Non-IPF Interstitial Lung Disease Therapeutic Options

Educational Objectives:
1. Describe the medical treatment options for various interstitial lung diseases
2. Review drug initiation and monitoring
3. Discuss additional non-pharmacologic therapeutic considerations

Scenario 1:
A 43-year-old man presented with 6 months of progressive dyspnea on exertion without associated cough, fevers, chills, chest pain, joint pains, skin changes, abdominal pain, nausea, or diarrhea. He did endorse 10 lbs. weight loss in the last 6 months. He was previously healthy and denies any prior surgeries. He currently takes no medications. He is married with 2 children. He works in an auto body shop but does not have any contact with brakes. He denies any asbestos exposure or dust fumes. His occupational history is also notable for prior minimal work in sandblasting, farming, and construction. He is a lifetime non-smoker. He denies any use of drugs or alcohol. There is no family history of lung disease. His exam is notable for rapid shallow respirations and bibasilar crackles.

His testing is notable for

PFT:
FEV1 of 1.67 (54%)
FVC 1.78 (50%)
DLCO 45%

6-minute walk test – Oxygen saturation of 91% on room air at rest and requires 2LPM with exertion. Imaging is shown below.
Question 1: What are the treatment options for this patient with NSIP?

This patient has a clinical diagnosis of idiopathic NSIP (iNSIP) rather than NSIP in the context of connective tissue disease or a specific exposure. To date, clinical trials evaluating the efficacy of treatment for idiopathic NSIP have been limited. The standard practice is guided by clinical experience and small retrospective studies, many of which included non-idiopathic NSIP cases.

For patients with moderate to severe disease (symptomatic and/or requiring supplemental oxygen), initial treatment with corticosteroids has been the mainstay of treatment. Usual daily dosing in clinical practice ranges 0.5-1 mg/kg of prednisone for ideal body weight. In patients with severe hypoxemia, such as those requiring high flow oxygen or intubation, some clinicians favor a pulse dose of methylprednisolone (typically 1 gram daily for three days) as a sort of induction before switching to prednisone.

After approximately 4-6 weeks, steroids are slowly tapered. A steroid-sparing agent can be initiated once a definite response to corticosteroids has been established. In patients who do not achieve any benefit from several months of corticosteroid therapy, the role of ongoing immunosuppression should be questioned. Particularly in patients with progressive disease unresponsive to immunosuppression, antifibrotic therapy should be considered.

Question 2: What are some steroid sparing agents to consider for treating NSIP?

Studies regarding best treatment options in NSIP are limited and mostly small case series. The only randomized clinical trial to include patients with iNSIP was the recently published EVER-ILD trial (Mankikian et al, ERJ 2023), in which 43 of the total 122 randomized patients had iNSIP. Subjects were randomized to mycophenolate plus placebo or mycophenolate and rituximab with outcomes favoring combination therapy.

