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Prognostic impact and factors associated with steroid-responsiveness in patients with hypersensitivity pneumonitis

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Abstract

Hypersensitivity pneumonitis (HP) is an immune-mediated interstitial lung disease in which systemic corticosteroids remain first-line therapy despite limited evidence, especially in fibrotic forms. This study aimed to identify clinical, radiological, and biological features associated with functional response to steroids. We retrospectively analyzed 43 consecutive patients with HP treated with systemic corticosteroids and followed for at least 6 months. Patients were classified according to changes in forced vital capacity (FVC) as responders (5% increase), non-responders (5% decrease), or indifferent (±5%). Eighteen patients (42%) were responders, 15 (35%) indifferent, and 10 (23%) non-responders. Non-responders showed a consistently worse functional trajectory. A fibrosing high-resolution computed tomography pattern and baseline consolidations were more frequent in this group, as were precipitating antibodies against P. notatum and A. fumigatus. Conversely, bronchoalveolar lavage lymphocytosis >20% was more common among responders. Baseline FVC% and relative diffusing capacity of the lung for carbon monoxide were higher in non-responders, whereas demographic characteristics, smoking history, antigen exposure, comorbidities and autoantibody positivity did not differ significantly across groups. Fewer than half of patients experienced functional improvement after steroid therapy. Radiological fibrosis, consolidations, and specific precipitating antibodies were associated with lack of response, whereas bronchoalveolar lavage lymphocytosis predicted improvement. These findings highlight the heterogeneity of HP and may help identify patients unlikely to benefit from corticosteroids, supporting earlier consideration of alternative therapeutic strategies.

Key words: hypersensitivity pneumonitis, steroid, interstitial lung disease, prognosis.

Introduction

Hypersensitivity pneumonitis (HP) is an immune-mediated interstitial lung disease (ILD) characterized by inflammation of the alveoli and small airways upon inhalation of various environmental antigens [1]. HP is divided into two phenotypes—non-fibrotic and fibrotic—that differ in imaging, diagnosis, and treatment [2]. Non-fibrotic HP involves lymphocytic alveolitis without structural changes and is managed with antigen avoidance and a short course of corticosteroids, often improving lung function [2,3]. On the other hand, fibrotic HP is marked by reticulation, traction bronchiectasis, and, ultimately, honeycombing on high-resolution CT scan (HRCT) [2,3]. Fibrotic HP is associated with a significantly reduced survival and worse prognosis compared to non-fibrotic HP [4]. Although antigen avoidance remains the primary intervention, the cornerstone of the therapy remains systemic steroids or immunosuppressants, adding antifibrotics in case of fibrosis progression [2,5]. The use of corticosteroids in the treatment of fibrotic HP is debated, and current evidence does not support a clear benefit [6]. In fact, multiple studies showed that in fibrotic HP corticosteroid therapy does not result in significant improvement in forced vital capacity (FVC) or diffusing capacity for carbon monoxide (DLCO) compared to no corticosteroid use [7-10].

Despite this low level of evidence and limited benefit, systemic steroids remain the first-line therapy for both non-fibrotic and fibrotic HP and, currently, few clinical factors are known that can reliably predict the response to systemic steroid therapy [2,11].

Purpose of this study is to evaluate whether there are differences in clinical variables and prognosis among patients responsive, unresponsive and indifferent to steroid treatment in a real-life monocentric cohort of patients with both fibrotic and non-fibrotic HP that started systemic steroids.

Materials and Methods

This single-centre, retrospective cohort study included consecutive HP patients with at least 6 months of follow-up, who attended the ILD clinic at the Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy, between 2008 and 2022. Diagnoses of HP were established through discussions among a multidisciplinary team, in line with the ATS/ERS/ALAT guidelines [2,3]. All patients received systemic steroid therapy, from a minimum of 5 mg prednisone to a maximum of 1 mg/kg/day, and none of them received other immunosuppresants or antifibrotic agents.

