# Traitement des PID des connectivites


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# Conflits d'intérêt

- **Consultant**: Actelion, CSL Behring, LFB Biotechnologies, Lilly, Pfizer, Octapharma
  - Financial support to ARMIIC
- **Invertigateur**: Actelion, CSL Behring, Pfizer
- **Soutien financier (ARMIIC)**: Actelion, CSL Behring, GSK, LFB Biotechnologies, Pfizer
- **Conférence invitée**: SOBI, Roche, Actelion, CSL Behring, Octapharma, GSK, LFB Biotechnologies, Pfizer, Lilly, UCB pharma

- Depuis janvier 2014: Président du groupe d'experts de l'AP-HP, juste prescription

# Traitement des PID de sclérodermie

**Table I.** Overview of the recent advances in the diagnosis and treatment of interstitial lung disease (ILD) in systemic sclerosis.

| Class | Treatment | Comments | Ref |
|---|---|---|---|
| Drug | Rituximab | • Patients successfully treated when they did not respond to prednisolone and cyclophosphamide, but no randomised controlled trials (RCTs) conducted | (42-46) |
| Drug | Mycophenolate mofetil | • Well-tolerated in patients, but no large RCTs conducted | (47-54) |
| Drug | Imatinib | • Well-tolerated in patients, but no large RCTs conducted | (56-60) |
| Drug | Methylprednisolone | • Used in combination with pulsatile cyclophosphamide, but no RCTs conducted | (61,62) |
| Drug | Cyclophosphamide | • Most wide-used and studied in patients with ILD in systemic sclerosis.<br>• The SLS and FAST study are the only 2 high quality RCTs conducted so far.<br>• EULAR and EUSTAR recommend use. | (67,78,79) |
| Surgical | Lung transplantation | • Used in end-stage lung fibrosis, but shortage of donors | (80,81) |

*Tam A, Experimental Rheumatology 2011, 29:S66*

Research article

Open Access

# Effects of cyclophosphamide on pulmonary function in patients with scleroderma and interstitial lung disease: a systematic review and meta-analysis of randomized controlled trials and observational prospective cohort studies

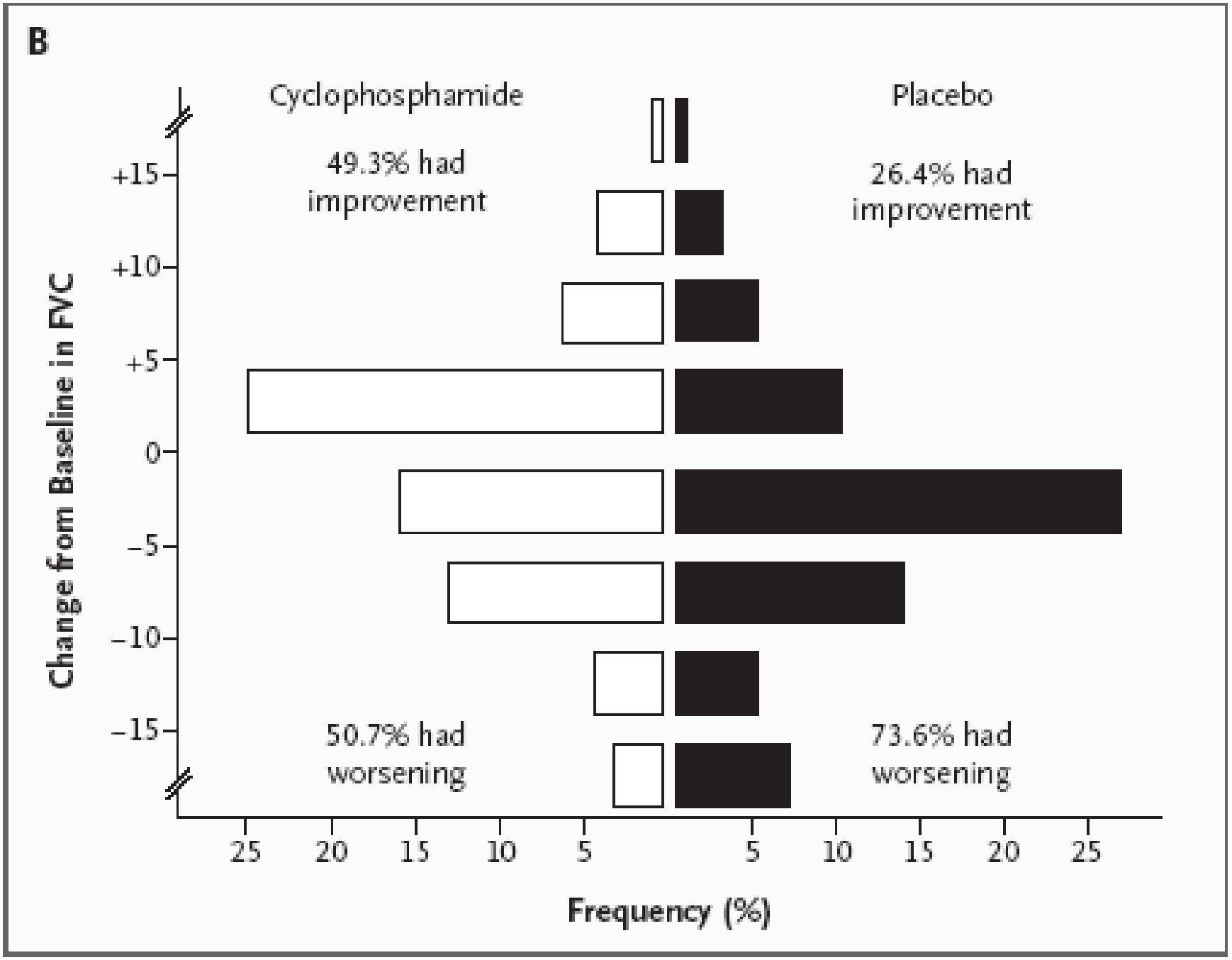
Carlotta Nannini[1], Colin P West[2,3], Patricia J Erwin[4] and Eric L Matteson[1]

