Case Report

Longstanding hypersensitivity pneumonitis and its response to roflumilast: A review of its likely immunological effects

V.A. Varney [a],[*], G. Quirke [b], Alaa Witwit [c], A.S. Bansal [d]

[a] Respiratory + Allergy & Immunology, St Helier Hospital, Wrythe Lane, Carshalton, Surrey, SM51AA, UK
[b] Respiratory Dept, St Helier Hospital, Wrythe Lane, Carshalton, Surrey, SM51AA, UK
[c] Dept of Radiology, St Helier Hospital, Wrythe Lane, Carshalton, Surrey, SM51AA, UK
[d] Dept of Immunology, St Helier Hospital, Wrythe Lane, Carshalton, Surrey, SM51AA, UK

A B S T R A C T

We describe the case of a 42yr old man with evidence of hypersensitivity pneumonitis referred with cough and breathlessness for several years which had further deteriorated in the prior 12 months. He had known atopic asthma without evidence of activation.

A chest CT scan showed widespread ground glass change in his lung fields. He had feather bedding at home and in his youth cleaned aviaries. His forced vital capacity and lung volumes were reduced along with oxygen saturations at rest (92% on air), overnight (83% on air) and upon walking (78%). Steroids were commenced for a total of 6 months with little consistent improvement in symptoms or objective measures and with no change in his CT scan appearance. As a result, a trial of roflumilast (a phosphodiesterase-4 inhibitor) was commenced due to its range of immunological effects and in order to avoid long-term immune suppression with mycophenolate motefil in a young patient.

On roflumilast treatment his cough and breathlessness improved at 4 weeks and the chest crackles cleared. An interval Chest CT scan showed resolution of the ground glass change with improved CT scores that are maintained 2 yrs. All oxygen measures improved and nocturnal oxygen was discontinued. His Lung function has remained largely stable on roflumilast and symptoms of cough and breathlessness have resolved. This case report reviews the immunology of hypersensitivity pneumonitis and the likely actions of Roflumilast relevant to this condition. It is the first published case report documenting its use in hypersensitivity pneumonitis.

1. Introduction

Hypersensitivity Pneumonitis (HP) is now recognised as an immune-mediated syndrome triggered by a wide variety of antigens [1–3]. Only a small minority of exposed individuals develop clinical disease, suggesting that host factors are important. As such, certain HLA-alleles are associated with bird fanciers lung [2]. While mixtures of antigens contribute to the disease, no cause is recognised in 30–60% of cases. The antigens cause immune mediated inflammation affecting the lung parenchyma especially the alveoli, terminal bronchi and interstitium [2,4].

Acute presentations of HP (aHP) include cough, dyspnoea, fever and lung crackles giving restrictive lung function; Symptoms may arise within hours of acute exposure [2,3,5]. In sub-acute or chronic HP, the onset is more insidious with cough, exertional dyspnoea and fatigue over months or years that may slowly progress to a fibrotic change with respiratory insufficiency in some subjects [1,6]. The term sub-acute HP is now less favoured, leaving the main division into acute or chronic HP, with chronic HP further subdivided into chronic non-fibrotic HP or chronic fibrotic HP [1,3,7,8].

In cHP, there is architectural distortion, reticular opacities, peribronchial interstitial thickening with ill-defined centrilobular ground glass change and mosaic attenuation that spares the lung bases. Fibrotic changes if present, show traction bronchiectasis and honeycomb change. Bronchoalveolar lavage (BAL) is characterised by lymphocytes (20%) in aHP that may be absent in cHP despite biopsy support for the disease. Typically, the lymphocytes are CD8^{+} activated Cytotoxic T-cells [5,7,9].

The exact immunological processes in HP remain unclear. Enigmatically, 80% of pigeon breeders have positive IgE skin tests to bird feathers. HP was considered to be a mixture of type III (immune complex disease) and type IV (cell mediated Immunity) Immune responses but defects in the suppressor T-regulatory lymphocytes (Tregs) appears more likely [4–7,10–13].

