Choice of the primary outcome:
Pro Lung

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Improved clinical trial design in systemic sclerosis

Lung assessment in clinical trials
Lung assessment

- Strengths and weaknesses
- Improvement versus prevention of worsening

Advantages:
- Clinically important
- Measurable
- Regulatory acceptance
- Feasibility
- Tools available

Disadvantages:
- Often trivial or stable
- Technical issues
- Mixed study cohort
- Best measures unclear
- "Standard of care" therapy emerging - placebo controlled studies difficult

Oral cyclophosphamide in SSc-PF: the Scleroderma Lung Study (SLS-I)

24 month follow-up data suggest maximum treatment effect on FVC at 18 months then benefit diminishes but improved dyspnoea score remains

1Tashkin et al NEJM 2006
2Tashkin et al Am J Respir Crit Care Med 2007
**SLS II Primary outcome assessment: the course of % predicted forced vital capacity (FVC) from 3 to 24 months by treatment group**

![Graph showing the course of % predicted FVC from 3 to 24 months by treatment group.](image-url)

**SLS II outcome data: Frequency distribution of changes from baseline to 24 months in % predicted FVC**

![Bar chart showing frequency distribution of changes.](image-url)

(A) The observed data of all patients with data at 24 months includes mycophenolate mofetil (n=58) and cyclophosphamide (n=51). (B) The completers population includes mycophenolate mofetil (n=49) and cyclophosphamide (n=36).

Average change in % predicted FVC for observed values (mean ±SE):

- **CYC**: 3.0±1.2
- **MMF**: 3.3±1.1

Deaths at 24 months:
- **MMF**: n=5
- **CYC**: n=11
Efficacy endpoints for a Phase III trial in SSc-PF

- **Primary endpoint**
  - Annual rate of decline in FVC (mL/year) over 52 weeks

- **Key secondary endpoints**
  - Absolute change from baseline in mRSS at week 52
  - Absolute change from baseline in SGRQ total score at week 52

- **Exploratory secondary**
  - Annual rate of decline in FVC % predicted
  - Absolute change from baseline in FVC % predicted at week 52
  - Absolute change from baseline in HAQ-DI score at week 52


Can skin and lung be examined in a single clinical trial in diffuse cutaneous SSc?

- Skin
  - n = 86
  - 1:1 randomisation

- Lung
  - FVC change cumulative distribution plot

- Weighted values for THBS1 and MS4A4A mRNA expression

- MRSS change over 48 weeks

- 24 weeks
- 48 weeks
- p=0.009
- p=0.0373

n = 86 1:1 randomisation


Key issues for lung as a primary end point in SSc trials

- Prevention of worsening versus improvement
  - May be “mechanism of action” dependent

- Best individual measure
  - FVC%, FVC absolute, Dyspnoea score, composite
  - Optimal application of CT data

- Best cohort enrichment for:
  - Developing lung fibrosis
  - Risk of severe or progressive lung fibrosis
  - Assessing skin and lung in one trial

- Definition of clinical relevance
  - Clinically significant lung fibrosis
  - Group level MCID

- Relevance or exclusion of pulmonary hypertension
Choice of the primary outcome:
Pro CRISS
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Composite measures of clinical outcome in SSc

- Strengths and weaknesses
- Improvement versus prevention of worsening

Advantages
- Clinically meaningful
- Broad assessment within organ system
- Global assessment
- Tools being developed

Disadvantages
- Tools unvalidated
- Generalisability
- Long and complex trials
- Changing therapeutic landscape

Composite event-driven studies work for CTD associated pulmonary arterial hypertension

*Composite endpoint*
Combined endpoint analysis – for an event-driven study in systemic sclerosis

1995-1999 Royal Free SSc cohort (n=398)

PF, PH, Cardiac, RC, Death

Time to endpoint

P<0.001


Development of the CRISS composite index


CRiSS index for diffuse SSC trials developed based on consensus and data-driven methodology


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Development of the CRISS composite index

**Methodology**
- 200 prospectively recruited dcSSc cases over 12 months
- 150 "paper cases" from established registries
- MTX versus placebo clinical trial cohort (Pope et al, 2011)

**Results**
- Composite score including gave AUC of 0.986; sensitivity of 0.982 (95% CI 0.981-0.983) and specificity of 0.931 (95% CI 0.929-0.932).
- modified Rodnan skin score
- FVC% predicted
- patient and physician global assessments
- HAQ-DI

In the patients with complete data in the MTX trial, 58% of MTX group vs. 19% in placebo group were considered improved.