**Table 2**

**Randomized clinical trial study characteristics**

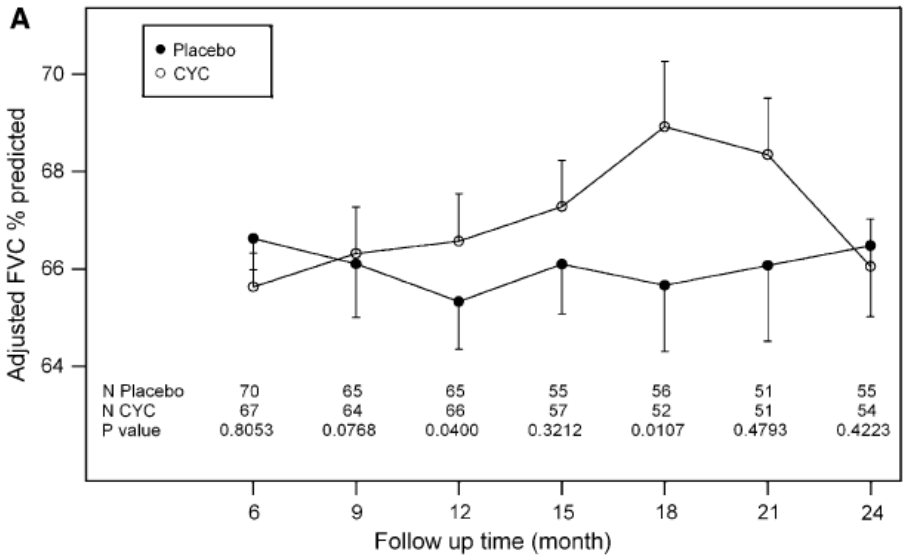
| Study | Number of patients | Mean age (years) | Outcome measure[a] | CYC treatment | Placebo/ alternative treatment | Corticosteroid | Length of follow-up (months) |
|---|---|---|---|---|---|---|---|
| Hoyles and colleagues [10] | 45 | 55 | FVC, 80.1 ± 10.3 | Intravenous, 600 mg/m$^2$ monthly | Placebo | Prednisone 20 mg alternate days | 12 |
| | | | DLCO, 52.9 ± 1.6 | | | | |
| Nadashkevich and colleagues [11] | 60 | 38 to 36 | FVC, 90.3 ± 1.9 | Oral, 2 mg/kg/ day monthly | AZA 2.5 mg/kg | Prednisolone 15 mg/day | 12 |
| | | | DLCO, 83.5 ± 1.6 | | | | |
| Tashkin and colleagues [1] | 158 | 47.9 ± 1.0 | FVC, 67.6 ± 1.3 | Oral, 1 mg/kg/ day | Placebo | None | 12 |
| | | | DLCO, 47.2 ± 1.6 | | | | |