The treatment of cHP presents considerable difficulties as there are no double-blinded trials of therapy and therapeutic regimens follow "Expert Opinions" from generally small treatment groups published as case series with very few large randomised studies [6,8, 14].

The mainstay of treatment is complete avoidance of the inciting agent if known, but progression can occur despite this. Corticosteroids resolve aHP symptoms faster than avoidance alone (0.5–1.0mg/kg for 2–4 weeks), but in cHP (0.5–1.0mg/kg for 4–8 weeks with tapering to 10mg/day) there are often limited responses that do not affect outcome nor prevent fibrotic changes (7–9). We report a case of cHP in whom treatment with roflumilast proved beneficial in the absence of a significant response to steroids.

2. Case report

A 42 year old office worker with known atopic asthma was referred in October 2018 with increasing cough and sputum associated with shortness of breath on exertion for over a year. The patient felt his cough was a problem for up to 13yrs, but had definitely become worse in the prior 12 months **despite prolonged courses of steroids from his general practitioner for presumed asthma activation in 2018 and early 2019.** He was a lifelong non-smoker taking regular **budesonide (160mcg) and formoterol (4.5mcg)** 1 puff BD for his asthma.

Skin tests confirmed him to be atopic with positive reactions to house dust mites, grass pollen, horse and dog dander, but negative to feathers, cats, tree pollen and mould spores. There was a family history of asthma in his father. He had 2 cats at home along with feather bedding and at work there was air-conditioning.

His Chest X Ray reported: the heart is enlarged without overt signs of cardiac failure. There are increased lung markings suggestive of inflammatory change in both lower lobes.

On auscultation crackles could be heard at the lung bases on auscultation.

Spirometry showed a peak expiratory flow rate (PEFR) of 520 (78% predicted), Forced expiratory volume in 1 second (FEV-1) of 1.53 (43% predicted), Forced Vital Capacity (FVC) of 1.71 (40% predicted) with a FEV-1/FVC ratio of 89%. His exhaled nitric oxide

Table 1
Summarised case report objective measures.

Treatment + date	Initial data Feb 2019	Prednisolone 30mg/day 4Wk April 2019	Prednisolone 10mg/day May–July 2019	Prednisolone Weaned 2.5mg/ month Aug–Dec 2019	Roflumilast 500mcg/day Commenced Jan 2020	Roflumilast Aug 2020	Roflumilast June 2021	Roflumilast Feb 2022
FEV1	43%	49%	44%	40%	46%	57%	51%	51%
FVC	38%	49%	40%	35%	42%	56%	48%	41%
PEFR	78%	78%	67%	86%	86%	93%	98%	82%
Total Lung capacity	46%		58%				45%	
Saturations On air	92%	92%	92%	92%	93%	95%	95%	97%
Residual Volume	69%		94%				56%	
Vital capacity	36%		44%				40%	
TLCO	46%		42%				37%	
Va	52%		44%				43%	
KCO	93%		96%				86%	
Mean overnight Saturations on air	83%					86%	89%	90%
Shuttle walk Distance(m)	670				630	630	690	680
Arterial PO2 (Air)	9.1 KPa				9.1 KPa		11.1 KPa	11.8KPa
+Total CT scores	28			28			16	16
Ground glass	25			25			8	8
Septal lines	1			1			5	6
Honeycomb	0			0			1	O
Emphysema	2			2			2	2

reading was 19 ppb (normal <25 ppb) with a normal methacholine PC_{20} > 32mg/ml **indicating no significant bronchial hyper-responsiveness**. Lab based lung function showed a FVC of 38%, Total lung capacity 46%, residual volume 69%, TLCO 46%, alveolar volume (VA) 52%, carbon monoxide uptake (KCO 93%) see Table 1.

Resting oxygen saturations on air were 92% with desaturation to 78% upon walking along the hospital corridor. Arterial gases on air confirmed type 1 respiratory failure with a PO_2 of 9.1KPa (normal ≥12KPa). See Table 1.

Further tests showed overnight mean oxygen saturations to be 83% on air dipping to 75% during episodes of nocturnal hypo-ventilation requiring overnight oxygen (at 2 L/min) to correct this.

