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Case report

Addition of antifibrotic therapy to immunosuppression in hypersensitivity pneumonitis: A case series

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ABSTRACT

Hypersensitivity pneumonitis has historically been treated with immunosuppression, but recently nintedanib was approved for the treatment of progressive fibrotic HP. One limitation of INBUILD is that the only immunosuppression (IS) permitted at the time of enrollment was glucocorticoids at a dose of less than 20mg per day, so the additive effect of antifibrotic (AF) therapy to IS in HP remains unclear. We present 5 cases of patients with HP for whom AF therapy was added to IS. Trends observed in the cohort include reduced decline in FVC, oxygen requirement, and symptoms in the year after adding AF to IS in 4 of the 5 patients. All 5 patients (100%) in our series demonstrated progression in the year prior to initiation of antifibrotic based on criteria outlined in the INBUILD trial, but only 1 of 5 (20%) progressed in the year after AF. There was a significant decrease in the rate of relative decline in % predicted FVC in the 12 months after initiation of antifibrotic compared to the 12 months prior to antifibrotic (0.4% ±7.6 vs −17.5% ±7.6, $p = 0.0495$). Compared to the 12 months prior to antifibrotic therapy, fewer patients met criteria for progression in the 12 months after initiating antifibrotic therapy ($p = 0.048$). Similarly, fewer patients met criteria for progression in the 6 months after initiating antifibrotic therapy compared to the 6 months prior ($p = 0.048$). A larger study with control groups on IS alone and AF alone is needed to confirm the role of AF therapy in combination with IS in patients with HP.

Hypersensitivity pneumonitis (HP) is a group of granulomatous, interstitial, bronchiolar, and alveolar-filling pulmonary diseases caused by repeated exposure and sensitization to a variety of organic and chemical antigens [1]. HP has historically been treated with immunosuppressive medications, including mycophenolate and azathioprine, which have been shown to improve diffusing capacity in patients with HP. Rituximab has also been used in HP and in one retrospective study led to stabilization or improvement in pulmonary function testing in a subset of patients [2]. Prednisone, while commonly used in the treatment of HP, has not been shown to reduce the decline in lung function in patients with HP [3].

Recently, nintedanib has been approved for the treatment of progressive fibrotic HP based on the INBUILD trial [4,5]. In this trial, 26.1% of patients had HP (25.3% of the intervention group and 26.9% of the placebo group), and progressive fibrosis was defined as one or more of the following occurring in the 24 months before screening: a relative decline in forced vital capacity (FVC) of at least 10% predicted, a relative decline in FVC 5–10% predicted and either worsening of respiratory symptoms or an increased extent of fibrosis on high-resolution computed tomography (HRCT), or worsening of respiratory symptoms and an increased extent of fibrosis on HRCT.

One limitation of INBUILD is that the only immunosuppression (IS) permitted at the time of enrollment was glucocorticoids at a dose of less than 20mg per day. Patients who were treated with azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, rituximab, cyclophosphamide, or oral glucocorticoids at a dose of more than 20 mg per day were excluded from the trial. These medica-

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tions could be initiated after 6 months of the clinical trial in patients with a clinically significant deterioration of interstitial lung disease (ILD) or connective tissue disease, though <5% of patients in the trial were on mycophenolate, azathioprine, or rituximab by week 52 [6]. Because patients on steroid-sparing immunosuppressive medications, which are the prior standard of care for HP, were excluded from the INBUILD trial, the additive effect of antifibrotic (AF) therapy to steroid-sparing IS in HP remains an unclear but clinically important research question [5]. We present 5 cases of patients with HP for whom AF therapy was added to IS that consisted of oral glucocorticoids as well immunomodulatory agents.

