Integrated Approach to Treating CTD-ILD

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Disclosures

• Industry relationships:  
  Actelion, aTyr Pharma, Boehringer-Ingelheim, Genentech-Roche, Gilead

Limitations

• Other than for SSc-ILD, no controlled data
• Even for SSc-ILD, minimal data
• Experience-based rather evidence-based

Relevant items to consider...

• Pace of disease
• Extent of disease
• Pattern of ILD
• Type of CTD
• Extra-thoracic disease
• Comorbid conditions
• What are the goals of therapy?
• Often experience-based, rather than evidence-based
• Some therapies with numerous side effects, toxicities
• In fibrotic ILD, goals may be about stabilization or modest improvement
• A desire to intervene “early” to minimize damage balanced against unwarranted Rx
Determining impairment

- Subjective
  - Dyspnea
  - Extra-thoracic disease burden
  **Treat: “clinically-significant”, progressive disease**

- Objective
  - PFTs (FVC, DLco)
  - 6MWT
  - Disease extent by HRCT

Clinical realities for SSc-ILD

- The majority of SSc patients have ILD
- Clinically progressive disease in ~ 1/3
- Treatment is not benign (especially CYC and stem cell transplant)
- Effective therapies only associated with stability or modest improvement (SLS I, II, FAST, MMF retrospective data)
  - (Fear of losing ground)
- Decisions whether to initiate immunosuppression are individualized

Predictors of progression?

**SSc:**
- Scl-70 antibody positivity
- Isolated nucleolar ANA
- “Early” disease
- Disease extent by HRCT
- Hx of progression

**PM/DM:**
- tRNA synthetase antibodies (e.g. Jo-1, PL-7, PL-12, etc.)
- MDA-5

**RA:** Men?, CCP?, smokers?

**Other CTDs:** ???

Pulmonary function testing

Although not adequate to diagnose ILD...

- Ideal modality for assessing progression in those with ILD
- Reproducible
- Relatively inexpensive
- Trend FVC, DLco over time
- SSc patients: pulmonary vasculopathy
  - Disproportionate reduction in DLco
  - Elevated FVC/DLco ratio (e.g., FVC 80%, DLco 40%)
Six minute walk test

- Measures distance walked, HR, oxygen desaturation
- Reproducible, inexpensive
- Effort / coach dependent
- MSK disease impacts performance / results
- Won’t distinguish ILD from PAH, other causes of hypoxia

- Not ideal for clinical trials, but does aid in assessment in longitudinal care of an individual patient

General approach to Rx

Corticosteroids
- Often high dose initially
- Not a good long term option

Steroid sparing agent
- Azathioprine
- Mycophenolate mofetil
- Cyclophosphamide
- Tacrolimus
- Cyclosporine

- Rituximab – select cases
- Others?

Current approach to treatment

Idiopathic UIP (IPF)  CTD-ILD (ANY pattern)  Idiopathic non-UIP

Clinical trials
Lung transplantation

Immunosuppression

Non-drug therapy

- pulmonary rehab
- use O2 correctly
- PH assessments
- GERD / aspiration
- N-acetylcysteine (NAC)?
- Pneumocystis prophylaxis
- vaccines
- mental health
Tashkin et al 2006 NEJM 354;2655-66

Scleroderma Lung Study

B

CYC
Placebo

49% improved
26% improved

51% worsened
74% worsened

Frequency [%]

FVC

Scleroderma Lung Study at 2 years

A

Adjusted FVC % predicted


Scleroderma Lung Study at 2 years

Tashkin et al AJRCCM 2007;176:1026-1034

Fibrosing alveolitis in SSc trial (FAST)

low-dose prednisone, IV CYC x 6 months followed by AZA vs. placebo

<table>
<thead>
<tr>
<th>BASELINE</th>
<th>1-YR FOLLOW-UP</th>
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<tbody>
<tr>
<td>Rx (n=22)</td>
<td>Placebo (n=23)</td>
</tr>
<tr>
<td>FVC 80</td>
<td>81</td>
</tr>
<tr>
<td>DLCO 53</td>
<td>55</td>
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<tr>
<td>TLC 82</td>
<td>77</td>
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Mycophenolate mofetil (MMF)

- Very popular for the treatment of CTD-ILD
- Numerous retrospective series in CTD-ILD
  - mostly scleroderma-ILD
  - all with few subjects
- MMF in CTD-ILD appears to be:
  - well-tolerated
  - associated with preservation of lung function

**MMF in CTD-ILD: retrospective study, 125 subjects, diverse CTDs**

**Mixed-effects model estimates for FVC%**

Fischer et al. J Rheumatol 2013

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**MMF was associated with steroid tapering effects**