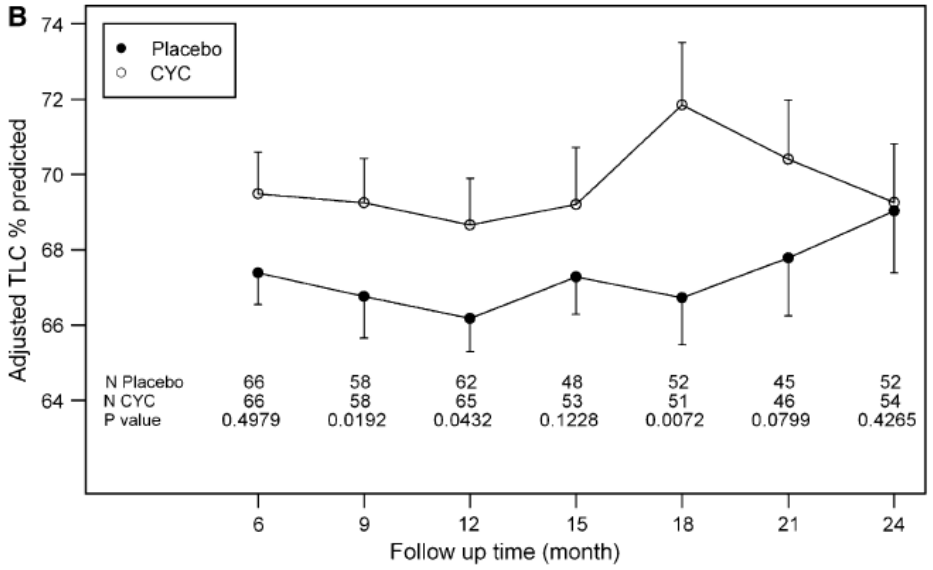
Data presented as mean ± standard deviation. AZA, azathioprine; CYC, cyclophosphamide; DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity. [a]Percentage predicted value at baseline.


B
Cyclophosphamide
Placebo
49.3% had improvement
26.4% had improvement
50.7% had worsening
73.6% had worsening
Change from Baseline in FVC
+15
+10
+5
0
−5
−10
−15
25
20
15
10
5
5
10
15
20
25
Frequency (%)

# Effects of 1-Year Treatment with Cyclophosphamide on Outcomes at 2 Years in Scleroderma Lung Disease

Donald P. Tashkin[1], Robert Elashoff[2], Philip J. Clements[1], Michael D. Roth[1], Daniel E. Furst[1], Richard M. Silver[3], Jonathan Goldin[4], Edgar Arriola[5], Charlie Strange[3], Marcy B. Bolster[2], James R. Seibold[6], David J. Riley[6], Vivien M. Hsu[6], John Varga[7], Dean Schraufnagel[7], Arthur Theodore[8], Robert Simms[8], Robert Wise[9], Fred Wigley[9], Barbara White[9], Virginia Steen[10], Charles Read[10], Maureen Mayes[11], Ed Parsley[11], Kamal Mubarak[12], M. Kari Connolly[13], Jeffrey Golden[13], Mitchell Olman[14], Barri Fessler[14], Naomi Rothfield[15], Mark Metersky[15], Dinesh Khanna[1], Ning Li[2], and Gang Li[2], for the Scleroderma Lung Study Research Group*



ARTHRITIS & RHEUMATISM
Vol. 54, No. 12, December 2006, pp 3962–3970
DOI 10.1002/art.22204
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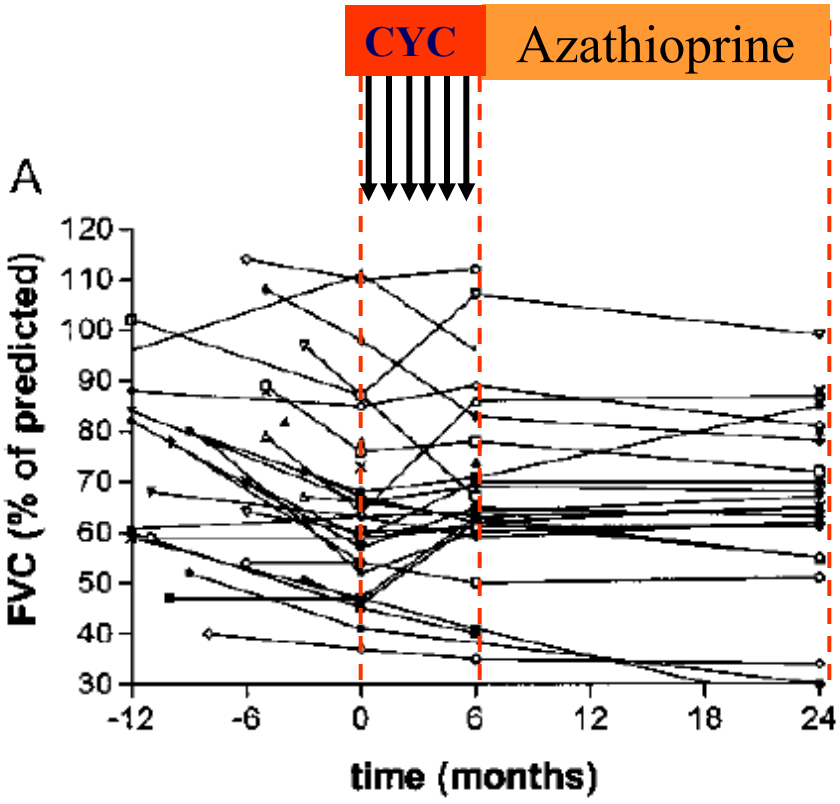
# A Multicenter, Prospective, Randomized, Double-Blind, Placebo-Controlled Trial of Corticosteroids and Intravenous Cyclophosphamide Followed by Oral Azathioprine for the Treatment of Pulmonary Fibrosis in Scleroderma