Preference for steroid sparing agents will vary by practice. Preferred agents come from extrapolation of experience in well-defined connective tissue disease ILD, especially scleroderma and myositis spectrum conditions, such as with mycophenolate, azathioprine, rituximab, and cyclophosphamide.
Table 1 Typical dosing, safety monitoring, and side effect concerns with specific agents.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Baseline Labs</th>
<th>Safety Monitoring Labs</th>
<th>Side Effects</th>
<th>Time to Expected Therapeutic Effect</th>
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<tbody>
<tr>
<td>Mycophenolate mofetil (CellCept), mycophenolate sodium (Myfortic)</td>
<td>Start at 500 mg BID and increase every 2 weeks by 500 mg BID (max dose 1.5g BID) Mycophenolate mofetil 500 mg = mycophenolate sodium 360 mg</td>
<td>CBC, CMP</td>
<td>CBC and CMP every 2-4 weeks for 3 months, then every other month thereafter</td>
<td>GI upset, marrow suppression, infection, PML, malignancy; avoid during pregnancy/lactation</td>
<td>~3 months</td>
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<tr>
<td>Azathioprine (Imuran)</td>
<td>2-3 mg/kg daily; start at 50 mg and increase every 1-4 weeks by 50 mg daily (max dose 150-200 mg daily)</td>
<td>CBC, LFT, TMPT*</td>
<td>CBC and LFT - every 2-4 weeks for 3 months, then every other month thereafter</td>
<td>Abnormal LFTs, leukopenia, GI upset, flu-like symptoms, pancreatitis, hypersensitivity, infection, malignancy</td>
<td>~3 months</td>
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<tr>
<td>Cyclophosphamide (Cytoxan)</td>
<td>Variable, recommend 500-750 mg/m2 monthly, oral 2mg/kg/day</td>
<td>CMP, CBC, UA</td>
<td>CBC, CMP, and UA 10 - 14 days post infusion</td>
<td>Abnormal LFTs, leukopenia, cystitis and bladder cancer, infection, GI upset, gonadal toxicity, infertility, malignancy</td>
<td>~2-3 months</td>
</tr>
<tr>
<td>Rituximab (Rituxan, Ruxience, Truxima, Riabni)</td>
<td>1 g on days 0 and 14, repeat every 6 months</td>
<td>HIV, Hepatitis B surface antigen and core antibody, hepatitis C antibody, Quantiferon Gold</td>
<td>CBC, CMP before each dose</td>
<td>Infusion reactions, hepatitis B reactivation, hypogammaglobulinaemia and infection, progressive multifocal leukoencephalopathy, arrhythmias, skin rash, hypophosphatemia, abdominal pain</td>
<td>~2-3 months</td>
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Table 1. Immunosuppressants used in the treatment of idiopathic NSIP.

*Not all practitioners check TMPT level prior to starting and choose to titrate dose per monitoring

**Question 3:** The patient achieves improvement with prednisone, and because his symptoms worsened when attempting to wean prednisone, you started him on CellCept. He achieves stability in his FVC and DLCO for 14 months, but he later returns for follow-up with worsening dyspnea, hypoxemia with exertion and worsening pulmonary function. You repeat a high-resolution CT chest that shows progression of fibrosis. How would this change your management?

In this patient with progressive fibrosis unresponsive immunosuppression, antifibrotic therapy would be indicated. Nintedanib (Ofev) has been studied in progressive fibrotic lung disease in non-IPF patients in the INBUILD study. Patients enrolled in the trial had to meet one of the following criteria for progression of ILD within 24 months prior to screening: progression of fibrosis and worsening respiratory symptoms on high resolution CT, decline in FVC of 10%, decline in FEV1 by 5-10% or worsening of respiratory symptoms or an increased extent of fibrosis. Patients who received nintedanib had a slower decline in forced vital capacity at 52 weeks compared to placebo: adjusted change in FVC -80 mL in nintedanib vs -188 mL with placebo (Flaherty et al NEJM, 2019).
This patient should also be referred for transplant evaluation given progression of disease, age, and (presumed) single organ failure.

**Scenario 2:**
A 50-year-old man who was otherwise well presents for evaluation of breathlessness with exertion, hand swelling, dry hands with cracking, and Raynaud’s phenomenon. He was well until a month ago, when he developed joint pain and fatigue. His physical exam was notable for Gottron’s papules, fissuring of his fingertips, facial erythema, and shawl sign. His HRCT is shown below.

After review at your multidisciplinary interstitial lung disease conference, the radiologic diagnosis is thought to be NSIP. He was ultimately diagnosed with dermatomyositis and thus CTD-ILD.

His PFTs are notable for moderate restriction with FEV1 62%, DLCO 55% predicted. His ambulatory saturation nadir on his 6MWT was 93% on room air.

**Question 4: What are the treatment options for ILD related to myositis?**

Regardless of radiographic or pathologic pattern, the first line treatment of ILD related to myositis is immunosuppression. The choice in agents is dictated by severity of illness and/or progression of disease on initial therapy. See the figure below for a proposed treatment approach for myositis-associated ILD (Hallowell & Danoff, Chest 2023).
Table 2 lists additional agents used for myositis-associated ILD that were not covered in Table 1.