1. Case presentations

1.1. Case 1

Patient 1 was a 41 year old white female former smoker with mold and avian antigen exposure, and a high resolution computed tomography (HRCT) inconsistent with usual interstitial pneumonia (UIP). Diagnosis of HP was made on the basis of exposure and surgical lung biopsy showing cellular interstitial pneumonia with multinucleated giant cells and non-necrotizing granulomas. Nintedanib was added when the patient experienced worsening of symptoms, progression of fibrosis by CT chest, increasing oxygen requirement from 2LPM to 6LPM with exertion, and decline in relative forced vital capacity (FVC) % predicted by 27.2% over 12 months despite antigen removal and an IS regimen of mycophenolate 1.5g twice daily and prednisone 10–30mg daily (Fig. 1). Following initiation of AF, FVC, symptoms, and oxygen requirement remained stable over 12 month follow-up; the patient has not had a repeat CT since initiation of AF.

1.2. Case 2

Patient 2 was a 69-year-old white male former smoker who was diagnosed with HP based on mold exposure and transbronchial biopsy showing non-necrotizing granulomas and lymphoplasmacytic infiltrate. His HRCT was notable for moderate fibrosis, ground glass, centrilobular micronodules, and air trapping in a pattern consistent with a non-IPF diagnosis; honeycombing was not present. He had a decline in relative FVC % predicted of 9.8% in 12 months, worsening dyspnea, and progression on HRCT chest despite mycophenolate 1000mg twice daily and prednisone 5mg daily after having removed his mold exposure. After nintedanib 150mg twice daily was added to his IS, his FVC declined by 10.8% in the subsequent year, symptoms worsened, and HRCT showed continued progression of fibrosis on AF and IS. Oxygen requirement remained stable over the 2-year period at 2LPM with exertion.

1.3. Case 3

Patient 3 was a 70 year old white male, former smoker, without an identifiable antigen, and an HRCT inconsistent with UIP. Diagnosis of HP was made on the basis of transbronchial biopsy revealing non-necrotizing granulomas and an interstitial mononuclear pneumonitis. Nintedanib was added when his symptoms worsened, oxygen requirement increased from 4LPM with exertion to 15LPM, relative FVC % predicted declined by 18.6%, and HRCT revealed progression over 1 year on mycophenolate 1000mg twice daily. In the year following initiation of AF, his symptoms stabilized, FVC improved by 9.1%, oxygen requirement remained stable at 15LPM, and HRCT remained stable.

1.4. Case 4

Patient 4 was a 65 year old white female never smoker with avian antigen exposure, and an HRCT inconsistent with UIP. Diagnosis of HP was made on the basis of exposure and surgical lung biopsy which displayed heterogeneous and predominantly bronchiolo-

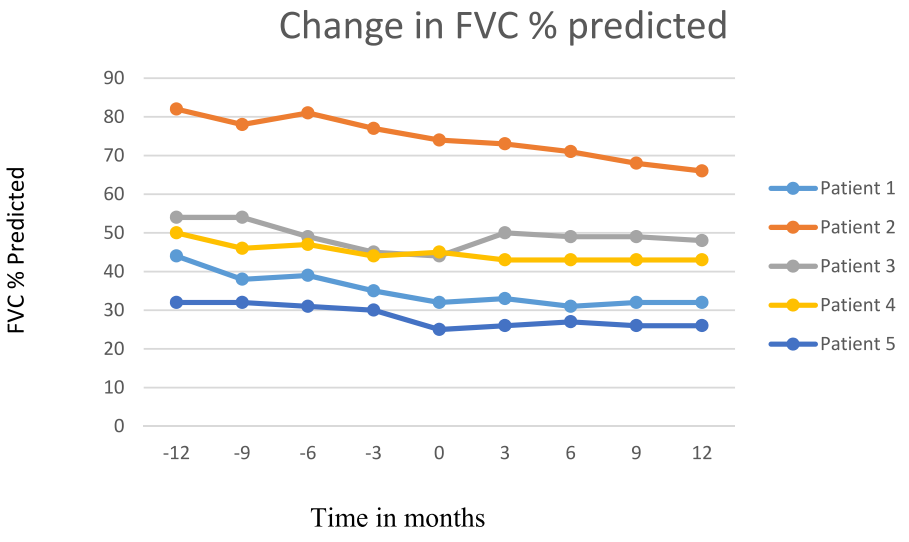

Fig. 1. Change in FVC % predicted by time. Time 0 is initiation of antifibrotic therapy.

