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Immunomodulatory Therapies in Hypersensitivity Pneumonitis: A Comprehensive Review

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ABSTRACT

Hypersensitivity pneumonitis (HP) is an immune-mediated interstitial lung disease (ILD) caused by repeated inhalation of environmental antigens. Clinically, it varies widely from temporary, reversible inflammation to long-term, progressive fibrosis. The primary approach in managing HP remains identifying and removing exposure to the causative antigens, and treatment often requires corticosteroids in acute or severe cases. However, many patients, especially those with chronic or fibrotic HP (cHP/fHP), may progress despite corticosteroid treatment, highlighting the urgent need for other effective and tolerable immunomodulatory and antifibrotic therapies. This review discusses the current and emerging treatments for HP, focusing on the rationale, clinical data, and practical aspects of traditional immunosuppressants such as corticosteroids, mycophenolate mofetil, and azathioprine, as well as new biologics and antifibrotic drugs that are transforming the treatment landscape for this complex disease.

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Introduction

Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis, is an interstitial lung disease resulting from the cumulative inhalation of a diverse range of environmental allergens, including mold, certain animal proteins, and some chemicals. HP is different from allergies which are mediated by Immunoglobulin E (IgE); it is a non-IgE mediated response coupled with an immune reaction involving both the alveoli and the small airways (1,2). There are notable gaps in the data collection efforts to establish the incidence and prevalence of HP. Its contribution to interstitial lung disease (ILD) diagnoses is approximately consistent in relation to other countries with different occupational exposures and methods of diagnostics (3). In the past, HP was commonly divided into acute, subacute, and chronic subtypes, primarily focused on the symptoms and the duration of exposure. More recently, international guidelines have changed the approach to focus on radiologic and pathologic patterns, resulting in the division of HP into two: fibrotic (fHP) and non-fibrotic (nfHP) and using high-resolution computed tomography (HRCT) as the primary mode of the diagnosis (4,5). This change corroborates the classification with the prognosis and guiding treatment. While both forms of classification exist, it is known that nfHP is more responsive to early intervention in the form of antigen removal, coupled with a corticosteroid tapering regimen. In contrast,

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fHP is known to be relentless and follows a progressive and unresponsive course resulting in progressive respiratory decline and increased mortality (6).

Environmental antigen avoidance remains the primary pillar in HP management. However, in patients where exposure cannot be completely mitigated, or in whom disease persists or progresses despite avoidance, pharmacological intervention becomes necessary. Corticosteroids have long been the mainstay in such cases, particularly during active inflammatory phases (7). Nevertheless, concerns regarding their long-term side effect profile and limited efficacy in halting fibrotic progression have led to growing interest in alternative immunomodulatory approaches (8).

Pathophysiology: Immunologic Mechanisms and Therapeutic Implications

HP remains an inflammatory disorder, so understanding the immunologic basis of its development is crucial for targeted interventions. The disease results from a complex immune cascade initiated by persistent inhalation of environmental antigens, leading to both innate and adaptive immune activation.

Innate Immune Activation

The initial immune response in HP is coordinated by alveolar macrophages and bronchial epithelial cells, which detect and respond to inhaled antigens. This antigenic interaction triggers the release of inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, and IL-8, which collectively recruit neutrophils and mononuclear cells into the alveolar spaces, initiating diffuse alveolar inflammation. These cellular responses create the pro-inflammatory environment that characterizes the initiation of HP (9).

Adaptive Immune Dynamics

- **T-helper 1 (Th1) Dominance:**
  Most forms of HP exhibit a predominant Th1-type immune profile, characterized by the secretion of interferon-gamma (IFN-γ) and the formation of poorly formed non-caseating granulomas within the lung parenchyma. This dominance also characterizes the presence of profound BAL lymphocytosis and CD4 and CD8 Cells. This response reflects a delayed-type hypersensitivity reaction, signifying a central role for cell-mediated immunity in disease pathology (10).

- **T-helper 2 (Th2) Skewing in Select Phenotypes:**
  In certain HP variants, such as those associated with bird antigen exposure (e.g., pigeon breeder's lung), a Th2-biased immune response may predominate. These cases are identified by elevated levels of IL-4, IL-5, and IL-13, along with peripheral eosinophilia, indicating an allergic-type immune mechanism that may overlap with classic atopic pathways (11).