<table>
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<th>Drug</th>
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<td><strong>Tacrolimus</strong></td>
<td>Start 0.5-1.0 mg bid; titrate to a trough of 5-10 ng/mL</td>
<td>CBC, CMP</td>
<td>CBC, CMP, tacrolimus trough every week for the first month and every 4 weeks thereafter; lipid panel and yearly dermatology skin examination</td>
<td>Renal toxicity, hypertension, hyperlipidemia, tremors, hyperglycemia, increased risk of malignancy</td>
<td>~2-3 months</td>
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<tr>
<td><strong>IVIG</strong></td>
<td>2 g/kg/mo divided over 3-5 d</td>
<td>Screen for IgA deficiency before initiation</td>
<td>N/A</td>
<td>VTE, volume overload, headaches (aseptic meningitis), antibody-mediated cytopenias, anaphylaxis, infusion reactions</td>
<td>~1-2 months</td>
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A retrospective review of 125 patients with CTD-ILD was performed in patients treated with mycophenolate. Thirty-two of these patients had polymyositis or dermatomyositis. Patients with a non-UIP pattern had improvement in their FVC and DLCO and patients with CTD and UIP pattern had stability in their lung function. (Fischer et al, J Rheumatology 2013). Azathioprine has been demonstrated to have similar efficacy based on case series (Marie et al, Arthritis Care Res 2013).

However, if patients are progressing despite first line therapy or presenting with more severe disease, there are further options including tacrolimus, rituximab, IVIG, and PLEX.
Data to support the use of these medications are also derived from retrospective data or case series.

The phase 2b RECITAL trial (Maher et al, Lancet Respir Medicine 2023) randomized patients with severe or progressive CTD-ILD to cyclophosphamide versus rituximab. Of the 97 participants, 44 had myositis-associated ILD. Both agents had similar improvement in FVC from baseline and quality of life at 24 and 48 weeks. At 48 weeks, the change in FVC was +138 mL in cyclophosphamide v +112 mL in rituximab (p=0.345). Participants in the rituximab group had fewer adverse events and lower corticosteroid exposure over 48 weeks compared to the cyclophosphamide group.

**Scenario 2 (cont.):**
The patient returns for follow up with progressive dyspnea, but CT chest shows stability in lung disease. Repeat pulmonary function is stable, except DLCO has declined significantly. You obtain an echocardiogram that shows new RV failure with an elevated estimated pulmonary artery systolic pressure.

**Question 5: While this patient may have combined Group 1 (CTD) and Group III (ILD) pulmonary hypertension, what therapeutic options should be considered for pulmonary hypertension related to ILD?**

In patients with pulmonary hypertension due to interstitial lung disease, patients treated with inhaled treprostinil compared to placebo had an increase in 6-minute walk distance from baseline at week 16. Additionally, there was a significant reduction in NT-proBNP levels in patients treated with inhaled treprostinil compared to an increase in levels in the placebo group (Waxman et al. NEJM 2021).

**Question 6: What are treatment options for scleroderma related ILD?**

Two randomized controlled trials have evaluated therapy for scleroderma related ILD: SLS-1 and 2.

SLS-1 (Tashkin, et al 2006) compared cyclophosphamide for 1 year vs. placebo and found an improvement in 2.5% of predicted FVC favoring cyclophosphamide, although the effect was lost once the drug was stopped.

SLS-2 (Tashkin, et al 2016) compared cyclophosphamide vs. mycophenolate mofetil. Both drugs had equal efficacy in improving FVC, dyspnea and skin thickness. However, cyclophosphamide was associated with greater withdrawal from the study due to side effects.

More recently, nintedanib and tocilizumab have been studied in scleroderma-ILD.

The nintedanib trial in systemic sclerosis (SENSCIS) included 576 patients, about half of which were already on mycophenolate. Patients had been diagnosed within the last 7 years and had at least 10% fibrosis on HRCT. Patients were treated with a nintedanib 150 mg twice-daily vs placebo. The annual rate of decline of FVC was lower in the nintedanib group compared to placebo~ 52 mL vs 93 mL per year. This effect was more pronounced in the subgroup of patients who were not already on mycophenolate (Distler et al. NEJM 2019).
Tocilizumab is FDA approved for scleroderma-ILD based on the FocuSSed trial (Khanna et al, Lancet Respiratory 2020), an RCT that assessed the safety and efficacy of tocilizumab to treat skin fibrosis and systemic-sclerosis-associated ILD. Patients received tocilizumab injections of 162 mg weekly or placebo. The tocilizumab group had less decline in FVC % predicted at 48 weeks compared to placebo (14 mL vs 255 mL). There was no change in skin fibrosis with tocilizumab.

