

The effectiveness of immunosuppressive cyclosporin in attenuating the progression of interstitial lung diseases

Mathew Suji Eapen¹, Archana Vijay Gaikwad¹, Isobel E. Thompson¹, Wenying Lu¹, Stephen Myers¹, Pawan Sharma^{2,3}, Sukhwinder Singh Sohal¹

¹Respiratory Translational Research Group, Department of Laboratory Medicine, College of Health and Medicine, University of Tasmania, Launceston, Tasmania, Australia; ²Medical Sciences, University of Technology Sydney, Sydney, NSW, Australia; ³Woolcock Emphysema Centre, Woolcock Institute of Medical Research, University of Sydney, Sydney, NSW, Australia

Correspondence to: Dr. Sukhwinder Singh Sohal. Respiratory Translational Research Group, Department of Laboratory Medicine, School of Health Sciences, College of Health and Medicine, University of Tasmania, Locked Bag – 1322, Newnham Drive, Launceston, Tasmania 7248, Australia. Email: sssohal@utas.edu.au.

Comment on: Takei R, Arita M, Tokioka F, *et al.* Cyclosporin A in idiopathic chronic fibrosing interstitial pneumonia without idiopathic pulmonary fibrosis. J Thorac Dis 2018;10:6695-701.

Submitted Mar 09, 2019. Accepted for publication Apr 09, 2019. doi: 10.21037/jtd.2019.04.44

View this article at: http://dx.doi.org/10.21037/jtd.2019.04.44

Interstitial lung diseases (ILDs) are a group of diseases that affects the lung parenchymal tissue causing irreversible damage through fibrosis and chronic inflammation, consequentially depriving gas exchange in affected individuals (1). The effects in ILDs are observed largely in the lung interstitium and differentiating them from one other is challenging as they often share comparable physiological, clinical and radiological features (2). Their aetiologies exist either in known or unknown forms. Known actiology of ILDs include those that may have genetic predisposition which includes pulmonary manifestation of existent rheumatoid arthritis (RA) (3) or other autoimmune diseases also known as interstitial pneumonia with autoimmune features (IPAF) (4), connective tissue diseases (CTDs) such as scleroderma (systemic sclerosis), inflammatory myositis (polymyositis and dermatomyositis), Sjögren syndrome and other undifferentiated CTD (5). Environmental factors such as bioaerosol induce hypersensitivity pneumonitis, while exposure to bird proteins, hay dust, molds and mycobacterium can also induce ILD to varying degrees. Occupation associated ILDs include asbestosis or silicosis while drugs such as amiodarone, methotrexate and nitrofurantoin are known to affect lung interstitium causing ILDs (6). Tobacco smoking is also linked to ILDs in some forms of desquamative interstitial pneumonia (DIP) and respiratory bronchiolitisassociated interstitial lung disease (RB-ILD) and pulmonary langerhans' cell histiocytosis (LCH) (7,8). There are however ILDs whose aetiologies are still unknown or are complex, these mainly constitutes the rare forms of ILDs such lymphangioleiomyomatosis (LAM) and granulomatous such as Sarcoidosis (2,9).

The unknown forms of ILDs can be broadly classified as non-specific, unclassifiable and rare idiopathic interstitial pneumonia (IIPs). These include both idiopathic pulmonary fibrosis (IPF) and non-IPF ILDs. IPF (previously called cryptogenic fibrosing alveolitis) forms the most common of the IIPs, is a chronic, progressive interstitial fibrotic that affects exclusively the lung and occurs primarily in older adults. IPF is essentially defined by a radiological and/or pathological pattern of usual interstitial pneumonia (UIP) (10). The non-IPF is broadly classified as IIPs which includes non-specific interstitial pneumonia (NSIP), cryptogenic organising pneumonia also previously known as bronchiolitis obliterans with organising pneumonia (BOOP), acute interstitial pneumonia (AIP), RB-ILD, DIP and lymphatic interstitial pneumonia (LIP) (11).

