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NHS Foundation Trust

Choice of the primary outcome: Pro Lung

Christopher P. Denton
Professor of Experimental Rheumatology
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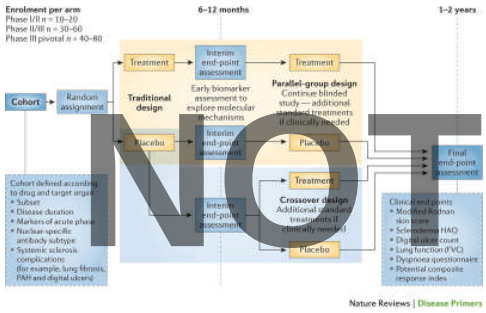
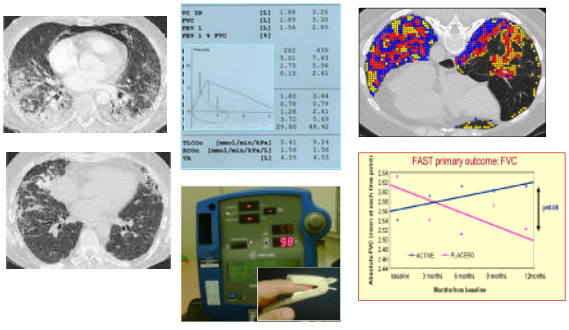
Improved clinical trial design in systemic sclerosis



Yannick Allanore, Robert Simms, Oliver Distler, Maria Trojanowska, Janet Pope, Christopher P. Denton and John Varga Systemic sclerosis. ***Nat. Rev. Dis. Primers*** 2015 ;1:15002. doi:10.1038/nrdp.2015.2

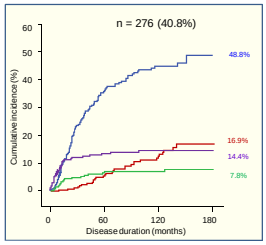
Lung assessment in clinical trials



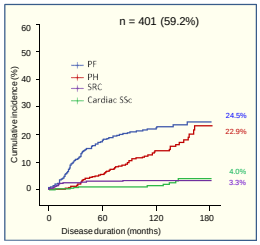
Cumulative frequency of major organ-based complications in systemic sclerosis

1995 – 2003 incident SSc cohort at RFH (n=677)

Diffuse SSc



Limited SSc



Data derived from: Nihtyanova, Denton *et al* **Arthritis Rheumatol** 2014 ;66:1625-35 including an additional validation cohort (unpublished)

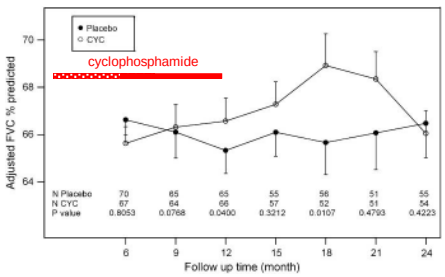
Lung assessment

- 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

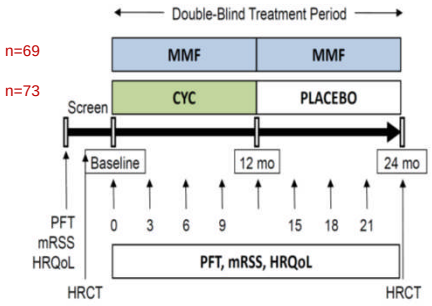
Oral cyclophosphamide in SSc-PF: the Scleroderma Lung Study (SLS-I)



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

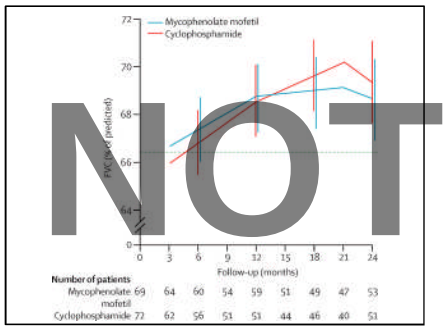
[1]Tashkin et al NEJM 2006
[2]Tashkin et al Am J Respir Crit Care Med 2007

Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II)



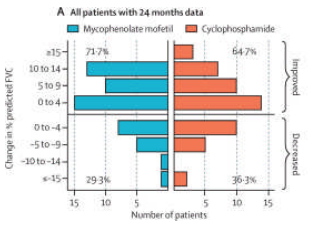
Tashkin DP, et al. **Lancet Respir Med.** 2016 Jul 25. pii: S2213-2600(16)30152-7.
Denton CP. **Lancet Respir Med**. 2016 Jul 25. pii: S2213-2600(16)30191-6.

SLS II Primary outcome assessment: the course of % predicted forced vital capacity (FVC) from 3 to 24 months by treatment group



Tashkin DP, et al. . Lancet Respir Med. 2016 Jul 25. pii: S2213-2600(16)30152-7.

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



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

(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).

Tashkin DP, et al. . Lancet Respir Med. 2016 Jul 25. pii: S2213-2600(16)30152-7.