**Conclusion**
- 2 stage process to predict probability of improvement
  - Step 1 – absence of major organ progression (SRC etc.) – score "0"
  - Step 2 – predicted probability of improvement – (score "0 – 1")


Application of CRISS in a randomized clinical trial (RCT)

**2 step process**
- Evaluate if a patient has meet criterion for NOT-IMPROVED. If yes, the patient is assigned a probability score of 0.0
- For remaining patients, calculate probability based on change in 5 measures
  - MRSS, FVC%, HAQ-DI, Patient global and MD global assessment
- Each patient has a probability score between 0.0-1.0
Expert consensus on definition of a patient who is not-improved during a trial - STEP 1

• Patient is considered not improved* if they develop any one of:
  • New scleroderma renal crisis
  • Decline in forced vital capacity (FVC) predicted ≥15% (relative), confirmed by another FVC% within a month, high resolution computer tomography (HRCT) to confirm interstitial lung disease (ILD; if previous high resolution computer tomography of chest did not show ILD) and FVC% predicted below 80% predicted*
  • New onset of left ventricular failure (defined as left ventricular ejection fraction ≤45%) requiring treatment*
  • New onset of pulmonary arterial hypertension (PAH) on right heart catheterization requiring treatment.

*Irrespective of change in other core items

STEP 2

• Step 2 involves computing the predicted probability of improving for each subject using the equation

\[ \Delta \text{MRSS} \text{ indicates the change in MRSS from baseline to follow-up, } \Delta \text{FVC} \text{ denotes the change in FVC% predicted from baseline to follow-up, } \Delta \text{Pt-glob} \text{ indicates the change in patient global assessment, } \Delta \text{MD-glob} \text{ denotes the change in physician global assessment, and } \Delta \text{HAQ-DI} \text{ is the change in HAQ-DI.} \]

• All changes are absolute change (Time₂ – Timeₙ₀baseline).

How does CRISS work in a contemporary clinical trial in dcSSc over 12 months – such as faSScinate


Weighted values for THBS1 and MS4A4A mRNA expression

MRSS change over 48 weeks

FVC change cumulative distribution plot

Skin

Lung
Comparison of TCZ and PBO using CRISS index and individual variables at 24 and 48 weeks.

<table>
<thead>
<tr>
<th>Variable</th>
<th>TCZ, N=43</th>
<th>PBO, N=40</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRISS (0.0-1.0), median [IQR] at 24 weeks</td>
<td>0.19 [0.006; 0.92]</td>
<td>0.28 [0.0001; 0.13]</td>
<td>0.0006*</td>
</tr>
<tr>
<td>FVC% predicted, mean change at 24 weeks</td>
<td>-4.19</td>
<td>-2.65</td>
<td>0.28</td>
</tr>
<tr>
<td>HAQ-DI (0-3), mean change at 24 weeks</td>
<td>0.17</td>
<td>0.18</td>
<td>0.93</td>
</tr>
</tbody>
</table>
| **Using Wilcoxon test as CRIS data is not normally distributed.**
| **There are 4 subjects in the PBO who met step 1 and were given a score of 0.0.**


JBT-101 (ajulemic acid, Resumab® now designated as Lenabasum)

- CB2 cannabinoid agonist
- Promotes release of resolution promoting/anti-inflammatory eicosanoids "resolvins"
- Stimulates PPARgamma – antifibrotic
- Reduces markers of fibrosis and pro-inflammatory cytokines (CTGF, IL6) in SSC fibroblasts
- Positive results reported November 2016, Phase I/II
- Statistically significant benefit for CRISS composite index
- CB2 agonist that may have anti-inflammatory and anti-fibrotic potential
- Phase III trial (RESOLVE) starting soon

Testing CRISS in a clinical trial

Phase III trial of JBT-101 Corbus Pharmaceuticals 2017

EULAR Oral presentation – June 2017

• CORBUS Pharmaceuticals
  – Positive results reported November 2016, Phase I/II
  – Statistically significant benefit for CRISS composite index
  – CB2 agonist that may have anti-inflammatory and anti-fibrotic potential
  – Phase III trial (RESOLVE) starting soon
Current key issues for CRISS in trials

- Provisional ACR index requiring validation
- Not accepted as primary endpoint by health authorities
- Development as a continuous outcome measure for STEP 2
  - Definition of MCID at individual and group level
- Presentation of CRISS data from several randomised trials imminent (ACR 2018)
- Key endpoint for ongoing phase III trial
- May become as acceptable as MRSS for trials if additional trial data are supportive (personal opinion)

Summary – Lung and CRISS as SSc trial endpoints

- Immunosuppression has beneficial effect for skin and lung in SSc
  - Autologous haematopoietic stem cell transplantation defines "gold standard" treatment effect
- Lung fibrosis endpoints and CRISS are feasible endpoints but require full validation for use in regulatory approval
- Clinical trials are ongoing – results awaited
  - Rituximab is being evaluated in Phase II study (RECITAL)
  - Abatacept has been tested in a Phase II trial (ASSET)
  - Nintedanib in Phase III trial (SENSCIS)
  - Tocilizumab Phase III trial in dSSc (focuSSced)
  - Cannabinoid (CB2) agonist against Phase III in dSSc (Lenabasum)
  - Lublinator (VA337, pan-FPAH agonist) tested in dSSc skin fibrosis (FASST)
  - OSM blockade is being tested in an early stage trial (GSK)
  - Anti IL4-IL13 antibody being tested (Sanofi-Aventis) for skin and lung