A shuttle walk test confirmed good exercise tolerance completing 670 m (level 10 of 12) with desaturation post shuttle down to 69% requiring 92 seconds to recover to 90%.

An echocardiogram reported normal left ventricle size and function with good systolic function and ejection fraction of 55%. Normal left atrium size, normal right heart size and function, essentially normal valves without evidence of raised pulmonary artery pressure.

An HRCT scan report stated: Bilateral diffuse ground glass changes with areas of mosaic perfusion mainly in the lower lobes. No reticular change or UIP pattern seen but Small areas of paraseptal emphysematous change in both upper lobes. The heart is enlarged, No pulmonary congestion is seen. There is no pleural or pericardial effusion.

The differential included pneumocystis infection, other opportunist infections or hypersensitivity pneumonitis.

Routine blood tests, immune tests, auto-antibodies and retroviral screen all returned normal/negative but positive avian precipitins were detected to budgerigar IgG at 22.5mg/l (normal <10mg/l) but were negative to pigeon. On enquiry there was a past weekend job of cleaning aviaries that housed parrots and McCaw's lasting 7 years from the age of 14–21 years. As a result, removal of his feather bedding was requested and avoidance if possible of his work based air-conditioning due to the risk of aerosolised bacterial and mould spores. The patient was asked to commence regular Vitamin D3 2000iu/day.

At bronchoscopy his whole airway looked inflamed and coughing generated some white mucopus from the right lower lobe. Bronchoalveolar lavage (BAL) taken from the upper and lower lobes was negative for bacterial, fungal, pneumocysts and atypical infections and there were no malignant cells. The BAL showed a $CD3^+$ lymphocytosis with a raised $CD8^+$ T cells at 47% (normal 10–39%) and $CD4^+$ T-cells 51% (normal 28–57%).

The working diagnosis was likely chronic hypersensitivity pneumonitis with lung biopsy was avoided in view of his reduced lung capacity. Further oral steroids were commenced in April 2019 initially at 30mg mane for 4 weeks (0.5mg/kg) and budesonide (160mcg) and formoterol (4.5mcg) was increased to 2 puffs BD.

At 4 weeks, spirometry showed improvement in FEV-1 by+400mls (49%), and FVC by +300mls (49%) with PEFR stable. FEF25-75% (small airway) was 91% predicted (Table 2).

Symptomatically his cough, sputum and breathlessness reduced somewhat in the first 4 weeks **but were still troublesome and responses were similar to the long prednisolone courses from his general practitioner in 2018 that produced no consistent change. Due to his prolonged steroid treatment over the last year before referral,** Prednisolone was maintained at 10mg mane for 3 months **with his feather bedding removed with a** follow-up CT scan at 4 month. This CT scan showed no resolution of the extensive ground glass change by the steroids (Table 1) nor improvement in objective measures despite 4 months of oral steroids and antigen avoidance with FEV-1 = 1.52 (44%), FVC 1.67 (40%), PEFR 67%, saturations 92% (Table 1). **No adverse effects of steroids were reported from his prolonged treatments in 2018–2019 except weight gain and increased appetite.**

At this stage, his CT scans were sent for a 2nd opinion to the London regional centre for interstitial lung disease to the Professorial Radiology Unit. This review considered the CT scan to be consistent with subacute/chronic hypersensitivity pneumonitis, with low attenuation lobules as part of a mosaic pattern characteristic for HP with occasional cyst formation but without significant fibrotic changes.

Prednisolone was planned to reduce by 2.5mg per month to zero (August–December 2019). In December 2019, spirometry showed: FEV-1 = 1.37 (40%), FVC = 1.45 (35%), PEFR 86% and saturations 92% on air. Total lung capacity 58%, TLCO 42%, VA 44%, KCO

Table 2

-Immunological effects of Roflumilast.