Median prednisone dose:
- At MMF initiation: 20 mg qd
- After 9-12 months on MMF: 5 mg qd (p<0.0001)

Fischer et al. J Rheumatol 2013

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**MMF in CTD-ILD**

- Well tolerated
- Low rate (10%) of discontinuation
- Effective corticosteroid tapering
- Associated with stabilization or improvement in lung function
- A longer term option (than CYC)
- Warrants prospective study
**SLS II**
FVC had modest improvement with both MMF and CYC; no significant between-treatment difference


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**SLS II:** MMF had fewer adverse events, fewer patients in the MMF arm prematurely withdrew from the study (20 vs. 32), and time to stopping treatment was shorter in the CYC group (p=0.019)


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**Other options?**

- **Azathioprine**
  - well tolerated
  - “familiar”
  - FAST trial (SSc)
  - case series suggest role for variety of CTD-ILD

- **Cyclosporine, Tacrolimus**
  - may be particularly effective in patients with myositis – ILD

- **Rituximab**
  - Refractory myositis-ILD
  - “Rescue therapy”

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**Open-Label, Pilot Study of the Safety and Clinical Effects of Rituximab in Patients with Rheumatoid Arthritis-Associated Interstitial Pneumonia**

Erin L. Matteson, Tim Bongartz, Jay H. Ryn, Cynthia S. Crowson, Thomas E. Hartman, David F. Deharja

10 subjects enrolled (6 NSIP, 4 UIP), 48 week open label

- decline in 1, stability in 5, improvement in 1
- 3 withdrew, 1 infusion rxn, 2 deaths (CHF, PNA)

Matteson et al, Open J Rheum 2012
RTX for severe refractory ILD (CTD-ILD n=33, HP n=6, misc n= 11)

- Median decline in FVC of 14.3% and DLCO of 18.8% in the 6–12 months pre-RTX
- Median improvement in FVC of 6.7% (P < 0.01) and stability of DLCO (0% change; P < 0.01) in the 6–12 months post-RTX
- 2 developed serious infections (pneumonia) requiring hospitalization
- 10 died from progression of underlying ILD, a median of 5.1 (1.2–24.5) months after treatment

Keir et al Respirology 2013

Rituximab in chronic CTD-ILD (9 RA, 15 other CTD)

Spaghetti plot showing trajectories for FVC% over time for each subject (n=24) and mixed-effects model estimates FVC% over time for the entire cohort

Chartrand et al. Sarcoidosis Vasculitis and DLD 2016

Rituximab in chronic CTD-ILD

Figure 3. Spaghetti plot showing trajectories for percentage of FVC% over time for subjects without or with RA

Chartrand et al. Sarcoidosis Vasculitis and DLD 2016

Should histopathology impact treatment decisions?

Are these all treated the same?

RA-OP
RA-LIP
RA-C-NSIP
RA-F-NSIP
RA-UIP
Should underlying CTD impact treatment decisions?

Are these all treated the same?

- SSc-NSIP
- MCTD-NSIP
- SjS-NSIP
- SLE-NSIP
- RA-NSIP

Individual CTD-ILDs

- Fischer is totally making it up...

SSc-ILD

- Early vs. late disease
- (they all have fibrotic interstitial pneumonia)
- Disease extent
- PFT disconnect / PFT challenges
- MMF >>>>> CYC
- Not very prednisone-responsive (concerns for renal crisis?)
- Aspiration, GERD
- Development of PH/PAH – FVC/DL ratio

Myositis-ILD (Synthetase-ILD)

- Window of opportunity
- “evolution” from NSIP/OP to fibrotic IP
- Often will use INTENSE corticosteroids
  - Pulse dose (1 gram methylpred x 3 days)
  - Weekly mini-pulses
  - MMF first line
  - Early trigger for rituximab
- IVIg for the myositis component
- AZA, tacrolimus, cyclosporine
- Long-term Rx needed
RA-ILD

- ILD pattern?
  - And these patients get bronchiolitis
- I do not extend from PANTHER (but I recognize some do...)
- AZA is more effective for synovitis than MMF
- I combine AZA or MMF with biologics
- Rituximab is a cool thing to recommend

RA-ILD: what’s driving therapy?

RA = RED
ILD = BLUE

Synovitis often impacts Rx

Joint disease
- Complex arena with lots of biologic DMARDs
  - TNF antagonists
  - IL-6 antagonist
  - T-cell agents
  - B-cell agents
  - JAK/STAT inhibitors

ILD
- Not as complex...
  - Corticosteroids
  - AZA, MMF, CYC...