NSIP holds prominence among the various ILDs with over a quarter of all associated IIPs. They exist in at least two forms or types-cellular and fibrotic. The cellular form is characterised by inflammation of the cells associated within interstitium and are observed to affect both innate and adaptive immune changes, while fibrosis is associated with the thickening and scarring of lung tissue (2,12). In high-resolution computed tomography (HRCT) NSIP demonstrates abnormalities predominantly lower lung reticular ground glass opacities with irregular lines. They are either diffused or peripheral in the axial dimension. Some of the commonest findings were reticular abnormalities, traction bronchiectasis and lobar volume loss, sub-pleural sparing and peribranchial thickening are observed (13). Unlike IPF, honeycombing is generally absent in patients with NSIP. Further distinguishing factors from that of IPF is the presence spatial and temporal homogeneity and also the fact that there is subpleural sparing. Patients with fibrosing NSIP have restrictive ventilatory defects on lung function and lower DLCO (2).

More recently, the term "chronic fibrosing interstitial pneumonia" (CFIP) has been used to describe entities that includes pathologies of both IPF and NSIP (14). One of the key understanding in the diagnostic characterisation of CFIP is eliminating them from other causes. For example, CTD such as IPAF are commonly encountered in patients with IIPs who have autoimmune clinical features but do not meet the definitive criteria for CTD, however, at times ILDs usually could precede the diagnosis of CTD (14). Considering the clinical complexities and indistinguishable similarities in the pathophysiological features involved in IIPs, the study by Takei et al. (15) places considerable effort in identifying a specific group of idiopathic CFIP (iCFIP) population wherein patients were excluded based on symptoms associated with both CTD and IPF patients. The study further examines the role of immunosuppressive drugs such as cyclosporin in these specific patient population. Cyclosporin (CsA) was shown to be effective in these patients illustrated clearly by the significant decrease in physiological parameters such as %FVC, %DLCO and composite physiologic index, since the years of CsA initiation with the best outcomes observed in 2 years after dosage. The effectivity was especially enhanced in these patients who were also on low doses of prednisolone (PSL); demonstrating an anti-inflammatory additive effect of these drugs, albeit through completely differential mechanisms, can attenuate the disease progression.

CsA is an effective immunosuppressive drug, which has been successfully used for suppressing immune cells in organ transplant patients to avoid rejection (16). They are known to efficiently block the transcription of cytokine genes that can activate T cells. CsA forms complex bond with cyclophilin, inhibiting the phosphatase activity of calcineurin. Calcineurin (CaN) is a calcium and calmodulin dependent serine/threonine protein phosphatase that regulates nuclear translocation and activation of transcription factors such as NFAT (17). Further, CsA also blocks JNK and p38 pathways triggered by self or nonself-antigen recognition, thus inhibiting T cell immune response (18). More recently the role of CsA in attenuating fibrosis have been explored in animal models of IPF and they have been shown to exhibit their anti-fibrotic effect by degrading hypoxia-inducible factor-1 α (19). The dual action of CsA may thus be of an advantage to achieving considerable attenuation in the overall progression of the disease.

Interestingly, previous studies indicate the use of other immunosuppressive agent such as cyclophosphamide in NSIP and IIPs with CTDs (20), are effective in attenuating the progress of the disease. Typically, in all ILDs, the treatment strategies only help restrict the progression of the disease, rather than complete cure and therapeutic decisions are undertaken by a multidisciplinary team that combines clinical, radiological and histological evidences. Depending on the overall primary outcome of whether inflammatory or fibrotic or both, treatment of ILDs are variable and would usually require more than one therapeutic agent. The standard mode of treatment is to first achieve a highdose corticosteroid and further use immunosuppressive drugs, and the latter is added on only when corticosteroids cannot be narrowed down to lower doses (21). There are several immunosuppressive drugs used as maintenance therapy that includes alkylating agents such as azathioprine, mycophenolate mofetil, colchicine and cyclophosphamide (22).

The effectivity of a therapy can be measured by identifying the physiological lung function parameters as well as biomarkers associated with the disease. The later involves invasive techniques such as extracting lung bronchial biopsies and bronchioalveolar lavage (BAL) through bronchoscopy. Although they are useful samples in the clinical diagnosis of ILDs (23), they are comparatively rarer, as it becomes increasing difficult to perform these procedures owing to the poor health conditions in these patients. In this study, the authors have acquired these samples from 94% of their unique patient population. Further, the authors through differential cell counts have determined the percentage of the corresponding inflammatory cells. Interestingly, the lymphocyte counts in these patient's treated with CsA and low dose PSL were close to 14% which was well within the normal range. In ILD a greater than 15% lymphocytes are usually