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
  - endpoints Absolute change from baseline in FVC (mL) at week 52
  - Relative change from baseline (%) in mRSS at week 52
  - Time to all-cause mortality
  - Absolute change from baseline in DLco % predicted at week 52
  - Absolute change from baseline in digital ulcer net burden at week 52
  - Absolute change from baseline in CRISS index score at week 52 (
  - Absolute change from baseline in HAQ-DI score at week 52
  - Absolute change from baseline in FACIT dyspnoea score at week 52

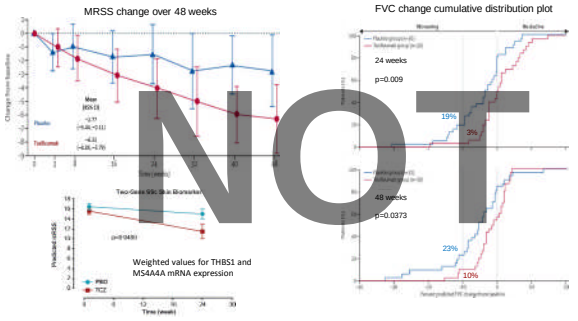
Distler O et al. Design of a randomised, placebo-controlled clinical trial of nintedanib in patients with systemic sclerosis-associated interstitial lung disease (SENSCIS ™). **Clin Exp Rheumatol**. 2017 Sep-Oct;35 Suppl 106(4):75-81.

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

Skin

n = 86 1:1 randomisation

Lung



Khanna D, Denton CP et al. **Lancet.** 2016, 387:2630-40

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

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Choice of the primary outcome: Pro CRISS

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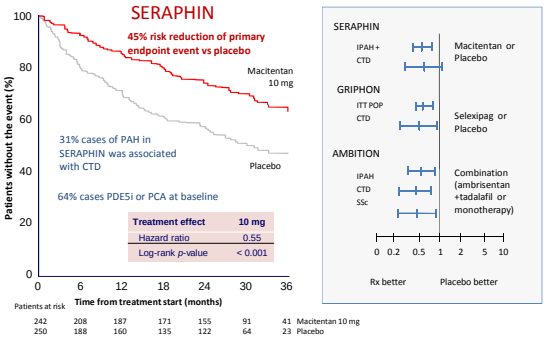
Composite measures of clinical outcome in SSc

- 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

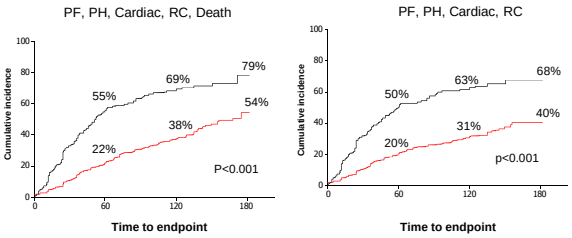


*Composite endpoint;

Pulido T, *et al. N Engl J Med* 2013; 369: 809-18.

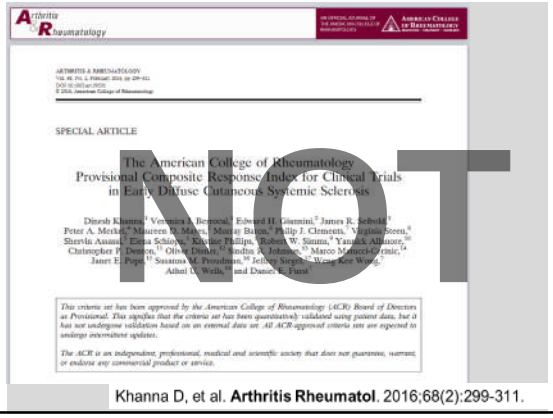
Combined endpoint analysis – for an event-driven study in systemic sclerosis

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



Nihtyanova, Denton et al **Arthritis Rheumatol** 2014 ;66:1625-35

Development of the CRISS composite index


Arthritis & Rheumatology

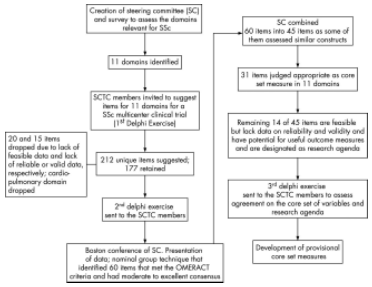
SPECIAL ARTICLE

The American College of Rheumatology Provisional Composite Response Index for Clinical Trials in Early Diffuse Cutaneous Systemic Sclerosis

Khanna D, et al. **Arthritis Rheumatol**. 2016;68(2):299-311.

CRISS index for diffuse SSc trials developed based on consensus and data-driven methodology

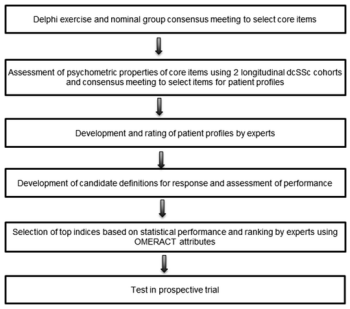
Process of choosing core set items.



