Management of Connective tissue disease-Interstitial Lung Disease (CTD-ILD)

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Connective tissue disease

• All components of the lung can be involved
• ILD major cause of morbidity and mortality
• Severity of lung disease usually unrelated to severity of systemic manifestations
• ILD can be the first manifestation of a CTD in a substantial proportion of patients
### Most frequent ILD patterns in CTD

<table>
<thead>
<tr>
<th>Chronic fibrotic ILD</th>
<th>NSIP</th>
<th>Systemic sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Idiopathic inflammatory</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Undifferentiated CTD</td>
</tr>
<tr>
<td>UIP</td>
<td></td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Undifferentiated CTD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic sclerosis</td>
</tr>
</tbody>
</table>

#### Stabilize Disease

<table>
<thead>
<tr>
<th>Subacute/Acute ILD</th>
<th>Organising pneumonia/NSIP/Diffuse alveolar damage</th>
<th>Idiopathic inflammatory myositis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Undifferentiated CTD Rheumatoid arthritis</td>
</tr>
</tbody>
</table>

#### Potential for reversibility/ (stabilization)
CHRONIC FIBROTIC ILD
Management Issues

• Should we treat?
• When to treat?
• How to monitor?
• What to treat with?
• How long to treat for?
• Future treatments
SHOULD WE TREAT?
CTD-ILD is common

• HRCT now widely used to screen for ILD in CTD patients
• Many CTD pts have limited/inherently stable ILD
• However, a substantial minority have progressive/severe disease
• Current treatments all have a degree of toxicity
WHEN TO TREAT?
Treat progressive/severe disease

- In limited disease, especially if longstanding, risk/benefit favour careful observation (MICO therapy)
- Threshold for initiating treatment is reduced in
  - recent onset of systemic disease (at least in SSc)
    > Steen Arthritis Rheumatism 1994
    > Moore ClinExp Rheumatol 2015
      - patients who have no decline in PFTs over 4 years have better outcomes
  - severe ILD
  - ongoing progression based on lung function and symptoms
Baseline Assessment
Scleroderma ILD: Staging and treatment

- **HRCT extent**
  - < 20%
  - Indeterminate
  - > 20%

- **FVC**
  - FVC ≥ 70%
  - FVC < 70%

- **Disease**
  - Limited Disease
  - Extensive Disease
Survival: limited vs extensive SSc-ILD

Goh AJRCCM 2008
Moore OA Rheumatology 2013
• When disease is severe, treatment decisions usually straightforward

• Treatment decisions more difficult in the large CTD-ILD subgroup with milder disease:

*The importance of longitudinal behaviour*
HOW TO MONITOR?
Which parameters to monitor?

• Lung function (% change from baseline):
  • FVC
  • TLC
  • DLCO
• HRCT
Forced vital capacity (FVC)

• Specific for interstitium, DLCO also reflects vasculature

• Variable consistent in reflecting change in SSc-ILD clinical trials, widely validated

• More repeatable across lung function labs
Significant change in lung function

- FVC ≥ 10%
- DLCO ≥ 15%

- Based on degree of inter-measurement variation for each test (>2 SD)

ATS/ERS guidelines
**FVC decline >10% at 12 months**

**Whole cohort**
- HR = 1.84
- 95% CI = 1.14, 2.97
- p = 0.01

**Extensive disease**
- HR = 2.31
- 95% CI = 1.16, 4.60
- P = 0.02
What if FVC fall is between 5 to 10%

- Corroborative evidence useful:
  - Downward trend in DLCO
  - Symptoms (breathlessness)
  - If worsening marginal, continue to observe
Composite Categorical Threshold (CCT):
either FVC decline >10%
or FVC decline of 5-10% + DLco decline >15%

Whole cohort
HR = 1.96
95% CI = 1.25, 3.08
P<0.005

Extensive disease
HR = 2.86
95% CI = 1.44, 5.71
P<0.005

Goh et.al.
WHEN IS REPEATING HRCT USEFUL?
• No evidence to suggest advantage of routine CT monitoring
• HRCT may be useful in providing corroborative data to lung function changes, although minimally important differences in CT scores not established in SSc or other CTD-ILDs
• HRCT is useful when other causes of worsening are suspected
  – PE
  – Infection
  – Lung cancer
WHAT TO TREAT WITH?
Current choice of drugs