This intricate interplay between Th1 and Th2 responses, along with chronic immune activation, underlies the variable presentation and progression of HP. These immunologic mechanisms provide the foundation for selecting immunomodulatory therapies tailored to specific disease phenotypes.

T-helper 17 (Th17) Cells

Recent evidence highlights the role of Th17 cells in the chronic inflammatory response seen in HP. IL-17A, the signature cytokine of Th17 cells, promotes neutrophilic inflammation and has been found to be elevated in both bronchoalveolar lavage fluid (BALF) and peripheral blood of patients with chronic HP (12,13).

Regulatory T Cells (Tregs)

A decrease in the number or function of regulatory T cells may contribute to immune dysregulation and persistent inflammation in HP. Tregs normally play a key role in maintaining immune tolerance and controlling excessive immune responses (14).

Humoral Immunity

Specific IgG antibodies against the inciting antigen are frequently detected in HP patients. While these antibodies are

considered markers of exposure rather than direct pathogenic agents, they may participate in immune complex formation and contribute to disease propagation (15).

In chronic HP, unresolved and ongoing immune activation leads to fibroblast proliferation, excessive deposition of extracellular matrix, and irreversible pulmonary fibrosis. This fibrotic remodeling is mediated by pro-fibrotic cytokines, particularly transforming growth factor-beta (TGF-β), and shares key pathogenic pathways with other progressive fibrosing interstitial lung diseases (PF-ILDs) (16). Recognizing these immune mechanisms forms the foundation for targeted immunomodulatory therapy in HP.

Therapeutic Strategies in Hypersensitivity Pneumonitis: Moving Beyond Corticosteroids

HP is fundamentally an immune-mediated ILD, making immunomodulation the cornerstone of its management. While corticosteroids remain the mainstay of therapy, their long-term utility is limited by a significant side-effect profile and questionable efficacy in chronic fibrotic forms. Antifibrotic agents, on the other hand, are now emerging as crucial tools in patients with progressive pulmonary fibrosis (PPF), including fHP. Despite promising observational data, robust randomized controlled trials (RCTs) validating alternative immunomodulatory agents are still lacking.

Corticosteroids: The Traditional Backbone, Yet Imperfect

Oral corticosteroids such as prednisone are the first-line pharmacologic option for HP, particularly in patients with active inflammation. Their mechanism involves broad immunosuppressive effects, including inhibition of pro-inflammatory cytokines, suppression of immune cell recruitment, and induction of apoptosis in activated immune cells (7).

Numerous observational studies have reported symptomatic and functional improvement in acute HP following corticosteroid therapy.

Table 1. Showing different studies with immunomodulator therapy in hypersensitivity pneumonitis.

Study by Author	Type of study	Sample size	Drug used	Primary outcome	Results	Side effects
Morrisett et al (Use of Mycophenolate Mofetil or Azathioprine for the Management of Chronic Hypersensitivity Pneumonitis)	Prospective cohort study	70 patients enrolled (51 treated with MMF) and (19 treated with AZA)	Mycophenolate mofetil or Azathiorpine	Longitudinal trajectories of FVC % predicted and DLCO % predicted before and after treatment initiation were the primary outcomes	Median follow-up after treatment initiation was 11 months. Prior to treatment initiation, FVC and diffusion capacity of the lung for carbon monoxide (DLCO)% predicted were declining at a mean rate of 0.12% (P < .001) and 0.10% (P < .001) per month, respectively. Treatment with either MMF or AZA was not associated with improved FVC (0.5% at 1 year; P =.46) but was associated with a statistically significant improvement in DLCO of 4.2% (P < .001) after 1 year of treatment	10 patients (14.3%) had adverse effects. GI symptoms were the most common adverse effects for both. The dose of MMF needed to be reduced in three of 70 patients (4.3%). In addition, MMF was discontinued in two patients for transaminitis (n = 1) and diarrhea (n =1). Finally, AZA was discontinued in two patients for transaminitis (n =1) and diarrhea (n =1), and five patients were switched from AZA to MMF.
Casal et al (Use of mycophenolate mofetil for the treatment of fibrotic hypersensitivity pneumonitis)	Prospective cohort study	73 total included. 58 completed study.	Mycophenolate mofetil	FVC and DLCO changes after treatment at 1 year.	FVC% and DLCO% decreased until starting MMF (year -1 to year 0). After completion of treatment (year 1), FVC% stabillised (p=0.336) and DLCO% improved significantly (p=0.004) compared to year 0. Dysnea and mean corticosteroid dose also improved (p< 0.0001)	45 side effects observed. Most common were GI side effects. 4 patients had to discontinue the treatment.