D Khanna et al. Ann Rheum Dis 2008;67:703-709

ARD

The American College of Rheumatology Provisional Composite Response Index for Clinical Trials in Early Diffuse Cutaneous Systemic Sclerosis



The American College of Rheumatology Provisional Composite Response Index for Clinical Trials in Early Diffuse Cutaneous Systemic Sclerosis, Volume: 68, Issue: 2, Pages: 299-311, First published: 25 January 2016, DOI: (10.1002/art.39501)

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")

Khanna et al. Arthritis Rheumatol. 2016 Feb;68(2):299-311

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

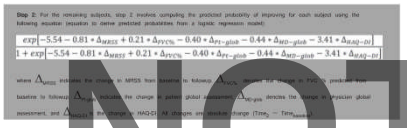
Expert consensus on definition of a patient who is not-improved during a trial - STEP 1

- 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



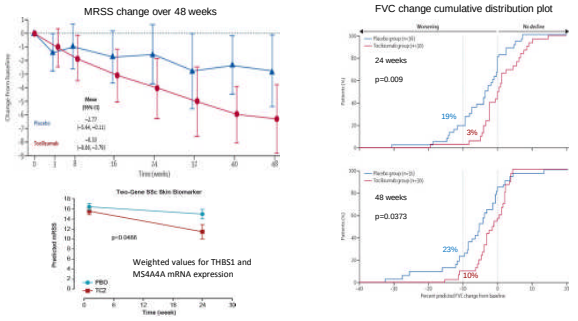
- where Δ_{MRSS} indicates the change in MRSS from baseline to follow-up, Δ_{FVC} denotes the change in FVC% predicted from baseline to follow-up, $\Delta_{Pt\text{-}glob}$ indicates the change in patient global assessment, $\Delta_{MD\text{-}glob}$ denotes the change in physician global assessment, and $\Delta_{HAQ\text{-}DI}$ is the change in HAQ-DI. All changes are absolute change ($Time_2 - Time_{baseline}$).

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

Skin

n = 86 1:1 randomisation

Lung



Khanna D, Denton CP et al. **Lancet.** 2016, 387:2630-40

Evaluation of American College of Rheumatology Provisional Composite Response Index in Systemic Sclerosis (CRISS) in the faSScinate Trial (post hoc)

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

	TCZ, N=43	PBO, N=40Ō	P value
CRISS (0.0-1.0), median [IQR] at 24 weeks	0.19 [0.006; 0.92]	0.0006 [0.0001; 0.13]	0.01*
CRISS (0.0-1.0), median [IQR] at 48 weeks	0.32 [0.01; 0.93]	0.001 [0.0002; 0.16]	0.002*
mRSS (0-51), mean change at 24 weeks	-4.19	-2.65	0.28
mRSS (0-51), mean change at 48 weeks	-5.26	-3.0	0.12
FVC% predicted, mean change at 24 weeks	-0.66	-4.20	<0.01
FVC% predicted, mean change at 48 weeks	-2.21	-6.5	<0.01
PT GA (0-10), mean change at 24 weeks	-0.36	-0.06	0.51
PT GA (0-10), mean change at 48 weeks	-0.85	-0.36	0.33
MD GA (0-10), mean change at 24 week	-1.92	-1.79	0.82
MDGA (0-10), mean change at 48 weeks	-3.18	-1.88	0.03
HAQ-DI (0-3), mean change at 24 weeks	0.17	0.18	0.93
HAQ-DI (0-3), mean change at 48 weeks	0.15	0.23	0.53

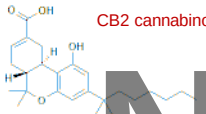
Comparison of TCZ and PBO using CRISS index and individual variables at 24 and 48 weeks

*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.

Khanna D, Berrocal VJ, Denton C et al. Arthritis Rheumatol. 2017; 69 (suppl 10).

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

JBT-101



CB2 cannabinoid agonist

Promotes release of resolution promoting/anti-inflammatory eicosanoids "resolvins"

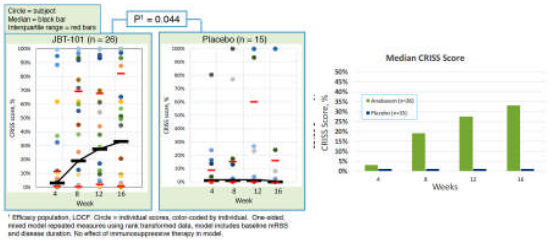
Stimulates PPARgamma – antifibrotic

Reduces markers of fibrosis and pro-inflammatory cytokines (CTGF, IL6) in SSc fibroblasts

- 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

Testing CRISS in a clinical trial

Phase I/II trial of JBT-101 Corbus pharmaceuticals 2017



EULAR Oral presentation – June 2017

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 is in Phase III clinical trial (SENSCIS)
  - Tocilizumab Phase III trial in dcSSc (focuSSced)
  - Cannabinoid (CB2) agonist Phase III in dcSSc (Lenabasum)
  - Labifranor (IVA337, pan-PPAR agonist) tested in dcSSc 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