Demographic data, including age, gender and body mass index (BMI), and comorbidities were collected along with details of occupational exposure and antigens. Pulmonary function tests were conducted according to the ERS/ATS guidelines [12,13]. Bronchoalveolar lavage (BAL) was performed before therapy, and cytological analysis revealed lymphocytosis, neutrophilia,

and eosinophilia. HRCT scans were classified as fibrosing or non-fibrosing by expert radiologists, with details on honeycombing, air trapping, ground-glass opacities, consolidations, reticulations, traction bronchiectasis and nodules. Autoimmunity tests included antinuclear antibodies (Ab), extractable nuclear antigen Ab, antineutrophil cytoplasmic Ab, Ab anti-Cyclic Citrullinated peptide, rheumatoid factor, and precipitating antibody testing. Treatment regimens along with vital status and total follow-up duration were recorded.

Patients were stratified in 3 groups according to the functional response to steroid treatment at 6-month follow-up: i) steroid-responders: those with FVC improvement 5% predicted; ii) steroid non-responders: those with FVC decline 5% predicted; and iii) those indifferent to steroids with an FVC that remained stable (between -5% and + 5% compared to baseline).

Quantitative variables were summarised with medians and interquartile range (IQR), whereas qualitative ones with absolute and relative (percentages) frequencies. Analyses were stratified by functional response and the characteristics of the three groups were compared either with the Mann–Whitney test, for continuous variables, or the Fisher's exact test for categorical variables. P-values <0.05 were considered statistically significant. Missing data were addressed using a complete case analysis, given the small number of missing observations. All analyses were carried out with SAS/STAT software, Version 9.4. The study received Institutional Review Board approval.

Results

The cohort included 43 patients (median [IQR] age: 67 [52-73] years; 48.8% female). The longitudinal evolution of lung function is illustrated in Figure 1, which shows the distribution and transitions of FVC% categories (improvement, stability, and decline) over time. Eighteen patients (41.9%) were steroid-responders, while the remaining were either indifferent to steroids (34.9%) or non-responders (23.2%). Demographic and clinical characteristics of the study cohort are summarized in Table 1. The majority of patients were never smokers (51.2%), and a history of significant environmental or occupational exposure was documented in 30 patients (69.8%), with no significant differences between groups. Cardiovascular and thromboembolic conditions were the most common comorbidities, with arterial hypertension (14.0%), ischemic heart disease (9.3%), pulmonary embolism (7.0%), and obstructive sleep apnea syndrome (4.7%). No differences were observed in regard to type of diagnosis (with or without lung biopsy), family history of ILD and pulmonary physical examination (presence of velcro crackles), Table 1. All patients exhibited abnormalities in baseline pulmonary function tests with an overall moderate FVC impairment (median [IQR] FVC% of predicted 76 [63–88]%), and a moderate-to-severe DLCO impairment (median [IQR] DLCO% of predicted 47.5

[38–65]%). Steroid non-responders had significantly higher baseline FVC% of predicted, p = 0.0095, and DLCO% of predicted, p = 0.0100 (Table 1).

HRCT at baseline revealed a fibrosing pattern—characterized by traction bronchiectasis and honeycombing—in most patients (31; 72.1%). This radiological pattern was less frequently observed among steroid responders (9; 50.0%), p = 0.0522 (Table 2). Air trapping was present in 55.8% of cases, while centrilobular micronodules were found in 18.6% of patients, compatible with a bronchiolocentric interstitial pneumonia (BIP) pattern. No significant intergroup differences were observed with respect to other radiological features, with the exception of the presence of consolidations, which were more common in steroid non-responders (3; 30.0%), p = 0.0338 (Table 2). BAL was performed in 30 patients: BAL lymphocytosis (lymphocytes >20%) was more frequently observed among steroid-responsive patients (Table 2). In regards to precipitating antibody testing, positive serum antibodies against *P. notatum* and *A. fumigatus* were more frequently observed in steroid non-responsive patients, while no difference was observed in regards to *A. alternata, A. niger, M. faenii*, and pigeons feces. All patients with positive antibodies to A. fumigatus were evaluated to rule out allergic bronchopulmonary aspergillosis (ABPA), and none displayed features consistent with this diagnosis.