• Prednisolone
• Cyclophosphamide (CYC)
• Azathioprine (AZA)
• Mycophenolate Mofetil (MMF)
Cyclophosphamide
Randomized placebo-controlled clinical trials so far only in SSc-ILD

- Scleroderma Lung Study I (SLS):
  - 1 yr of oral CYC vs placebo; 158 patients
  - 2.53% FVC improvement at 12 months in CYC group (p=0.03)

*Tashkin NEJM 2006*
The greatest treatment effect was seen in patients with the most severe fibrosis on CT
Fibrosing alveolitis in Scleroderma trial (FAST)

- 45 patients
- monthly IV CYC for six months followed by azathioprine and low dose pred for six months:

  Similar changes in FVC
  +2.4% in active vs -3.0% in placebo
  (p=0.07)
Azathioprine
• Other than in FAST, the data for AZA are limited to small and retrospective series

• Maintenance therapy
  – Hoyles A & R 2006
  – Berezne J Rheumatol 2008

• Induction therapy
  – Dheda Clin Rheumatol 2004
  – Poormoghim Rheumatol Int 2014
  – Deheinzelin AJRCCM 1996
  – Mira-Avendano Respir Med 2013
• AZA is generally well-tolerated and is a plausibly effective CS-sparing agent for long-term treatment of CTD-ILD

• AZA can help control both synovitis and ILD
Mycophenolate Mofetil
MMF is safe, well tolerated and is associated with small improvements/stabilization in PFT

-Meta-analysis
Tsouveleakis et.al. Pulmonary Medicine 2012

-Retrospective studies
Swigris JJ et.al. Chest 2006
Nihtyanova et.al. Rheumatology 2007
Koutroumpas et.al. Clin Rheumatol. 2010
Zamora et.al. Respir Med 2008
Gerbino et.al. Chest 2008

-Prospective studies
Simeon-Aznar et.al. Clinical Rheumatology 2011
Fischer A et al. J Rheumatol 2013
MMF in CTD-ILD

- Prospective trial
- 125 patients treated with MMF
- At least 6 months of follow up data
- Well tolerated
- 10% of patients discontinued
- 2.5 yrs median follow up

Fischer A et al. J Rheumatol 2013

<table>
<thead>
<tr>
<th>Disease</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic sclerosis</td>
<td>44</td>
</tr>
<tr>
<td>Polymyositis/dermatomyositis</td>
<td>32</td>
</tr>
<tr>
<td>Lung-dominant connective tissue disease</td>
<td>19</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>18</td>
</tr>
<tr>
<td>Sjögren disease</td>
<td>5</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>4</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>3</td>
</tr>
</tbody>
</table>
Reduction of mean prednisone dose after introduction of MMF

Fischer A et al. J Rheumatol 2013
FVC and DLCO improve after the introduction of MMF

Fischer A et al. J Rheumatol 2013
The Scleroderma Lung Study II (SLS II) Shows That Both Oral Cyclophosphamide (CYC) and Mycophenolate Mofitil (MMF) Are Efficacious in Treating Progressive Interstitial Lung Disease (ILD) in Patients with Systemic Sclerosis (SSc)

Philip J. Clements1, Donald Tashkin1, Michael Roth1, Dinesh Khanna2, Daniel E. Furst3, Chi-hong Tseng1, Elizabeth R. Volkmann1 and Robert Elashoff4, 1Medicine, University of California Los Angeles, David Geffen School of Medicine, Los Angeles, CA, 2Medicine, University of Michigan, Ann Arbor, MI, 3Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, 4Biomath, University of California Los Angeles, David Geffen School Of Medicine, Los Angeles, CA