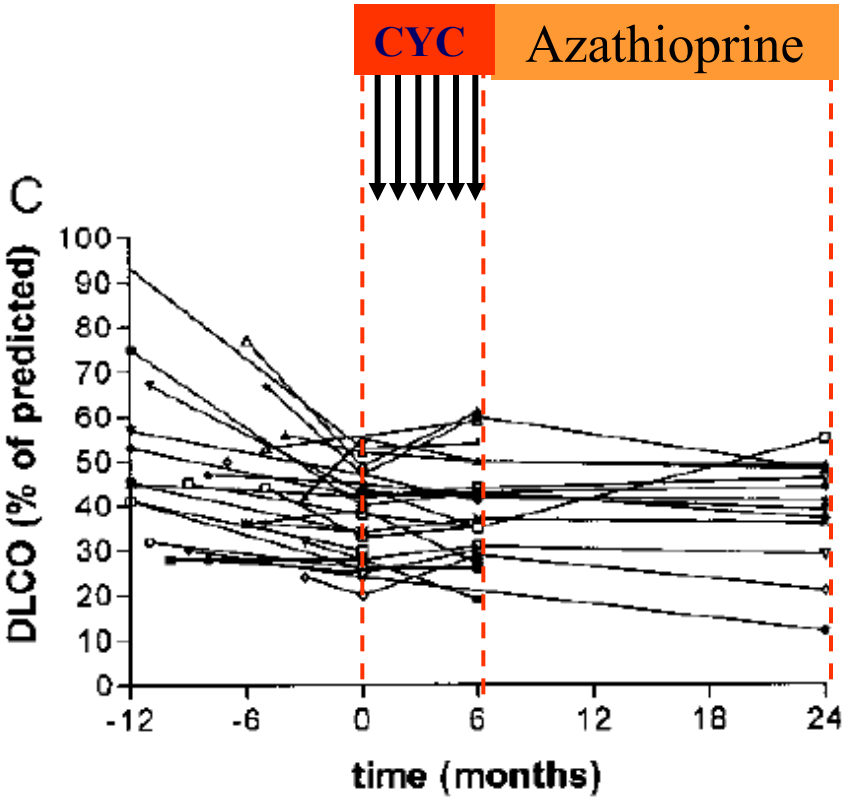
Rachel K. Hoyles,[1] Ross W. Ellis,[1] Jessica Wellsbury,[1] Belinda Lees,[1] Pauline Newlands,[1] Nicole S. L. Goh,[1] Christopher Roberts,[2] Sujal Desai,[3] Ariane L. Herrick,[4] Neil J. McHugh,[5] Noeleen M. Foley,[5] Stanley B. Pearson,[6] Paul Emery,[6] Douglas J. Veale,[6] Christopher P. Denton,[7] Athol U. Wells,[1] Carol M. Black,[7] and Roland M. du Bois[1]

**Table 3.** Efficacy end point variables*

| | Baseline | | 1-year followup | | |
|---|---|---|---|---|---|
| | Treatment group (n = 22) | Placebo group (n = 23) | Treatment group (n = 19) | Placebo group (n = 18) | $P$† |
| Lung function, % predicted | | | | | |
| FVC | 80.1 ± 10.3 | 81.0 ± 18.8 | 82.5 ± 11.3 | 78.0 ± 21.6 | 0.08 |
| $DLCO_c$ | 52.9 ± 11.5 | 55.0 ± 12.9 | 49.6 ± 10.7 | 51.8 ± 14.9 | 0.64 |
| TLC | 81.8 ± 10.1 | 76.8 ± 16.9 | 80.2 ± 9.8 | 74.4 ± 16.7 | 0.61 |
| $FEV_1$ | 79.6 ± 11.5 | 79.7 ± 19.1 | 81.3 ± 12.5 | 77.0 ± 21.3 | 0.16 |
| Kco | 71.3 ± 13.4 | 82.7 ± 19.1 | 71.5 ± 13.9 | 77.9 ± 23.3 | 0.32 |
| Baseline HRCT‡ | | | | | |
| Disease extent, mean (range) % | 20 (6–40) | 19 (5–40) | – | – | – |
| Ground-glass attenuation, mean (range) % | 50 (15–91) | 47 (0–95) | – | – | – |
| Improvement on serial HRCT, no (%)‡ | – | – | 6 (40) | 3 (20) | 0.39 |
| Dyspnea score, mean (range)§ | 7.7 (2–14) | 7.2 (0–18) | 8.75 (0–14) | 7.80 (2–14) | 0.23 |