Discussion

According to our data, only a minority of patients (42%) experience an improvement in FVC > 5% at 6 months after initiation of steroid therapy. Patients with HP who exhibited a decline in FVC greater than 5% (steroid non-responders) showed a worse functional trajectory over time compared to those with stable or improved lung function. These findings highlight the importance of early assessment of treatment response and suggest that an inadequate short-term improvement or early functional deterioration should prompt consideration of alternative or adjunctive therapies, including immunosuppressive or antifibrotic approaches.

Among the clinical features potentially associated with pulmonary function trends in HP, we observed that BAL cellularity differed among the three groups. In particular, BAL lymphocytosis >20% was more frequently observed in steroid responders. This finding is consistent with previous studies, in which BAL lymphocytosis was associated with a favorable response to corticosteroid therapy [8,10].

In line with the recent literature, our cohort showed a remarkably high rate of serological autoimmunity. In most cases, autoantibody positivity involved low-titer or isolated findings, without clinical or radiological features suggestive of connective tissue disease (CTD). A multidisciplinary team thoroughly reviewed all cases, and no patients met criteria for CTD-ILD or idiopathic interstitial pneumonia with autoimmune feature (IPAF). The frequent detection of

circulating autoantibodies in chronic HP has been proposed to reflect an underlying immune activation secondary to persistent antigen exposure rather than a distinct autoimmune disorder. Nonetheless, the potential prognostic implications of serological autoimmunity in this setting remain unclear.

Moreover, in our study, the presence of a fibrosing pattern and of pulmonary consolidations on chest HRCT was more frequently observed in steroid non-responders, as was the presence of serum precipitating antibodies against *P. notatum* and *A. fumigatus*. These findings were previously discussed in studies that identified radiological predictors of response and non-response to systemic corticosteroids and/or immunosuppressive therapy in patients with HP [6]. Radiological patterns indicative of acute inflammation (e.g., ground-glass opacities and poorly defined centrilobular nodules) have been associated with a positive steroid response, whereas features suggestive of fibrotic evolution (e.g., traction bronchiectasis, honeycombing and reticulations) have been linked to a poor therapeutic response [6,8].

Our study has limitations due to its retrospective design and small sample size, which limit the ability to generalize findings. However, this design enabled a homogeneous cohort for clinical management. While initial prednisone-equivalent doses were comparable across response groups, potential confounding by indication cannot be ruled out. Although we carried out antigen removal when the causal agent was identified, we could not systematically assess the timing and effectiveness of antigen avoidance. Moreover, while fibrotic and non-fibrotic HP represent different phenotypes, stratified analyses were not possible due to the limited sample size. Further studies with a larger sample size are necessary to confirm these findings, identify further predictive biomarkers of response, and evaluate the effectiveness of alternative therapeutic strategies or antifibrotic treatments for patients with fibrotic HP or those who do not respond to steroids.

Conclusions

In conclusion, in our cohort of patients with HP receiving systemic steroid treatment, only a minority (42%) experienced functional improvement. A fibrosing pattern and consolidations at baseline chest HRCT, as well as positivity for precipitating antibodies against *P. notatum* and *A. fumigatus*, were more frequent among steroid non-responders. Conversely, BAL lymphocytosis (>20%) was more frequently observed in steroid responders. These findings support the potential prognostic value of early functional decline, radiological features of fibrosis, and BAL lymphocytosis in predicting corticosteroid responsiveness and guiding therapeutic decisions in chronic HP.

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Table 1. Demographics, clinical and functional characteristics of the study cohort according to the functional response to steroid treatment at 6 months.