Meeting: 2015 ACR/ARHP Annual Meeting

Date of first publication: September 29, 2015
SLS 2 study: AIM

• “Demonstrate that the course of FVC over 2 years was **better** in SSc patients with symptomatic ILD treated with oral MMF for two years than with oral CYC for one year followed by placebo during the second year in a blinded randomized controlled trial”
SLS 2 study: METHOD

- 142 patients randomized (14 centres across US);
  105 completed 2 year evaluation

- Entry criterion:
  - 1980 ACR criteria for SSc
  - Disease duration of <= 7 years from 1st non-Raynaud sign or symptom
  - Moderate dyspnoea (Level 2 of the Magnitude of Task scale of the Mahler Baseline Dyspnea Index [BDI])
  - %FVC between 45% and 80%; and any ground-glass opacification on chest HRCT
SLS 2 study: METHOD

• At baseline and every 3 months during the 2-year trial
  – Physical exams (including modified Rodnan skin scoring or MRSS)
  – Lung function testing
  – Patient-reported outcomes
    > Scleroderma Health Assessment Questionnaire
    > SF-36
    > Transition dyspnea index (TDI).

• Patients randomized to
  – Arm A (oral CYC 2 mg/kg/day for one year followed by matching placebo for the second year) OR
  – Arm B (MMF up to 1500 mg BD for 2 years)
Improvement in %FVC was similar in the 2 treatment groups
CYC was associated with more premature withdrawal

• The TDI and MRSS improved in both treatment arms but there was a trend favouring improvements in the CYC group
• More patients in the CYC arm withdrew from study treatment prematurely (36 in CYC and 20 in MMF) (p=0.02).
• Of all the subjects with end-point data:
  – 23% assigned to CYC received alternative therapy after stopping study treatment (MMF in 8, Rituximab in 1, tocilizimab in 1 and IV-CYC in 2)
  – 4% assigned to MMF received alternative treatment (po CYC in 1 and IV-CYC in 1) after stopping study treatment
MMF was associated with less side effects

- Weight loss (NS)/ Leukopenia/thrombocytopenia (p<0.05) were significantly less in the MMF arm

- It is unclear how the use of alternative medications in patients who withdrew prematurely from study treatments, particularly in the CYC patients, could have influenced the results
Take home message

• Oral MMF is as effective as oral CYC in improving FVC
• Oral MMF is associated with less side effects
• Oral MMF is now off patent and widely accessible/available
Rituximab
Unmet clinical need in ILD-CTD: severe unresponsive disease

A proportion of CTD-ILD patients are refractory to intense immunosuppression, including iv cyclophosphamide
Audit of Rituximab use as rescue therapy in ILD

- 50 patients treated from 2007-April 2012
  - 35 had CTD-ILD
    > 14 idiopathic inflammatory myopathy (DM/PM)
    > 8 undifferentiated CTD
    > 6 systemic sclerosis
    > 4 overlap syndrome
    > 2 mixed CTD
    > 1 rheumatoid arthritis
- Follow up of at least six months

Keir et al Respirology 2014
<table>
<thead>
<tr>
<th></th>
<th>N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ILD severity</strong></td>
<td></td>
</tr>
<tr>
<td>FVC</td>
<td>48% (31-99)</td>
</tr>
<tr>
<td>DLco</td>
<td>25.9% (14-56)</td>
</tr>
<tr>
<td><strong>Treated course previous 12 months</strong></td>
<td></td>
</tr>
<tr>
<td>Δ FVC</td>
<td>18% (0-47)</td>
</tr>
<tr>
<td>Δ DLco</td>
<td>19% (0-67)</td>
</tr>
<tr>
<td><strong>Previous immunosuppression</strong></td>
<td></td>
</tr>
<tr>
<td>IV cyclo</td>
<td>42</td>
</tr>
<tr>
<td>AZA/MMF</td>
<td>4</td>
</tr>
<tr>
<td>IV methylpred</td>
<td>4</td>
</tr>
</tbody>
</table>
Response to treatment