DMARDs proven to be effective in RA

Traditional
- Methotrexate
- Sulfasalazine
- Leflunomide
- Azathioprine
- Cyclosporine
- (Gold)

Biologic
- Anti-TNFs
  - Infliximab (Remicade)
  - Etanercept (Enbrel)
  - Adalimumab (Humira)
  - Golimumab (Simponi)
  - Certolizumab (Cimzia)
- Anakinra (Kineret)
- Abatacept (Orencia)
- Rituximab (Rituxan)
- Tocilizumab (Actemra)
- Tofacitinib (Xeljanz)
DMARDs proven effective in RA-ILD

Controlled trials for RA-ILD

Compared to other CTDs, UIP is disproportionately represented in RA

Survival for RA-UIP = IPF

Moua and Zamora Martinez et al. Respiratory Research 2014

Kim CHEST 2009
RA with radiographic UIP has similar survival as IPF

Kim ERJ 2010

Methotrexate-pneumonitis

- Incidence of 3.5–7.6% (??)
- Not dose-dependant, or duration of Rx
- Acute onset
- Peripheral infiltrates on chest imaging
- Peripheral eosinophilia in ~40%

- BAL lymphocytosis
- Transbronchial or surgical lung biopsy:
  - may reveal a hypersensitivity pattern
  - occasionally organizing pneumonia
- Often, the diagnosis is not definitive; i.e., exclusionary


Influence of TNFs on mortality in RA-ILD

Dixon et al. Ann Rheum Dis. 2010
Influence of TNFs on mortality in RA-ILD

- Mortality in RA-ILD is NOT increased with anti-TNF therapy

- Deaths attributable to RA-ILD is higher in those with anti-TNF therapy

Dixon et al. Ann Rheum Dis. 2010

The safety of biologic therapies in RA-associated interstitial lung disease

- “at present, insufficient data are available to differentiate the safety profiles of the different agents licensed in RA”


BMJ Open

Potential risk of TNF inhibitors on the progression of interstitial lung disease in patients with rheumatoid arthritis

- Single center, Japan, 163 patients, retrospective
- Anti-TNFs administered to more patients with ILD events than without ILD events (88% vs 60%, p<0.05)
- No increase in ILD events with tocilizumab or abatacept
- Of 58 patients with pre-existing ILD, 14 had ILD events, and that proportion was greater than for those without pre-existing ILD (24% vs. 3%, p<0.001).
- Of these 14, all were treated with TNF inhibitors


Suggested algorithm for monitoring RA-ILD on biologics

55 year old man with UIP
RF and CCP both high-positive
no arthritis

**RA-ILD: My approach?**

- I tend to avoid MTX in any patient with any type of significant lung disease
- Before I use MTX, I like to know if my RA patient has ILD or not – CXR vs. HRCT
- I use biologics in my RA patients with ILD – for their RA, not their ILD
- I make decisions on an individualized basis
- I use corticosteroids + MMF or AZA mostly – to treat their ILD
- I combine the MMF or AZA with any of the biologics (like we do with MTX or LEF)

**SjS-ILD**

- Depends on histopathology
- Profound cystic lung disease tends to not be responsive to immunosuppression
- (SS-A does not mean they have SJS)
- These patients get bronchiolitis

**SLE-ILD**

- Is it really SLE?
- Pleuro-parenchymal disease
- AZA (esp with serositis), MMF, CYC, pred
Longitudinal assessment

- Subjective
  - Symptoms
  - Medication tolerance
- FVC
- *DLco
- 6MWT
- HRCT

*In the absence of PH, DLco provides the best overall estimate of HRCT-measured lung disease in SSc

A comprehensive approach is needed

Is this where we are heading?

Idiopathic UIP (IPF)  CTD-ILD (ANY pattern)  Idiopathic non-UIP

CTD-UIP/NSIP  Pirfenidone

Clinical trials  Lung transplantation  Immunosuppression  Immunosuppression

### Summary

- Not every patient with CTD-ILD needs treatment
- Consider what's driving need for treatment
  - Extra-thoracic vs. intra-thoracic disease activity
- Determine degree of impairment, pace of the disease
  - Treat only those with clinically-significant, progressive ILD
- Management is not evidence-based
- Consider underlying CTD and ILD pattern
- MMF use is popular – warrants further prospective study
- Desperate need for better therapies

### Longitudinal assessment:

- CTD and ILD phenotypic aspects
  - Pace of disease
  - ILD extent
  - PFTs
  - 6MWT
- Comorbid conditions
  - PH/PAH
  - Aspiration
  - CAD
- Stability = success