Mediator	Action of mediator	Effect of roflumilast	Reference
Tregs	Suppresses T cell responses to antigen but suppressive function subverted by IL-17 driven TNFα release in HP	↓↓	30
Tumour Necrosis factor α	From leucocytes + dendritic cells suppress Tregs ability to down regulate T-cell proliferation and antigen responses	↓↓↓	34,35,37, 39
IL-17	From T-cells where it ↑TNFα secretion that suppress Tregs	↓	20, 31, 37
Transforming growth factor β1	Activates fibrotic processes in the presence of chronic inflammation	↓↓	12,38
IFN-γ	From TH2 cells + drives the lymphocytic alveolitis + fibrosis. Its blockade reduces HP disease.	↓	12
IL-10	Produced by Tregs and reduces antigen presentation with tolerogenic effects on dendritic cells	↑↑	30
Fibroblast growth factor	Activates fibrotic processes + wound repair	↓	38
IL-18	Stimulates lymphocytes to produce IFN-γ secretion that drives TNFα, IL-17 + IL-6 production.	↓↓	31
Il-1β	From monocytes + dendritic cell enhanced by IL-17 and drives further IL-17 + TNFα production that reduces Tregs function	↓↓	25
Interleukin-6	↑ IFN-γ production by monocytes + B cells	↓	38

96% (Table 1).

In January 2020, it was decided to try the oral phophodiesterase-4 inhibitor roflumilast 500 μg/day due to its range of immunological effects on the airway that may offer benefit and avoid further steroids or long-term immunosuppression especially **with concerns over a looming Covid-19 pandemic and following discussion with the patient.**

At 1 month, the patient announced himself to be better with reduced cough, sputum and improved exercise tolerance but again there was little change in spirometry FEV-1 = 1.57 (46%), FVC 1.73 (42%), PEFR 86% with saturations on air of 93%. Arterial gases showed no improvement PO_2 (9.1KPa). Shuttle walk performance was maintained at 630 m with post shuttle lowest saturations of 71% recovering in 85 seconds (Table 1).

Roflumilast treatment was continued as Immune benefit is slow usually between 3 and 6 months in COPD studies. Due to the 1st Covid lockdown further assessment between March–June 2020 were by telephone.

In August 2020, spirometry showed an FEV-1 = 1.97 (57%), FVC 2.35 (56%), PEFR 93% with resting saturations in clinic improved to 95% on air. Overnight mean saturations on air had improved to 86% (lowest nocturnal reading now 82%). Shuttle walk performance was maintained at 630 m with post shuttle lowest saturations of 72% recovering in 60 seconds. His symptoms were minimal leading to the patient discontinuing overnight oxygen himself.

Due to a 2nd Covid-19 lockdown, the next face to face assessment was April 2021 when no chest crackles could be heard in the lung fields and saturations were 95% on air. His FEV-1 was 1.76 (51%), FVC was 2.0 (48%) and PEFR 98%. Overnight mean saturations on air were 89% (without any desaturation). Arterial PO_2 improved to 11.1KPa. Shuttle walk test had improved to 690 m (level 10) lowest saturations 72% recovering in 83 secs.

In June 2021, lab based lung function taken during the grass pollen season gave a total lung capacity of 45%, with residual volume of 56%. Vital capacity was 40% with TLCO 37.5% and VA 43% and KCO 86%.

In August 2021 following 18 months of roflumilast, the total HRCT score (Hansel & Wells) had fallen to 16 from 28. This was due to a dramatic reduction in ground glass scores but a small increase in septal lines was observed (Table 1).

A repeat assessment in Feb 2022 shows the HRCT score to be stable and resting saturations 96% with overnight mean saturation 90% on air (lowest reading 89% overnight).

No side effects from the roflumilast occurred and his asthma has remained stable with only one course of steroids required for a cold induce wheeze in the 2 yrs. Otherwise respiratory symptoms of cough, sputum and breathlessness have been minimal or completely absent.

3. Discussion

In 1932, Campbell gave the first description of farmer's lung that became the classic example of extrinsic allergic alveolitis. By 1960 a similar disease was recognised in bird keepers as "Bird fanciers lung" and since then there are a growing list of recognised causes of HP [1,15].