Journal of Thoracic Disease, Vol 11, Suppl 9 May 2019

encountered leading to lymphocytosis, thus raising the question of the effectiveness of high dose corticosteroids in these patients. However, more astonishingly, perhaps the authors have missed out is the increase in eosinophil counts which stood at 2% almost more than double of the normal subject range of less than 1% (23). This suggest possible condition of eosinophilic pneumonias that seems again uncontrolled with the current regimen used in the study (24). Further, the observed decrease in macrophage may be desirable but perhaps more importantly the identification of the of macrophage sub-population (M1 or M2) might determine the overall outcome of the disease. Previous observations in other chronic lung diseases such chronic obstructive pulmonary diseases (COPD) have demonstrated that the presence of specific macrophage subtypes can determine the fate of the surrounding tissues, either being inflammatory or fibrotic (25). Another vital factor which the authors haven't investigated is the role of microbiome in the lung of these patients. It is well established that normal lung flora of these patients are almost completely replaced by the more pathogenic forms of bacteria especially streptococcus pneumonia and haemophilus influenzae. The use of immunosuppressive drugs like CsA and PSL may could provide further sanctuary to these harmful infections to proliferate and colonize (26). Thus, strategies have to be in place to counteract these pathogens (27,28).

Finally, perhaps the most important is the increased toxicity that largely looms when using strong immunosuppressive's as treatment strategies. CsA has been associated with a numerous side effects which includes nephrotoxicity, renal vascular damage and hypertension (29). In this study the authors did report a patient who suffered from renal dysfunction with the treatment regimen, considering low number of patients used in the study can be major drawback. The authors did overcome this debacle by monitoring the dosing regimen based on the values derived from areas under curve (AUC). The study found an effective dose that would avoid any probable adverse side effect, however this may have to be verified in another independent study.

In conclusion as in many other research areas, the challenge lies in better understanding basis of disease manifestation and progression. In-depth analysis of the molecular mechanisms that are in play needs to be better deciphered and perhaps more personalised therapeutic approach for specific ILDs could be used to develop a more comprehensive clinical trial in these patients. The current study strength lies in the fact that the authors have chosen a very specific population transgressing the complexities involved in diagnosing such clinically overlapping disorders. The role of CsA and other immunosuppressive drugs needs to be further validated by using efficient strategies that includes identifying appropriate biomarkers through proteomic and transcriptomic methodologies as this will help better predict therapeutic outcomes. The use of similar treatment strategies in other ILDs of unknown aetiology would be beneficial and research in this area is further warranted.

Acknowledgements

SS Sohal is supported by Clifford Craig Foundation Launceston General Hospital, Lung Foundation Australia and LAM Australia Research Alliance. P Sharma is supported by Rebecca L. Cooper Medical Research Foundation, Australia and Chancellors Fellowship Programme, University of Technology Sydney (UTS).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

- Raghu G, Brown KK. Interstitial lung disease: clinical evaluation and keys to an accurate diagnosis. Clin Chest Med 2004;25:409-19, v.
- Cottin V, Hirani NA, Hotchkin DL, et al. Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. Eur Respir Rev 2018;27. doi: 10.1183/16000617.0076-2018.
- Kim EJ, Collard HR, King TE Jr. Rheumatoid arthritisassociated interstitial lung disease: the relevance of histopathologic and radiographic pattern. Chest 2009;136:1397-405.
- Fischer A, Antoniou KM, Brown KK, et al. An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. Eur Respir J 2015;46:976-87.
- Antoniou KM, Margaritopoulos GA, Tomassetti S, et al. Interstitial lung disease. Eur Respir Rev 2014;23:40-54.
- Sack C, Raghu G. Idiopathic pulmonary fibrosis: unmasking cryptogenic environmental factors. Eur Respir J 2019;53. doi: 10.1183/13993003.01699-2018.