<table>
<thead>
<tr>
<th>Measure</th>
<th>12 months pre rituximab</th>
<th>Nadir</th>
<th>12 months post rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC%</td>
<td>57.5 (34-110)</td>
<td>48.0 (31-99)</td>
<td>53.0 (32-105)</td>
</tr>
<tr>
<td>Tlco %</td>
<td>33.0 (18-63)</td>
<td>25.9 (14-67)</td>
<td>28.0 (14-62)</td>
</tr>
<tr>
<td>PaO2</td>
<td>10.4 (6.3-12.6)</td>
<td>8.3 (6.1-11.9)</td>
<td>9.5 (5.6-12.2)</td>
</tr>
</tbody>
</table>

Keir et al Respirology 2014
Most striking responses seen in the anti-synthetase cases
RCT Rituximab

• Royal Brompton Hospital trial:
• Rituximab (1 gr x 2) vs iv cyclophosphamide (monthly for six months) in CTD-ILD
  – Systemic sclerosis
  – Mixed Connective tissue disease
  – Idiopathic inflammatory myositis
• Primary outcome: FVC change at twelve months
HOW LONG TO TREAT FOR?
Follow up of SLS I study

End of SLS 1
Unanswered questions……

• Treat RA-UlP aggressively like IPF?
• Use of other anti-fibrotic agents?
• How to treat patients with IPAF?
Haemopoietic Stem Cell Therapy
Haemopoietic stem cell transplantation (HSCT)

- Pioneered in 1960s
- High dose chemotherapy (conditioning) would ablate residual marrow or malignancy of the host
- Infusion of donor (allogeneic) bone marrow would allow engraftment of a new immunohaemopoietic system from the pluripotential stem cell
- Autologous (patient’s own) HSCT has become a standard and safe procedure for a variety of diseases (e.g. lymphoma and myeloma) since mid 1980s
Autologous HSCT

• Use in severe autoimmune disease over last 18 years
  – International Registry (EBMT) (MS, SSc, RA, SLE, juvenile arthritis, haematological immune cytopaenias)

• Possible mechanisms of action
  – High dose immunosuppression
  – May “reset” the immune system (prolonged responses)

• Associated with significant transplant related morbidity and mortality (TRM)
  – Reduce with careful patient selection
Autologous HST: Local experience

- 10 patients failed IV CYC
- October 2002 and November 2009 at St Vincent’s Hospital, Sydney
- Rapidly progressive inflammatory diffuse scleroderma, within 3 years of onset, involving lungs and/or heart (6 pulmonary fibrosis)

### Table 1. Patient and disease characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43</td>
<td>(23–46)</td>
</tr>
<tr>
<td>Diagnosis to HSCT (months)</td>
<td>16</td>
<td>(10–35)</td>
</tr>
<tr>
<td>ANA</td>
<td>1.640</td>
<td>(160–2640)</td>
</tr>
<tr>
<td>Total lung capacity (%N)</td>
<td>83%</td>
<td>(68–118)</td>
</tr>
<tr>
<td>TLCO (%N)</td>
<td>66%</td>
<td>(57–100)</td>
</tr>
<tr>
<td>Previous lines of therapy</td>
<td>3.5</td>
<td>(2–6)</td>
</tr>
<tr>
<td>CY dose (g/m²)</td>
<td>3.75</td>
<td>(1.5–6.5)</td>
</tr>
<tr>
<td>Skin score</td>
<td>25</td>
<td>(15–40)</td>
</tr>
<tr>
<td>HAQ</td>
<td>2.25</td>
<td>(0.75–3)</td>
</tr>
<tr>
<td>VAS (disease, mm)</td>
<td>68.5</td>
<td>(20–100)</td>
</tr>
<tr>
<td>VAS (pain, mm)</td>
<td>47</td>
<td>(28–100)</td>
</tr>
</tbody>
</table>