The prevalence of HP in Europe varies from 0.3–0.9 cases per 100 000 population, rising to 30 per 100 000 in New Mexico and is even higher in India [1,2,4,7,16]. Heat and humidity, seasonal changes, farming and lifestyle practices affects the generation of antigens with repeat exposures from home, work or hobbies inducing HP [8]. Generally HP affects younger patients (mean age <50yr) unlike other interstitial lung diseases (mean age >70).

In our patient with cHP, daily symptoms were present with past bird antigen exposure, feather bedding and possible air-conditioning at work judged the most likely source of causal antigens. His initial lung function was concerning due to a low FVC (40%) and TLCO (46%) with desaturation on exertion and nocturnal hypoxia. Further oral steroids with antigen avoidance in the first 4 months showed some spirometry improvement but no consistent reduction in cough, breathlessness and sputum akin to the prolonged courses from his general practitioner in 2018 for presumed asthma. Likewise objective findings did not support on-going steroid treatment past 6 months with the avoidance measures.

The off-label use of azathioprine and mycophenolate motefil in cHP is common, although azathioprine and prednisolone are generally avoided in fibrotic cHP [17-19]. A recent Rituximab trial showed improvement in TLCO and Forced Vital Capacity in 3 out of 6 patients in a case series. The anti-fibrotic drug pirfenidone added to immunosuppression, produced no change in lung function although some improvement in quality of life scores (The St Georges Hospital Respiratory Questionnaire) [9].

Roflumilast was therefore commenced as a trial due to its range of immunological effects that may offer benefit to his condition and avoid long-term Immune suppression with the looming Covid pandemic.

After the first month of roflumilast our patient announced definite improvement in all symptoms and exercise tolerance and he continued to feel better and latterly stopped his own overnight oxygen. This was 13 months after his initial referral date when feather bedding and air-conditioning avoidance measures had already been implemented along with steroids therapy for 6 months without definite benefit. This would suggest that the effects of roflumilast were real and the source of his improvement after Jan 2020 separate from his avoidance measures. Arterial PO2, resting and overnight saturations, HRCT all improved along with loss of lung crackles with roflumilast.

To date HP is understood to be an impaired immune tolerance mechanism secondary to defective T-regulatory cell function (Tregs) [6]. Since Tregs are involved in antigen tolerance and suppress immune responses to inhaled antigens they should prevent the responses that causes HP [20,21]. Defective Tregs could explain these exaggerated responses to antigens with lymphocytosis and unregulated T cell proliferation that is known to produce HP. Tregs are a unique population of $CD4^+$ T cells that exhibit the surface markers of CD25, IL-2Rα and FoxP3+. The latter is specific for Tregs and distinguishes them from other T cells [3,20].

Studies have examined the ability of isolated blood and BAL derived Tregs to suppress T-cell proliferation. This has confirmed Tregs dysfunction, with healthy controls able to suppress T cell proliferation by 42–47%, while asymptomatic antigen exposed cases show intermediate suppressive activity of 29–32%. For cases of HP disease, blood and BAL derived Tregs showed zero ability to suppress T cell proliferation [20]. Loss of Tregs function is needed to develop HP and move from an asymptomatic antigen exposed case to disease. Reduced Foxp3 expression allows TH1 to TH2 lymphocyte switching as seen in HP; with the TH2 subtype being pro-fibrotic [3].

Interleukin-17 (IL-17) is a proinflammatory cytokine believed to be causal in Tregs malfunction [6,11]. Animal studies suggest HP to be an IL-17 driven disease, whose severity correlates with IL-17 levels. Deletion or neutralisation of IL-17 protects against Mouse HP. Healthy controls and asymptomatic antigen exposed cases have low levels of IL-17 in BAL and blood, while high levels are present in patients with HP disease. IL-17 promotes several cytokines (Interleukin-1β (IL-1 β), IL- 6 and tumour necrosis factor-α(TNF-α)) that can subvert normal Immune suppression by Tregs, with TNFα generated by IL-17 considered to play an important role in defective Tregs function [11,22,23].