Variabile	Decline in FVC 5%	Stable FVC*	Increase in FVC 5%	Total	p
	N=10	N=15	N=18	N=43	
Demographics					
Female	4 (40.00%)	6 (40.00%)	11 (61.11%)	21 (48.84%)	0.3932
Age at diagnosis, Median (IQR)	69.50 (61.00-78.00)	67.00 (52.00-75.00)	66.00 (44.00-71.00)	67.00 (52.00-73.00)	0.6456
Medical history and physical exam at diagnosis					
Family history of ILD	2 (20.00%)	0 (0.00%)	0 (0.00%)	2 (4.65%)	0.2142
Known antigen exposure	7 (70.00%)	10 (66.67%)	13 (72.22%)	30 (69.77%)	1.0000
History of smoking					
Never smoker	4 (40.00%)	6 (40.00%)	12 (66.67%)	22 (51.16%)	0.3183
Current smoker	0 (0.00%)	1 (6.67%)	0 (0.00%)	1 (2.33%)	
Former smoker (>1 year)	6 (60.00%)	8 (53.33%)	6 (33.33%)	20 (46.51%)	
Basal crackles (2 missing)	9 (90.00%)	12 (80.00%)	11 (61.11%)	32 (74.42%)	0.3452
Type of diagnosis					
Type					
Radiological	4 (40.00%)	10 (66.67%)	10 (55.56%)	24 (55.81%)	0.4209
Histological	6 (60.00%)	5 (33.33%)	8 (44.44%)	19 (44.19%)	
Pulmonary function tests at baseline					
FVC%, Median (IQR)	85.00 (76.00-103.00)	81.00 (73.00-88.00)	63.50 (52.00-81.00)	76.00 (63.00-88.00)	**0.0095**
DLCO%, Median (IQR)	49.50 (46.00-65.00)	70.00 (43.00-82.00)	39.00 (31.00-48.00)	47.50 (38.00-65.00)	**0.0100**

*Stable FVC, variation between -5% and 5%; FVC, forced vital capacity; DLCO, diffusing capacity for carbon monoxide.

Table 2. Radiological, bronchoalveolar lavage and serological characteristics of the study cohort according to the functional response to steroid treatment at 6 months.

Variabile	Decline in FVC 5%	Stable FVC*	Increase in FVC 5%	Total	p
	N=10	N=15	N=18	N=43	
Baseline HRCT scan (1 missing)					
Pattern					
Fibrotic	9 (90.00%)	13 (86.67%)	9 (50.00%)	31 (72.09%)	**0.0522**
Non fibrotic	1 (10.00%)	2 (13.33%)	8 (44.44%)	11 (25.58%)	
Reticulation	8 (80.00%)	15 (100.00%)	13 (72.22%)	36 (83.72%)	0.1278
Traction bronchiectasis	6 (60.00%)	10 (66.67%)	8 (44.44%)	24 (55.81%)	0.5234
Ground glass opacities	10 (100.00%)	12 (80.00%)	14 (77.78%)	36 (83.72%)	0.4015
Consolidations	3 (30.00%)	2 (13.33%)	0 (0.00%)	5 (11.63%)	**0.0338**
Micronodules	1 (10.00%)	2 (13.33%)	5 (27.78%)	8 (18.60%)	0.4101
Honeycombing	3 (30.00%)	5 (33.33%)	4 (22.22%)	12 (27.91%)	0.9083
Air trapping	6 (60.00%)	7 (46.67%)	11 (61.11%)	24 (55.81%)	0.6223
Bronchoalveolar lavage (executed on 30 patients)°					
Lymphocytes > 20%	3 (37.50%)	2 (16.67%)	7 (70.00%)	12 (40.00%)	**0.0347**
Neutrophils > 5%	3 (37.50%)	1 (8.33%)	3 (30.00%)	7 (23.33%)	0.2989
Eosinophils > 3%	0 (0.00%)	2 (16.67%)	1 (10.00%)	3 (10.00%)	0.7635
Autoimmunity test (2 missing)					
Positive	9 (90.00%)	12 (80.00%)	13 (72.22%)	34 (79.07%)	0.8823
Serum precipitating antibodies					
P. Notatum positivity (3 missing)	6 (60.00%)	1 (6.67%)	4 (22.22%)	11 (25.58%)	**0.0354**
A. Fumigatus positivity (4 missing)	6 (60.00%)	2 (13.33%)	2 (11.11%)	10 (23.26%)	**0.0280**
A. Alternata positivity (3 missing)	3 (30.00%)	1 (6.67%)	1 (5.56%)	5 (11.63%)	0.3954
A. Niger positivity (3 missing)	3 (30.00%)	1 (6.67%)	2 (11.11%)	6 (13.95%)	0.5758
M. Faenii positivity (3 missing)	2 (20.00%)	0 (0.00%)	1 (5.56%)	3 (6.98%)	0.4506
Pigeon feces positivity (4 missing)	3 (30.00%)	3 (20.00%)	5 (27.78%)	11 (25.58%)	0.9656