Eapen et al. Cyclosporin and ILDs

- S1142
- Margaritopoulos GA, Vasarmidi E, Jacob J, et al. Smoking and interstitial lung diseases. Eur Respir Rev 2015;24:428-35.
- 8. Hagmeyer L, Randerath W. Smoking-related interstitial lung disease. Dtsch Arztebl Int 2015;112:43-50.
- Bradley B, Branley HM, Egan JJ, et al. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax 2008;63 Suppl 5:v1-58.
- Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2018;198:e44-68.
- Coley CJ, Tolle LB, Hasvold J, et al. Non-specific, Unclassifiable, and Rare Idiopathic Interstitial Pneumonia: Acute Interstitial Pneumonia, Respiratory Bronchiolitis Interstitial Pneumonia, Desquamative Interstitial Pneumonia, Nonspecific Interstitial Pneumonia. In: Cottin V, Cordier J-F, Richeldi L, editors. Orphan Lung Diseases: A Clinical Guide to Rare Lung Disease. London: Springer London, 2015:349-62.
- Walsh SL, Devaraj A, Enghelmayer JI, et al. Role of imaging in progressive-fibrosing interstitial lung diseases. Eur Respir Rev 2018;27. doi: 10.1183/16000617.0073-2018.
- Belloli EA, Beckford R, Hadley R, et al. Idiopathic non-specific interstitial pneumonia. Respirology 2016;21:259-68.
- Yoshimura K, Kono M, Enomoto Y, et al. Distinctive characteristics and prognostic significance of interstitial pneumonia with autoimmune features in patients with chronic fibrosing interstitial pneumonia. Respir Med 2018;137:167-75.
- Takei R, Arita M, Tokioka F, et al. Cyclosporin A in idiopathic chronic fibrosing interstitial pneumonia without idiopathic pulmonary fibrosis. J Thorac Dis 2018;10:6695-701.
- Colombo D, Ammirati E. Cyclosporine in transplantation

 a history of converging timelines. J Biol Regul Homeost Agents 2011;25:493-504.
- 17. Matsuda S, Koyasu S. Mechanisms of action of cyclosporine. Immunopharmacology 2000;47:119-25.
- Rincón M, Flavell RA, Davis RA. The JNK and P38 MAP kinase signaling pathways in T cell-mediated immune responses. Free Radic Biol Med 2000;28:1328-37.

- 19. Yamazaki R, Kasuya Y, Fujita T, et al. Antifibrotic effects of cyclosporine A on TGF- β 1-treated lung fibroblasts and lungs from bleomycin-treated mice: role of hypoxia-inducible factor-1 α . FASEB J 2017;31:3359-71.
- Silver RM, Warrick JH, Kinsella MB, et al. Cyclophosphamide and low-dose prednisone therapy in patients with systemic sclerosis (scleroderma) with interstitial lung disease. J Rheumatol 1993;20:838-44.
- Richeldi L, Varone F, Bergna M, et al. Pharmacological management of progressive-fibrosing interstitial lung diseases: a review of the current evidence. Eur Respir Rev 2018;27. doi: 10.1183/16000617.0074-2018.
- Cappelli S, Guiducci S, Bellando Randone S, et al. Immunosuppression for interstitial lung disease in systemic sclerosis. Eur Respir Rev 2013;22:236-43.
- 23. Meyer KC, Raghu G, Baughman RP, et al. An official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. Am J Respir Crit Care Med 2012;185:1004-14.
- 24. Akuthota P, Weller PF. Eosinophilic pneumonias. Clin Microbiol Rev 2012;25:649-60.
- 25. Eapen MS, Hansbro PM, McAlinden K, et al. Abnormal M1/M2 macrophage phenotype profiles in the small airway wall and lumen in smokers and chronic obstructive pulmonary disease (COPD). Sci Rep 2017;7:13392.
- 26. Eapen MS, Sohal SS. Understanding novel mechanisms of microbial pathogenesis in chronic lung disease: implications for new therapeutic targets. Clin Sci (Lond) 2018;132:375-9.
- Salisbury ML, Han MK, Dickson RP, et al. Microbiome in interstitial lung disease: from pathogenesis to treatment target. Curr Opin Pulm Med 2017;23:404-10.
- Sohal SS, Hansbro PM, Shukla SD, et al. Potential Mechanisms of Microbial Pathogens in Idiopathic Interstitial Lung Disease. Chest 2017;152:899-900.
- 29. Gijtenbeek JM, van den Bent MJ, Vecht CJ. Cyclosporine neurotoxicity: a review. J Neurol 1999;246:339-46.

Cite this article as: Eapen MS, Gaikwad AV, Thompson IE, Lu W, Myers S, Sharma P, Sohal SS. The effectiveness of immunosuppressive cyclosporin in attenuating the progression of interstitial lung diseases. J Thorac Dis 2019;11(Suppl 9):S1139-S1142. doi: 10.21037/jtd.2019.04.44