diagnose case and already taking treatment or was recently diagnosed if the patient full filled the established classification criteria ATS/ERS-2010 at our institution. We initiated MMF with 640 mg/day and maintain the patient on same dose. The dose of N-Acetyl cysteine at 1.2 to 1.8 gm. /day. All patients received bone protection with vit-D3 60000 I.U week and calcium≥600mg/day. Anti-reflux therapy with proton-pump inhibitor. Patient classified according to underling ILD pattern either as non-specific interstitial pneumonia (NSIP) and unspecific interstitial pneumonia (UIP), based on radiological or histological findings. Inclusion criteria is patient diagnosed on basis of ATS/ERS-2010. Exclusion criteria were as follows: ILD pattern other than UIP and NSIP, a diagnosis of drug induced or unclassified pulmonary fibrosis, and pregnancy. Written informed consent was waived because of the retrospective nature of the study. The multidisciplinary team consisted of pulmonologist, radiologist, pathologists who met on bimonthly basis to discuss clinical serological and radiological and pathological findings of patients with ILD.

Physiological measurements

Pulmonary function test (PFT) were performed using standard methods spirometry, and measurement of the diffusion capacity of the lung for carbon monoxide (DLco). Arterial blood gas were obtained for the partial pressure of oxygen (PaO2), the partial pressure of carbon dioxide (PaCO2). Patient were asked to perform the 6-min walk test (6MWT) in accordance with American Thoracic Society guidelines (ATS statement, 2002). Oxygen saturation was recorded at the beginning and end of 6-min walk test. Total distance walked in meter was recorded.

Chest high-resolution computed tomography (HRCT)

All patients underwent computed tomography scanning. Full volume scans reconstructed every 2.5 mm were obtained

through the entire thorax. Scans were performed during suspended inspiration with the patients in the supine position. Additional limited scans using 1.25 mm thin collimation at 10 mm intervals at aortic arch to the base of lung, with high spatial resolution reconstruction, were obtained at end-expiration with patients in prone position.

Statistical Analysis

Descriptive statistics are presented as the mean standard deviation or number (percentage). The used as appropriate to compare the studied variables. More or equal to 10% changes in the forced vital capacity (FVC) and DLco values and a change of 30m in the 6MWT. A two-sided p value <0.10 was considered statistically significant. Chest high-resolution computed tomography (HRCT).

RESULTS

Thirty two patients were included in the final analysis. Baseline characteristics and underlying disease are shown in Table 1. There was a female predominance 20(62.5%) with a mean (± standard deviation) age 52.1 ± 16.2 years. The mean body mass index was 28.4 ± 5.9. The mean FVC and DLco of the studied group 52.6 ± 18.0% and 60 ±14.2%, respectively (Table 2). There were 20 patients in the NSIP (62.5%) group and 12 patients in UIP (37.5%) patient in NSIP are of younger (mean 48.2 ± 15.6) age group and had a lower PaCO2 at baseline

Table 1. Baseline characteristics of the study group

Characteristic	Overall (n=32)
Age, years	52.1 ± 16.2
Female gender, n%	20 (62.5)
Ever smoker, n%	5 (15.6)
Disease duration, months	63.5 ± 75.5
Duration of therapy, months	16.3 ± 11.4
BMI	28.4 ± 5.9
Overweight, n (%)	13 (40.6)
Obese	13 (40.6)
Co-morbidities	
Ischemic heart disease	4 (12.5)
Hypertension	12 (37.5)
Diabetes mellitus	6 (18.75)
The data are presented as the mean ± standard deviation or number of (percentage)	

Table 2. Baseline physiological parameters of the study group

	Overall n=32
Pulmonary function test	
FVC,% predicted	52.6 ± 18.0
TLC, % predicted	60 ± 14.2
DLco. % predicted	38.8 ± 20.5
6-minute walk test	
Initial Spo2, %	95.6 ± 2.7
Final Spo2%	85.8 ± 6.4
Distance meters	352.3 ± 64.8
Arterial blood gas	
PaO2, mm Hg	75.0 ± 17.2
PaCO2, mm Hg	40.4 ± 5.9
The data are presented as the mean ± standard deviation	

ILD IN 64 YR OLD MALE

High-resolution CT image obtained at presentation shows reticular opacities, honeycombing (arrowhead), and focal ground-glass opacity (thick arrow). Moderate traction bronchiectasis is present (thin arrow). These findings are consistent with the UIP pattern (Figure 2).