centric fibrous interstitial pneumonia with moderate chronic inflammation, fibroelastotic foci, and non-necrotizing granulomas. Nintedanib was added when relative FVC % predicted declined by 10%, oxygen requirement increased from room air to 2LPM with exertion, and symptoms worsened despite antigen removal and IS regimen of mycophenolate 1 g twice daily and prednisone 7.5–40 mg daily. The relative FVC % predicted declined by only 4.4% and oxygen requirement remained stable at 2LPM in the year following addition of nintedanib. HRCT was not performed at time of initiation of AF so radiographic progression could not be assessed following AF initiation.

1.5. Case 5

Patient 5 was a 51 year old white male former smoker with avian antigen exposure and a family history of ILD, and an HRCT with possible UIP pattern. Diagnosis of HP was made on the basis of exposure, HRCT findings, and transbronchial biopsy demonstrating giant cells and interstitial inflammation. Immunosuppression regimen consisted of mycophenolate 1 g twice daily and prednisone 10 mg daily. Pirfenidone was added when relative FVC % predicted declined by 21.8%, HRCT demonstrated progression, and oxygen requirement worsened from room air to 6 LPM with exertion after exposure removal while on IS. In the year following the addition of pirfenidone, FVC improved by 4%, HRCT did not reveal progression of fibrosis, and oxygen requirement remained stable at 6LPM.

2. Discussion

Our case series adds to the literature by describing the trajectories of patients for whom AF was added to IS. Trends observed in the cohort include reduced decline in FVC, oxygen requirement, and symptoms in the year after adding AF to IS in 4 of the 5 patients. All 5 patients (100%) in our series demonstrated progression in the year prior to initiation of antifibrotic based on criteria outlined in the INBUILD trial, but only 1 of 5 (20%) progressed in the year after AF. There was a significant decrease in the rate of relative decline in % predicted FVC in the 12 months after initiation of antifibrotic compared to the 12 months prior to antifibrotic (0.4% $\pm$7.6 vs $-$17.5% $\pm$7.6, $p = 0.0495$) (Fig. 1 and Table 1). Compared to the 12 months prior to antifibrotic therapy, fewer patients met criteria for progression in the 12 months after initiating antifibrotic therapy ($p = 0.048$). Similarly, fewer patients met criteria for progression in the 6 months after initiating antifibrotic therapy compared to the 6 months prior ($p = 0.048$). Further, the treatment was tolerable, with no patients discontinuing AF or IS due to adverse events.

The role of combination AF and IS therapy in HP remains unclear in the literature. The cornerstones of treatment of HP have historically included IS and antigen removal [2–4]. Despite the use of IS, many patients with fibrotic HP continue to progress, and additional therapies are needed to prevent death or transplant in these patients [5]. Pirfenidone and nintedanib were first demonstrated to reduce decline in FVC in patients with idiopathic pulmonary fibrosis (IPF), a progressive and often fatal ILD that worsens with immunosuppression [7–9]. It has been suggested that progressive fibrotic ILD of any etiology may share a pathophysiologic mechanism with IPF and therefore may respond similarly to antifibrotic therapy [10], so clinical trials of antifibrotic therapy in non-IPF ILDs were conducted. The INBUILD trial demonstrated lower rates of decline in FVC in patients with progressive fibrotic ILD of various etiologies, though IS other than a low-dose glucocorticoid was not permitted at time of enrollment [5]. In the subset of patients in INBUILD who were on glucocorticoids, the effect of nintedanib vs placebo in reducing the rate of decline in FVC was maintained [6].