# Therapeutic Strategy Combining IV cyclophosphamide Followed by Oral Azathioprine to Treat Worsening SSc-ILD: A Retrospective Multicenter Open-label Study




Bérezné A et al. J Rheumatol. 2008 May 1. [Epub ahead of print]

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

# Cyclophosphamide Systemic Sclerosis Associated Interstitial Lung Disease (SCLEROCYC)

**This study is not yet open for participant recruitment.**

Verified April 2012 by Assistance Publique - Hôpitaux de Paris

First Received on April 2, 2012. Last Updated on April 12, 2012 History of Changes

| | |
|---|---|
| **Sponsor:** | Assistance Publique - Hôpitaux de Paris |
| **Collaborator:** | Service de Médecine Interne de l'hôpital Claude-Huriez, Lille, France - Pr David Launay |
| **Information provided by (Responsible Party):** | Assistance Publique - Hôpitaux de Paris |
| **ClinicalTrials.gov Identifier:** | NCT01570764 |

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Hôpitaux Universitaires Paris Centre
Cochin Broca Necker
Site Tarnier - Paris

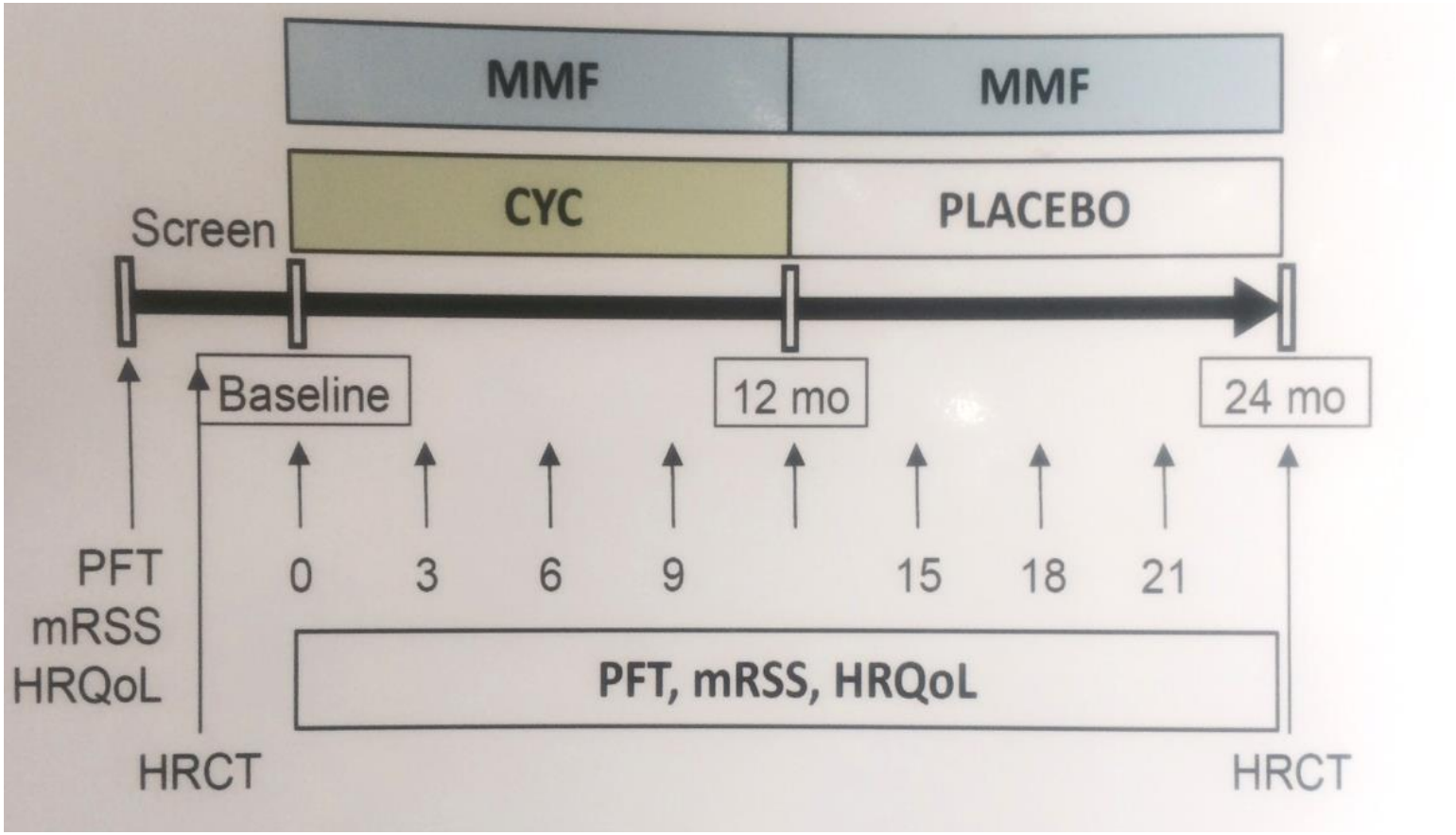
# Essai multicentrique prospectif randomisé contre placebo évaluant l'efficacité d'un traitement par cyclophosphamide IV dans les PID-ScS (I)