**Scenario 3:**
A 65-year-old woman presents with shortness of breath and cough. She had a CXR and was told that she had a viral infection. However, her symptoms persisted, so she had another CXR and HRCT (see images below). She was diagnosed with IPF with moderate restriction and started on pirfenidone. When she presents to you for a second opinion months later, she feels much better. She tells you that she owns a plant nursery, and her symptoms are temporally associated with peat moss deliveries. She undergoes surgical lung biopsy that demonstrates extensive interstitial fibrosis and patchy inflammation, numerous fibroblast foci and non-necrotizing granulomas in a bronchovascular distribution, most prominent in the upper lobes. These features are suggestive of hypersensitivity pneumonitis.


**Question 7: What factors do you consider in the diagnosis of hypersensitivity pneumonitis?**

There are now joint society clinical practice guidelines on the diagnosis of hypersensitivity pneumonitis. Hypersensitivity pneumonitis is classified as fibrotic or nonfibrotic (Raghu et al, AJRCCM 2020). Clinical factors to take into consideration for a diagnosis include the presence of an antigen associated with HP (bird dropping and feathers, molds, yeast, bacteria, etc), HRCT pattern (mosaic attenuation, air trapping, three density pattern – previously referred to as “headcheese” pattern), BAL lymphocytosis, and histopathologic findings of poorly formed granulomas.

The following diagram from the Clinical Practice Guideline referenced above combines clinical factors to ascribe levels of confidence to a clinical diagnosis of HP:
**Question 8: What are the therapeutic options for management of hypersensitivity pneumonitis (HP)?**

Regardless of subtype of HP, the mainstay of therapy is removal of the antigen followed by thorough cleaning of the house or workplace.

In mild cases of nonfibrotic hypersensitivity pneumonitis, removal of the offending antigen may be sufficient to reverse the injury. Patients with greater symptoms and/or hypoxemia can be treated with immunosuppression for reversal of inflammatory findings. For those patients that are treated, initial therapy involves corticosteroids at 0.5-1mg/kg, tapered over months. If patients cannot tolerate high dose corticosteroids, fail attempts at tapering, or do not respond to initial therapy then steroid sparing agents can be considered.

There is greater uncertainty about the role of immunosuppression in fibrotic HP, particularly in the absence of inflammatory findings (BAL lymphocytosis, ground glass attenuation). In a retrospective review of 70 patients with HP, both mycophenolate and azathioprine were associated with increased DLCO after 1 year, although no improvement in FVC was seen (Morisset et al Chest, 2017). Other retrospective reports have also failed to demonstrate improvement in lung function with immunosuppression in fibrotic HP (Adegunsoye et al, Eur Respir J 2022). Furthermore, a large multicenter retrospective cohort analysis reported shorter survival in patients with fibrotic HP with short telomere length who received immunosuppression (Zhang et al, Eur Respir J 2023). Unfortunately, routine telomere length testing for clinical decision-making is currently limited by cost.
**Question 9: For patients on long-term corticosteroid therapy, when should you start pneumocystis prophylaxis?**

Typically, PJP prophylaxis should be initiated if patients are receiving prednisone 20 mg daily or more (or equivalent dosing of another corticosteroid) for greater than 3 weeks. For patients on another immunosuppressant in addition to prednisone, even if the prednisone dose is less than 20 mg daily, PJP prophylaxis should be considered. First-line therapy is with trimethoprim-sulfamethoxazole. Dapsone (if G6PD deficiency is excluded), atovaquone, or inhaled pentamidine are other options.

**References:**
9. Morisset, et al Use of mycophenolate mofetil or azathioprine for the management of chronic hypersensitivity pneumonitis Chest 2017