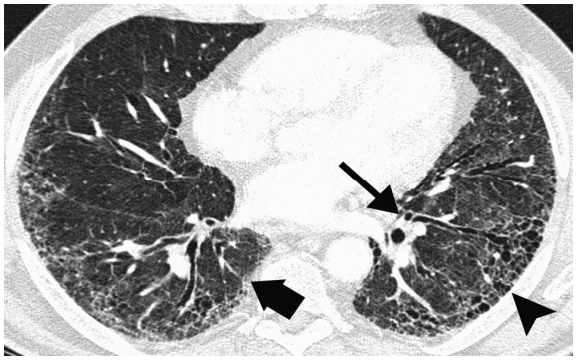


Table 3.

End points	
Death – no. (%)	
From any cause	
2(6.6%)	
From respiratory causes	
1(3.2%)	
Hospitalization for any cause – no.%	5(15.6%)
Acute exacerbation – no (%)	
3(9.37%)	
Serious adverse event – no. (%)	
2(6.6%)	

Physiological measures

At the time of last follow up, treatment with MMF & NAC resulted in stabilization or improvement of FVC in 25 (78.1%) patients, of DLco in 22(68.7%) patients , of 6MWT in 15 (46.8%) and of PaO_2 in 23 (71.8%) patients.

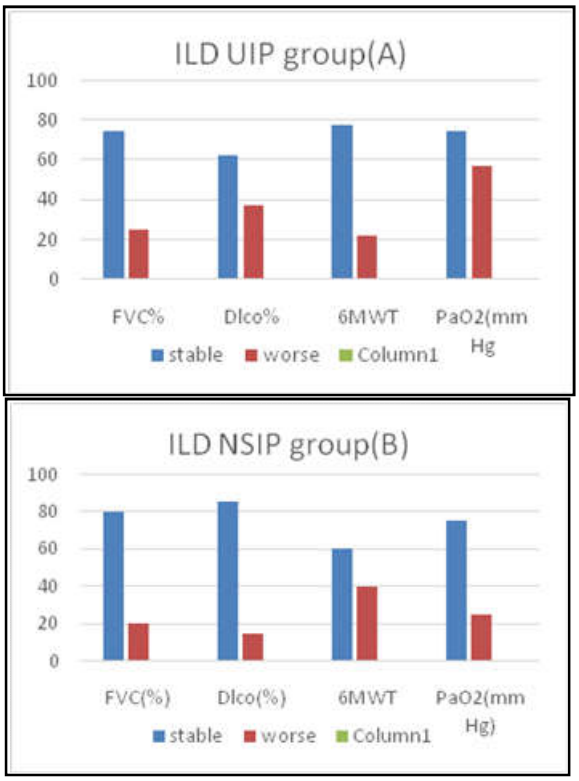


Figure 3. change over time in the forced vital capacity (FVC), diffusion capacity of the lung for carbon monoxide(DLco), partial pressure of oxygen (PaO2), and 6-min walk test (6MWT) for the whole cohort (A) ILD-UIP group (B) ILD-NSIP GROUP

The response to MMF & NAC was similar for both ILD types. PaO_2 values were more likely to stable or improved in the NSIP group than in UIP (76% vs. 52%, p=0.0046). 4 patients showed neither improvement nor dec. in there physiological measures. 5 patients need to hospitalize in emergency for acute exacerbation and serious adverse event. There is one mortality from respiratory cause and 2 from any cause

Radiological measures

Follow up HRCT was available for 10 and 13 patients with UIP and NSIP. Both ILD showed similar radiological outcomes Table (4).

Table 4. HRCT Result

Variable	ILD- UIP	ILD- NSIP	p-Value
HRCT interval months	25.1 ± 15.2	17.6 ± 6.4	0.122
HRCT available	N=10	N=13	
worse	0	3 (23.1)	0.229
Stable or improved	10 (100)	10(76.9)	0.229

Adverse effects

A total of 4 patients in the studied population reported adverse events at the starting of the treatment like headache, flu-like symptoms, nausea/vomiting and diarrhea which were treated symptomatically on OPD basis. During follow up, there was no documented incidence of pancytopenia, malignancy, or bacterial or opportunistic infection.

DISCUSSION

Treatment of ILD can be challenging and it is essential that the chosen immunosuppressive agents target the lung and other involved organs. The most common reason of starting MMF at lower dose was to intolerance to higher dose of Mycophenolate mofetil and other immunosuppressive agents. A total of 4 patients developed adverse events which were treated symptomatically on OPD basis. MMF resulted in stabilization of physiological parameters and a reduction in daily steroid doses.

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