- Essai multicentrique prospectif randomisé contre placebo évaluant l'efficacité d'un traitement associant cyclophosphamide intraveineux (0.7 g/m²/mois) pendant 12 mois et prednisone 15 mg/j comparativement à une traitement par prednisone 15 mg/j et placebo de cyclophosphamide.
- Les patients sous cyclophosphamide recevront du mesna et les patients sous placebo de cyclophosphamide recevront un placebo de mesna (conditionnement pharmacie agréée).
- Seuls les patients abaissant leurs LT CD4+ en dessous de 300/mm3 recevront du triméthoprime sulfamethoxazole.

# Essai multicentrique prospectif randomisé contre placebo évaluant l'efficacité d'un traitement par cyclophosphamide IV dans les PID-ScS (II)

- Patients ayant une ScS et PID aggravative (diminution d'au moins 15% de la DLCO et/ou d'au moins 10% de la CVF et/ou de la CPT dans les 12 ± 3 mois précédant l'inclusion).
- 84 patients (42 dans chaque groupe), puissance 80% pour mettre en évidence une augmentation de la fréquence de stabilisation/amélioration des sujets à 12 mois estimée à 15% sous prednisone et placebo de cyclophosphamide et à 50% sous cyclophosphamide et prednisone (au risque alpha conventionnel de 5%).

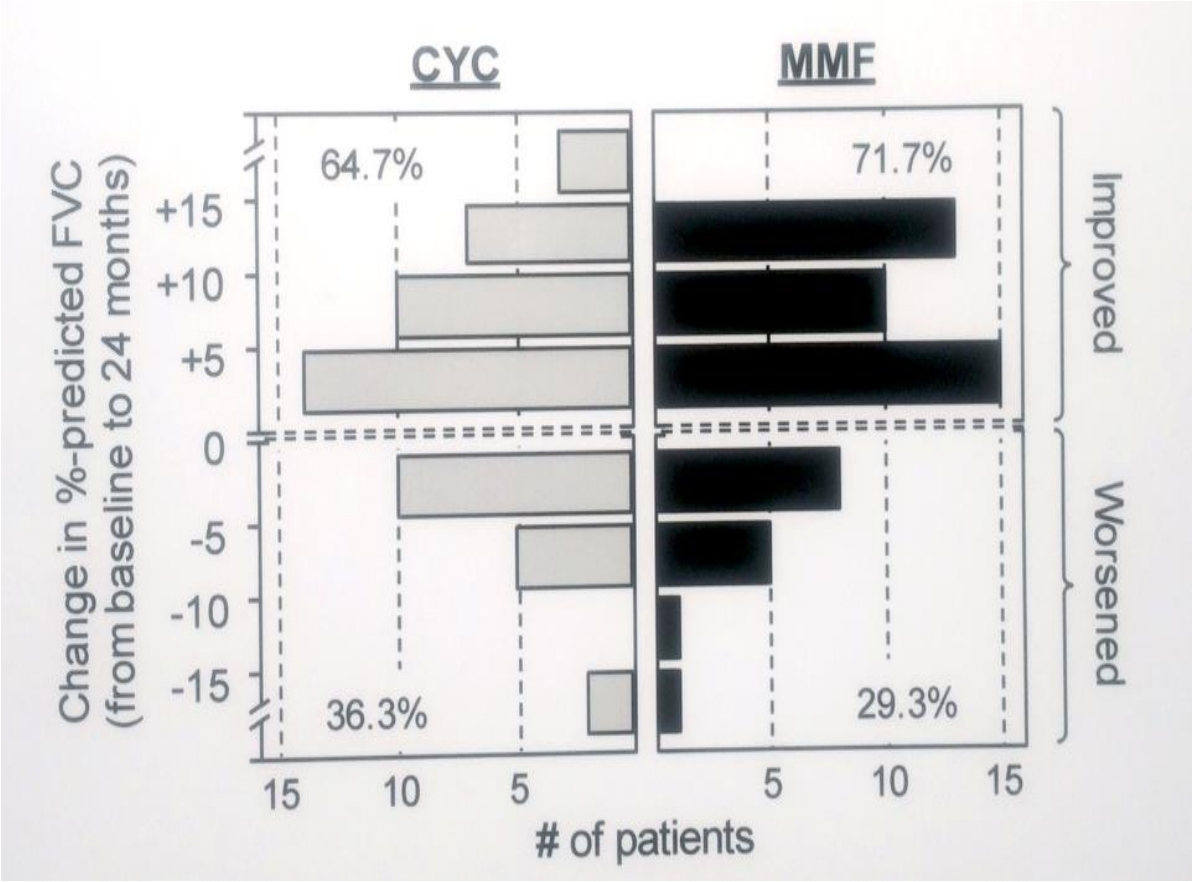
# SCLERODERMA LUNG STUDY II




142 patients with SSc-ILD were randomized in the SLS II
Patients received MMF (≤3 g daily) for two years or oral CYC (≤2 mg /kg