Study by Author	Type of study	Sample size	Drug used	Primary outcome	Results	Side effects
De Sadeleer et al (Effects of Corticosteroid Treatment and Antigen Avoidance in a Large Hypersensitivity Pneumonitis Cohort: A Single-Centre Cohort Study)	A Single-Centre Cohort Study	202 patients (93 nfHP and 109 fHP)	Corticosteroid was given in (n=67 in nfHP and n=82 In fHP)	Effect of corticosteroid therapy and antigen avoidance on survival and FVC and DLCO was assesed	No difference in survival with corticosteroid in entire cohort and worse survival in fHP seen (p=0.0902) No difference in PFT evolution in fHP (p-0.41) For nfHP reversal of FVC decline (p-0.001) and no difference in DLCO decline seen	-
Gibbon et al (oral Corticosteroids in patients witH fibrOtic hypeRsensitivity pneUmonitiS(CHORUS)	Randomized double-blind placebo-controlled parallel-group trial	Expected 222 patients	Corticosteroid versus placebo in patient of fibrotic HP	Assess the effectiveness of 26 weeks of treatment with prednisolone vs placebo on disease progression, as measured by the pulmonary function test, forced vital capacity (FVC).	Currently enrolling and results awaited	-

Study by Author	**Type of study**	**Sample size**	**Drug used**	**Primary outcome**	**Results**	**Side effects**
INBUILD trial (Nintedanib in Progressive Fibrosing Interstitial Lung Diseases)	Double blind, placebo-controlled RCT, multicentre study	663 patients 332 patients in the nintedanib group and 331 patients in the placebo group.	Nintedanib 150 mg twice daily versus placebo	Annual rate of decline in the FVC, as assessed over a 52-week period	Rate of decline in the FVC was −80.8 ml per year with nintedanib and −187.8 ml per year with placebo, for a between-group difference of 107.0 ml per year (95% confidence interval (P<0.001) 26.1% were diagnosed as Chronic HP and 25.6 % as autoimmune ILD	Diarrhea 222 (66.9) Nausea 96 (28.9) Bronchitis 41 (12.3) Nasopharyngitis 44 (13.3) Vomiting 61 (18.4) Alanine aminotransferase increased 43 (13.0) Aspartate aminotransferase increased 38 (11.4)
RELIEF trial (Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis)	Double-blind, randomised, placebo-controlled,multicentre study, phase 2b trial	127 patients to treatment: 64 to pirfenidone, 63 to placebo	Oral pirfenidone (267 mg three times per day in week 1, 534 mg three times per day in week 2, and 801 mg three times per day thereafter) or matched placebo	The primary endpoint was absolute change in percentage of predicted FVC (FVC % predicted) from baseline to week 48	After 127 patients had been randomised, the study was prematurely terminated on the basis of an interim analysis for futility triggered by slow recruitment. After 48 weeks significantly lower decline in FVC % predicted in the pirfenidone group compared with placebo (p=0·043)	GI symptoms were most common in those receiving pirfenidone which include nausea, diarrhea, and dyspepsia.

Study by Author	Type of study	Sample size	Drug used	Primary outcome	Results	Side effects
Keir et al (Rituximab in severe, treatment-refractory interstitial lung disease)	Retrospective study	50 patients of progressive ILD Had hypersensitivity pneumonitis in 6 patients Excluding IPF	Rituximab	Change in pulmonary function tests compared with pre-rituximab levels was assessed at 6-12 months post-treatment.	At the time of rituximab administration, patients had severe physiologic impairment with a median forced vital capacity (FVC) of 44.0% (24.0-99.0%) and diffusing capacity of carbon monoxide (DLCO) of 24.5% (11.4-67.0%). In contrast with a median decline in FVC of 14.3% and DLCO of 18.8% in the 6-12 months prior to rituximab, analysis of paired pulmonary function data revealed a median improvement in FVC of 6.7% (P < 0.01) and stability of DLCO (0% change; P < 0.01) in the 6-12 months following rituximab treatment.	Two patients had severe pneumonia and died because of it.