The SENSCIS trial demonstrated that patients on both IS and nintedanib had a slower decline in FVC compared to nintedanib alone, IS alone, or placebo [11]. Pirfenidone and nintedanib have each been shown to slow the rate of decline of FVC in patients with HP who are not on IS [5,12,13]. However, because HP, like scleroderma related ILD, is traditionally treated with immunosuppression, studies are needed to demonstrate the efficacy of combination therapy with IS and AF in patients with HP. Ours is the first to report the addition of antifibrotic therapy to patients who were declining on steroid-sparing agents and suggests that some patients may stabilize after addition of AF to IS, which may suggest a shared pathophysiologic process between progressive fibrotic HP and other progressive fibrotic ILDs. Whether these patients would have done better with AF alone without IS as in IPF or with IS and AF in combination as in scleroderma-related ILD should be the subject of future large prospective studies.

It is unclear why patient 2 progressed despite AF treatment; he did not have familial ILD or an unidentified or ongoing antigen exposure, each of which has been associated with progressive decline in lung function in patients with HP [14,15]. While he did not have a UIP pattern by HRCT, SLB was not performed, so the presence of a pathologic UIP pattern, which has been associated with progression, cannot be excluded [16]. Our finding that patient 3 significantly improved FVC after adding nintedanib, while rare, has been previously described in patients on nintedanib in the INBUILD trial [5].

Our study also adds to the literature regarding the tolerability of the combination of IS and AF therapy. The most common adverse events in the SENSCIS trial, which studied nintedanib vs placebo in patients with scleroderma-related ILD who were permitted to be on IS at the time of enrollment, included diarrhea, which was present in 75.7% of the nintedanib group and 31.6% of the placebo group [11]. Elevated alanine aminotransferase and/or aspartate aminotransferase, nausea, vomiting, weight decrease, and abdomi-

Table 1
Relative change in FVC % predicted in 12 months prior to and 12 months after initiation of antifibrotic.

	Relative change in FVC % predicted 12m prior to AF	Relative change in FVC % predicted 12m after AF
Patient 1	−27.2%	0%
Patient 2	−9.8%	−10.8%
Patient 3	−18.6%	9.1%
Patient 4	−10%	−4.4%
Patient 5	−21.8%	4%

nal pain were seen more commonly in the nintendanib group than in the placebo group. Sixteen percent of patients in the nintedanib group discontinued therapy due to adverse events, compared to 8.7% in the placebo group, though the authors did not describe whether discontinuation of nintendanib was more common in patients on concomitant IS [11]. In a report by Cottin et al. analyzing the subset of patients in INBUILD who were on IS, 100% of the patients in the nintedanib group and 97.5% of patients in the placebo group reported an adverse event, with serious adverse events occurring in 69.2% of the treatment group and 56.3% of controls [6]. Adverse events included diarrhea, nausea or vomiting, decreased appetite, nasopharyngitis, dyspnea or cough, headache, bronchitis, or elevated alanine aminotransferase. Twenty percent discontinued treatment due to adverse event in the treatment group and 12.5% in the control group [6].

A larger study with control groups on IS alone and AF alone is needed to confirm the role of AF therapy in combination with IS in patients with HP. Further studies are also needed to predict which patients might respond more favorably to IS or AF and to confirm our findings in patients on IS other than MMF.

3. Conclusion

The additive effect of AF and IS in HP is unclear. We present a case series in which 4 of 5 patients demonstrated no progression in the year after initiation of AF. Larger prospective studies are needed to further define the role of AF in combination with IS in patients with HP.

Declarations

This study was approved by the Institutional Review Board at University of Texas Southwestern Medical Center.
No identifiable information is used, so consent for publication is not required.
All data generated or analysed during this study are included in this published article.
CAN has received consulting fees from Boehringer Ingelheim.

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Author contribution

MK, CAN, TB, CSG, and TNA contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

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