EULAR 2016; FRI0252 - D. Khanna

# SCLERODERMA LUNG STUDY II




142 patients with SSc-ILD were randomized in the SLS II
Patients received MMF (≤3 g daily) for two years or oral CYC (≤2 mg /kg

EULAR 2016; FRI0252 - D. Khanna

# SLS II: Conclusion

1) At 24 months the improvement in %FVC was comparable in the two treatment groups.

2) The TDI and MRSS improved in both treatment arms but there was a trend favoring improvements in the CYC group.

3) Significantly fewer premature withdrawals were noted in the MMF arm.

4) Leukopenia/thrombocytopenia were noted significantly less frequently in the MMF arm

5) It is unclear how the use of alternative medications in SSc patients who withdrew prematurely from study treatments, particularly in the CYC patients, could have influenced the results.

# RITUXIMAB

- **Small sized randomised study**
  - 14 pts (8 rituximab and 6 conventional treatments)
  - 1 year
  - 2 courses, weeks1 and 24, 375 mg/m2
- **Evaluation**
  - Rodnan
  - Lung function tests
  - CT scann
- **Results**
  - Decrease in FVC (p<0,001)
  - Improvement of CO diffusion 19.4% vs –7.5%
  - Improvement of Rodnan score 13.5 vs 8.7 (p<0,001)

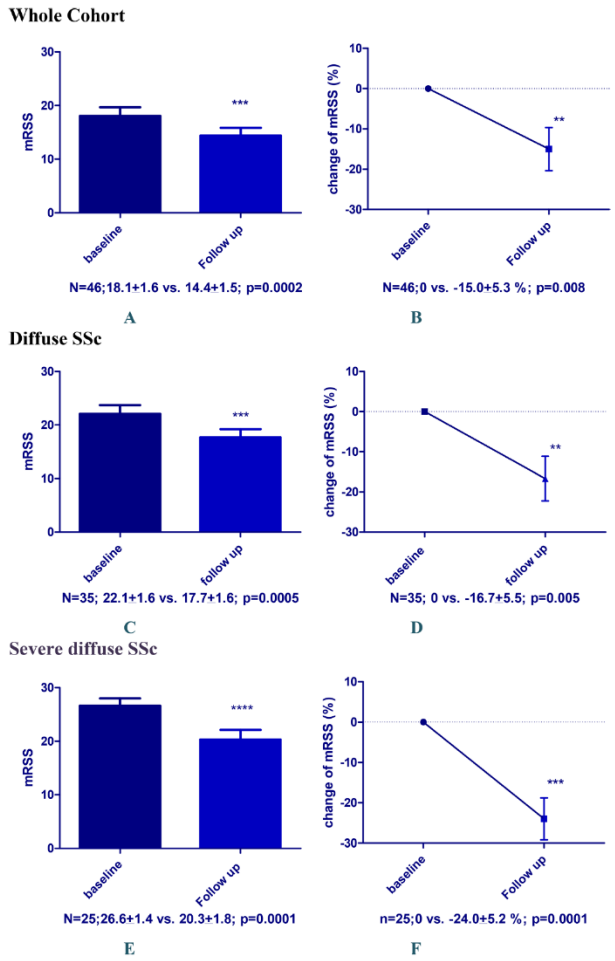
Daoussis Rheumatology 2009

# Effects and safety of rituximab in systemic sclerosis: an analysis from the European Scleroderma Trial and Research (EUSTAR) group

Suzana Jordan,[1] Jörg H W Distler,[2] Britta Maurer,[1] Dörte Huscher,[3] Jacob M van Laar,[4] Yannick Allanore,[5] Oliver Distler,[1] on behalf of the EUSTAR Rituximab study group

63 patients treated with RTX.
The case-control analysis in patients with severe diffuse SSc showed that mRSS changes were larger in the RTX group versus matched controls (N=25; −24.0±5.2% vs −7.7±4.3%; p=0.03).
In RTX-treated patients, the mean mRSS was significantly reduced at follow-up compared with baseline (26.6±1.4 vs 20.3±1.8; p=0.0001).
In patients with interstitial lung disease, RTX prevented significantly the further decline of FVC compared with matched controls (N=9; 0.4±4.4% vs −7.7±3.6%; p=0.02).
Safety measures showed a good profile.

The comparison of RTX treated vs untreated matched-control SSc patients from the EUSTAR cohort demonstrated improvement of skin fibrosis and prevention of worsening lung fibrosis, supporting the therapeutic concept of B cell inhibition in SSc.