Tregs are very sensitive to TNFα with their function restored by anti-TNF treatments [24]. TNFα is low in BAL from healthy controls (210pg/ml) but is raised in asymptomatic exposed cases (1498pg/ml) and is very high in HP disease (3233pg/ml) [20] Macrophages and dendritic cells can produce TNFα and IL-1 β upon antigen stimulation. IL-1 β acts directly on memory B cells and CD4 T cells to enhance antigen driven expansion of IL-17 levels giving further TNFα production [6,25].

Viral infections in murine models of HP promote maturation of dendritic cells with the production of IL-17 that further impairs Tregs function with disease activation [6]. Lack of adequate Tregs function and Foxp3 expression allows T-Helper-1 cells to change phenotype to the T-helper-2 [20]. This change is implicated in fibrotic processes in animal and human HP, where transforming growth factor- β1 (TGFβ1) activation of fibroblasts through chronic inflammation drives the fibrotic process [26]. The cytokine interferon-gamma (IFNγ) secreted by T helper cells also appears central to the lymphocytic alveolitis, granuloma formation and fibrosis [12]. Blockade of IFNγ attenuates mouse HP. Adoptive transfer of T cells absent in IFNγ (−/−), reduced HP while the addition of IFNγ is shown to aggravate the condition [6,26–29].

Animal studies show that Vitamin D3 increases antigen-specific Tregs numbers leading to a more immunosuppressive phenotype. Oral supplementation of 12,000–30,000 IU/week can increase circulating CD3 + CD4$^+$ Tregs cells by 37% over 3 months [30]. 1, 25 dihydroxy Vitamin D induces Foxp3 transcription factor that aids this polarisation of lymphocytes with the release of interleukin-10 (IL-10) by Tregs that reduces antigen presentation by tolerogenic effects on dendritic cell [30].

Roflumilast has anti-inflammatory effects in COPD and asthma by increasing levels of intracellular cyclic AMP and changing mediator release (Table 2) [26,31–34]. It significantly reduces cellular influx into the lung, microvascular leak and reduces a range of pro-inflammatory mediators upon antigen challenge in animal models. Both neutrophils and monocytes can generate TNF-α along with reactive oxygen series. Roflumilast suppresses TNFα and thereby reduces neutrophil and monocyte infiltration and activation [30,33]. TNFα is thought to account for 70% of the emphysematous lung changes in smokers, and in cHP is linked to the emphysema-cysts that occur in non-smokers where TNFα levels are known to be high [35,36].

Roflumilast has been shown to interrupt the chain of inflammatory events by inhibiting TNFα secretion both in vivo and in vitro that reduces mucus production via effects on epithelial growth factor receptor [6]. Roflumilast has been shown to down regulate IFN-γ leading to the reduced expression of mRNA for the fibrogenic cytokine TGFβ1 and also fibroblast growth factor-2 (FGF-2) in airway epithelium in sensitized mice [12]. Animal studies show increased levels of IL-10 by 79% at roflumilast doses of 1mg/kg and by 129% at 5mg/kg; and this cytokine is both is tolerogenic and reduces antigen presentation which could reduce active disease in HP.

Interleukin-18(IL-18) comes from a wide range of immune cells with its main function to stimulate lymphocytes to produce IFNγ and regulate cell activity by increasing further IL8, TNFα and IL-6 [6,20,31,37]. Roflumilast reduces IL18 production in a dose dependant way which also produces an inhibitory effect on IL-17 production and these various actions may be the basis of roflumilast action in this patient [31].

4. Conclusion

The ability of roflumilast to likely influence many of the immunological processes in cHP was the reason for its use. The benefit included resolution of his cough, improvements in oxygenation and nocturnal hypoxia and resolution of extensive ground glass change. There were some improvements in spirometry although limited, and probably reflecting the duration of this condition prior to referral. This is the first case report of Roflumilast use in HP and the authors consider that a future comparison of roflumilast with other immunosuppressant treatments and their effects on TNF-α and IL-17 levels in blood and BAL would being interesting in HP and may pave the way for further understandings in this condition and its treatment.

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