Table 2. Showing proposed drugs and their side effects.

Name of drug	Dosing	Monitoring and precautions
Corticosteroid (Prednisolone)	0.5 mg/kg to 1 mg/kg once daily	Monitoring requires blood glucose, gastritis, bone mineral density, cataract, hypertension, mood changes, and weight gain
Mycophenolate mofetil	1 – 1.5 gm twice daily	Myelosuppression causes anemia and leukopenia. Monitor CBC weekly for the first month, twice monthly second and third months, then Monthly
Azathioprine	1-2 mg/kg/day	Myelosuppression, hepatitis, and opportunistic infections. Monitor CBC and hepatic function every 2 weeks for the first month, then monthly. Measure TPMT; if low, use a smaller dose adjustment.
Cyclophosphamide	1-2 mg/kg/day or 500-1000 gram per day	Myelosuppression, hemorrhagic cystitis, infertility, infection, secondary malignancy Monitor CBC, renal function, and urinalysis at baseline, then twice monthly
Rituximab	1 gram intravenously every 2 weekly for 2 doses and repeat after 6 months if needed	Infusion reactions, infections, hypogammaglobulinemia, reactivation of hepatitis B.
Nintedanib	150 mg orally twice daily	Diarrhea (most common), nausea, vomiting, elevated liver enzymes, bleeding risk, cardiovascular events
Perfenidone	2403 mg/day (801 mg TID after titration: 267 mg TID → 534 mg TID → 801 mg TID)	GI upset, anorexia, photosensitivity rash, fatigue, liver enzyme elevation
Mg- milligram, Kg-Kilogram		

However, the picture is less optimistic in chronic HP. Although short-term gains in forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO) are observed, these improvements often wane over time. Although the result of the CHORUS trial are awaited, De Sadeleer et al. noted a lack of sustained benefit, with many patients ultimately experiencing disease progression (18). Moreover, prolonged steroid therapy is associated with significant adverse effects such as osteoporosis, diabetes, weight gain, infections, cataracts, and mood disturbances, prompting the need for steroid-sparing strategies (8).

Beyond Steroids: Expanding the Immunomodulatory Arsenal

Given the limitations of corticosteroids—particularly in chronic or fibrotic HP—several immunosuppressive agents have been employed as adjuncts or alternatives. Although data are largely retrospective, their use is gaining traction in clinical practice.

Azathioprine (AZA)

A purine synthesis inhibitor, AZA suppresses T-cell mediated immune responses central to HP pathogenesis. Warren et al reported corticosteroid-sparing benefits in chronic pigeon breeder's disease (19). Morisset et al. noted that AZA, alone or with mycophenolate mofetil (MMF), may slow FVC decline in chronic HP (20). Limitations for use include GI toxicity, myelosuppression, hepatotoxicity, and infection risks, necessitating careful monitoring. TPMT enzyme activity testing is advised prior to initiation.

Mycophenolate Mofetil (MMF)

MMF selectively inhibits lymphocyte proliferation and is generally better tolerated than AZA. Morisset et al. supported MMF use in chronic HP cohorts (20). Casal et al. showed MMF slowed FVC decline, especially in patients with histological or BAL evidence of inflammation (21). Adverse effects mostly include GI side effects, leukopenia, teratogenicity; regular monitoring with CBC is essential.

Cyclophosphamide (CYC)

A potent alkylating agent, CYC is typically reserved for severe, rapidly progressive cases of HP, especially with features such as vasculitis or diffuse alveolar damage. Limited to case reports and small series. Risks associated are haemorrhagic cystitis, infertility, bone marrow suppression, and malignancy, limiting its use.