Abbreviations: ANA = antinuclear Ab; HAQ = Health Assessment Questionnaire; HSCT = haematopoietic SCT; TLCO = carbon monoxide transfer corrected for alveolar volume; VAS = visual analogue scale.
• No TRM at D100 or 1 year post HSCT
• At median follow-up of 33 months
  – significant reduction in skin scores
  – All patients experienced a significant reduction in Health Assessment Questionnaire (HAQ) and visual analogue scale (VAS) scores (disease and pain)
  – 4 patients - recurrence of disease at 12 months post HSCT
    > 2 died of progressive disease
    > 2 alive with HAQ and VAS scores lower than pre-HSCT values.
• Respiratory function stable in all patients (DLco 66% (57-100)
• 7 patients returned to full-time work post HSCT
### Table 2  Randomized control trials of hematopoietic stem cell transplantation in systemic sclerosis

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Patients</th>
<th>Controls</th>
<th>Number</th>
<th>Outcome</th>
<th>TRM</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASTIS(^{14})</td>
<td>mRSS 15 for disease duration 4 yr, mRSS 20 if disease duration is 2 yr; and major organ involvement</td>
<td>IV CYC</td>
<td>156 (79 HSCT, 77 CYC)</td>
<td>5 yr survival: 52% (40 patients) in CYC; 70% (55 patients) in HSCT</td>
<td>10.01%</td>
<td>At 2 yr: significantly better event free survival, mRSS, EuroQol. HAQ; decline in creatinine clearance and increase in FVC/VC. Median follow up 5.8 yr</td>
</tr>
<tr>
<td>ASSIST(^{15})</td>
<td>mRSS 14 with internal organ involvement or coexistent pulmonary involvement if mRSS was &lt; 14</td>
<td>IV CYC</td>
<td>19 (10 HSCT, 9 CYC)</td>
<td>HSCT: all improved; CYC: 8 progressed</td>
<td>None</td>
<td>Small study, 7/8 that progressed in CYC group switched to HSCT. All HSCT patients (including switches) had significant improvement in mRSS and FVC and TLC. Follow up 2 yr</td>
</tr>
<tr>
<td>SCOT(^{16})</td>
<td>mRSS &gt; 16, significant visceral organ involvement, disease duration &lt; 4 yr</td>
<td>IV CYC</td>
<td>75</td>
<td>Not reported</td>
<td>-</td>
<td>Recruitment competed, yet to be published. Identical regimen to ASTIS except total body irradiation in HSCT</td>
</tr>
</tbody>
</table>

mRSS: Modified Rodnan skin score; IV: Intravenous; CYC: Cyclophosphamide; HSCT: Hematopoietic stem cell transplantation; HAQ: Health Assessment Questionnaire.
Autologous SCT in CTD-ILD

• Stem cell transplantation is a viable option in severe autoimmune diseases, in particular for systemic sclerosis

• Careful patient selection is crucial (SSc) to reduce TRM
  – Age <60 yrs
  – Non smoker
  – mPAP<25mmHg
  – TLC>50%
  – TLCO>50%
  – Diffuse Disease
  – Duration <5 yrs
Treatment for extra-thoracic manifestations

- Prednisolone
- Rituximab
- Azathioprine
- Methotrexate
- Anti-TNF therapy (infliximab/ etanercept/ adalimumab/ golimumab)
- Leflunomide
- Sulphasalazine

[www.pneumotox.com](http://www.pneumotox.com)
Non pharmaceutical treatments

• Symptomatic management
  – dyspnoea/ cough/ anxiety/ depression
• Pulmonary rehabilitation/ exercise
• Vaccination
  – Vaccinate before immunosuppression
• Lung transplantation
Summary: Mx of fibrotic CTD-ILD

• WHO TO TREAT
  – Most CTD-ILD are limited and non progression
  – Substantial proportion are progressive and warrant treatment
  – Aim: to stabilise disease

• HOW TO MONITOR
  – Lung function tests- FVC

• WHEN TO TREAT
  – Severe disease
  – Progressive disease
  – Disease within first 4 yrs of systemic manifestation

• WHAT TO TREAT
  – Induction – IV cyclophosphamide (6 months) / oral MMF
  – Maintenance – oral MMF/ AZA

• HOW LONG TO TREAT
  – >12 months

• THE FUTURE
  – Stem Cell Therapy