*Stable FVC, variation between -5% and 5%; FVC, forced vital capacity. °Percentages in this section refer to patients with BAL results.

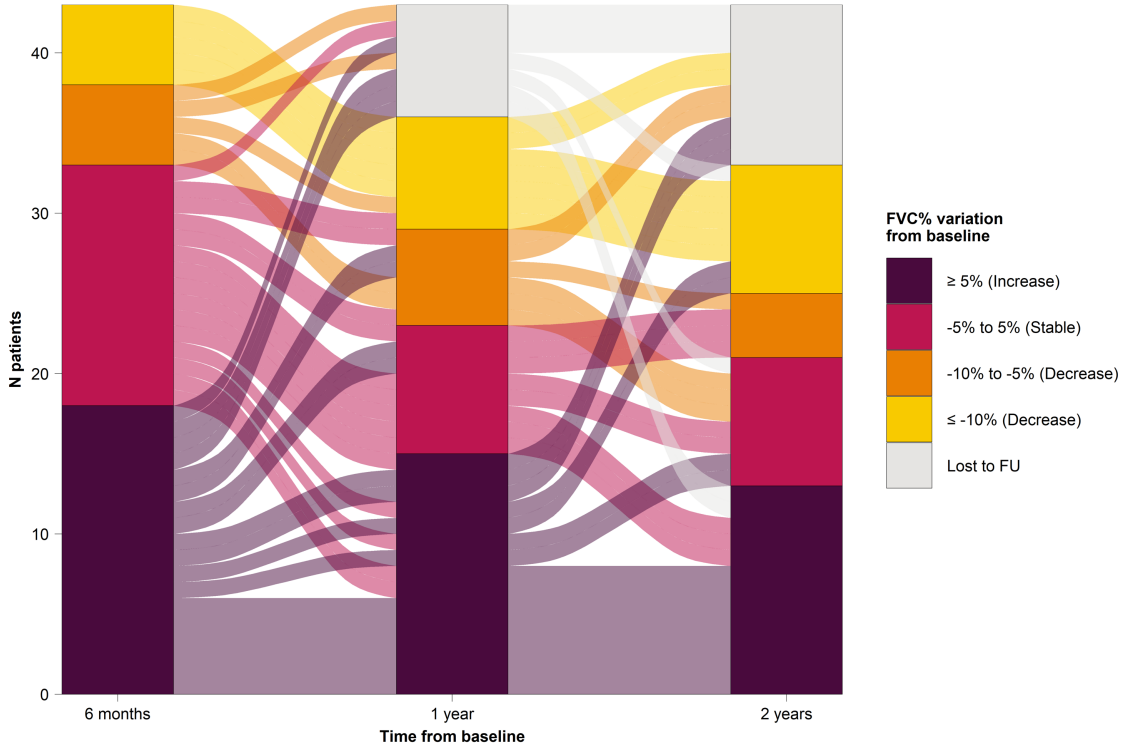

Figure 1. Alluvial plot representing the variation of FVC% at 6 months, 1 and 2 years of follow-up.