Calcineurin Inhibitors (Cyclosporine, Tacrolimus)

These agents inhibit T-cell activation via IL-2 suppression. Sparse and limited case reports are present. Drawbacks with use include nephrotoxicity, neurotoxicity, hypertension, and metabolic disturbances.

Rituximab (RTX)

Rituximab, an anti-CD20 monoclonal antibody, depletes B-cells and may be beneficial in cases where humoral immunity contributes to disease progression. Case series and retrospective studies by Keir et al. show stabilization or improvement in lung function (22). Since HP remains a disease primarily secondary to an immune mediated process, the indirect evidence from the RECITAL trial, which primarily focused on connective tissue disease-ILD, supports its utility in immune-mediated fibrosing ILDs (23). Risks with its use include infusion reactions, infection, hepatitis B reactivation, delayed neutropenia and rare cases of PML. Currently considered for refractory fHP or autoimmune overlap syndromes.

Emerging Biologics and Small Molecules

Novel agents targeting cytokines or signaling pathways are under consideration, though clinical evidence in HP is limited:

- **TNF-α inhibitors:** Although currently used as third line therapy in sarcoidosis, not routinely recommended for HP management due to limited clinical data and the risk of side effects consistent with interstitial lung disease (24).
- **Anti-IL-4/13, Anti-IL-5, Anti-IL-17 agents:** Theoretical benefits based on Th2/Th17 involvement; no clinical data in HP.
- **JAK inhibitors:** Active area of investigation; currently no HP-specific trials.

Antifibrotic Therapy in Fibrotic HP: Shifting the Paradigm

Recognizing of progressive fibrosis as a common pathway in ILDs, antifibrotic agents like nintedanib and pirfenidone are now established options in fHP.

- **Nintedanib:** A tyrosine kinase inhibitor targeting VEGFR, FGFR, and PDGFR. The INBUILD trial (Flaherty et al.) demonstrated reduced FVC decline in PF-ILDs, including fHP (25). Now approved for PF-ILDs, including progressive fHP.
- **Pirfenidone:** Exhibits anti-fibrotic and anti-inflammatory activity. The RELIEF trial (Behr et al.) suggested benefit in a subset of patients with fHP, though the primary endpoint was not met (26).
- **Combination Therapy:** For patients with both active inflammation and fibrosis, combining immunomodulators with antifibrotics is a logical and increasingly adopted approach. The INBUILD trial permitted background immunosuppressant use, supporting this strategy (25).

Challenges and Future Directions

Despite therapeutic progress, managing HP—especially the fibrotic phenotype—remains complex:

- **Diagnostic Delays:** Difficulty identifying causative antigens and overlapping radiologic/pathologic features complicate early intervention.
- **Disease Heterogeneity:** Varying clinical courses hinder standardization of care.
- **Evidence Gaps:** Most immunosuppressants lack prospective RCT data.
- **Biomarkers Needed:** Tools to predict progression and response—e.g., BAL lymphocytosis, KL-6, SP-D—remain investigational (27,28).
- **Patient Stratification:** Phenotyping (e.g., inflammatory vs. fibrotic) may allow personalized treatment approaches.
- **Antigen Avoidance:** Still crucial but often insufficient once fibrosis is established.

Looking Forward:

- Prospective RCTs comparing MMF, AZA, and novel agents.
- Exploration of IL-17, chemokine receptor, and JAK-STAT pathway inhibitors.
- Refinement of combination strategies.

- Advances in molecular diagnostics for better antigen identification.

Conclusion

The treatment paradigm for hypersensitivity pneumonitis is rapidly evolving. While antigen avoidance and corticosteroids remain foundational, the emergence of immunomodulatory and antifibrotic therapies—especially for fibrotic HP—has significantly broadened the therapeutic arsenal. Agents such as azathioprine, mycophenolate mofetil, and rituximab show promise in steroid-refractory or chronic disease, while nintedanib has a clearly established role in slowing fibrotic progression.

However, the path ahead demands rigorous clinical trials, improved biomarkers, and individualized treatment strategies. A multidisciplinary approach—combining environmental assessment, radiologic and histologic characterization, and patient-centered therapeutic decisions—will be key to improving outcomes in this complex, immune-driven interstitial lung disease.

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