ARD 2013

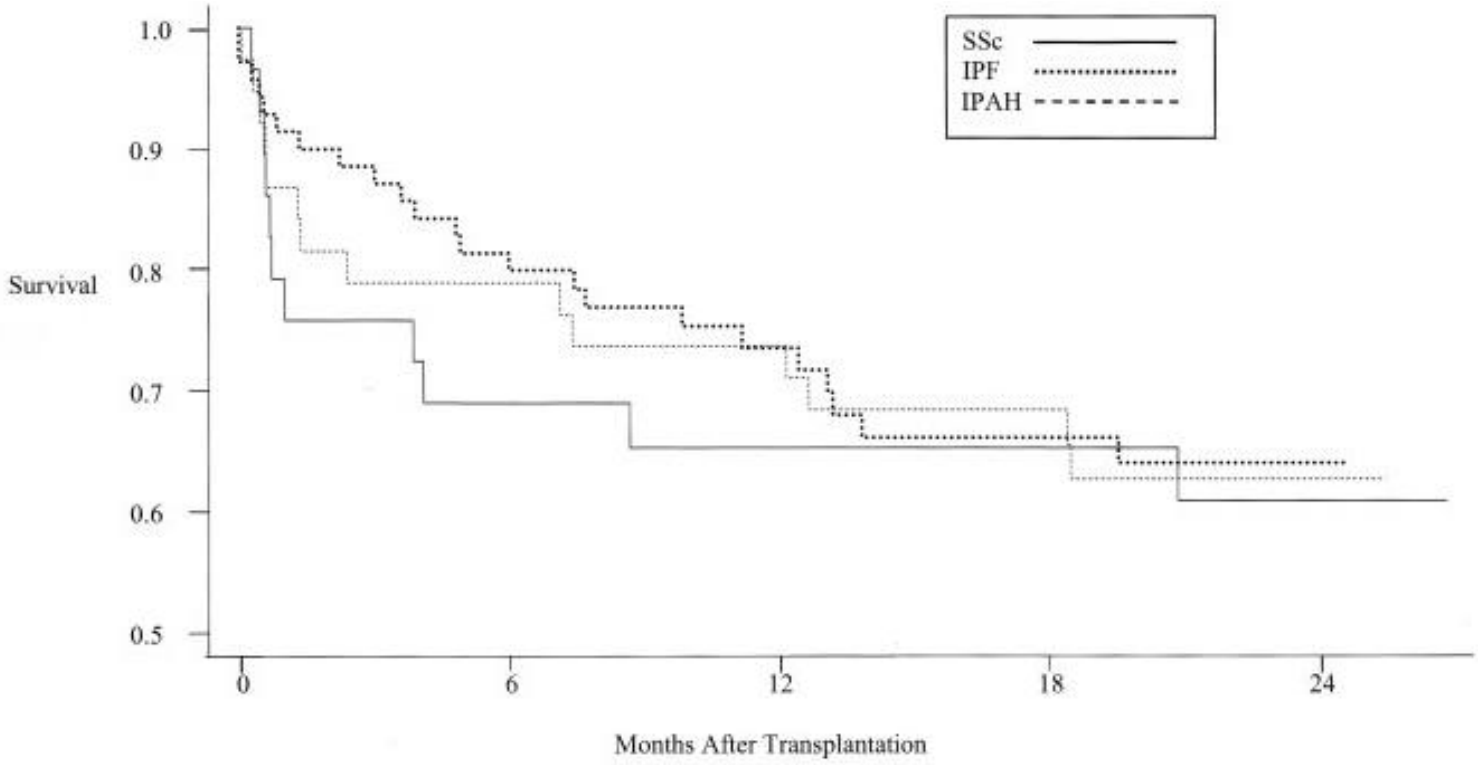
# Rituximab in systemic sclerosis: Interventional studies. ClinicalTrials.gov (10 – 12 – 2014)

- Rituximab in Systemic Sclerosis (RECOVER) (NCT01748084)
  - To determine whether rituximab is effective in the treatment of articular symptoms that occur in systemic sclerosis related **polyarthritis**

- Rituximab for Treatment of Systemic Sclerosis-Associated PAH (SSc-PAH) (NCT01086540)
  - To determine if rituximab has a marked beneficial effect on clinical disease progression, in patients with **SSc-PAH** when compared to placebo
- Rituximab Versus Cyclophosphamide in Connective Tissue Disease-ILD (RECITAL) (NCT01862926)
  - To evaluate the efficacy of rituximab (compared with standard therapy) in patients with progressive **CTD related ILD**.

# Lung transplantation

- **29 SSc patients,70 patients with IPF and 38 with IPAH**
- **During 2 years of followup, 11 patients with scleroderma (38%), 23 with IPF (33%), and 14 with IPAH (37%) died.**
- **Cumulative survival at 2 years was comparable (64%).**



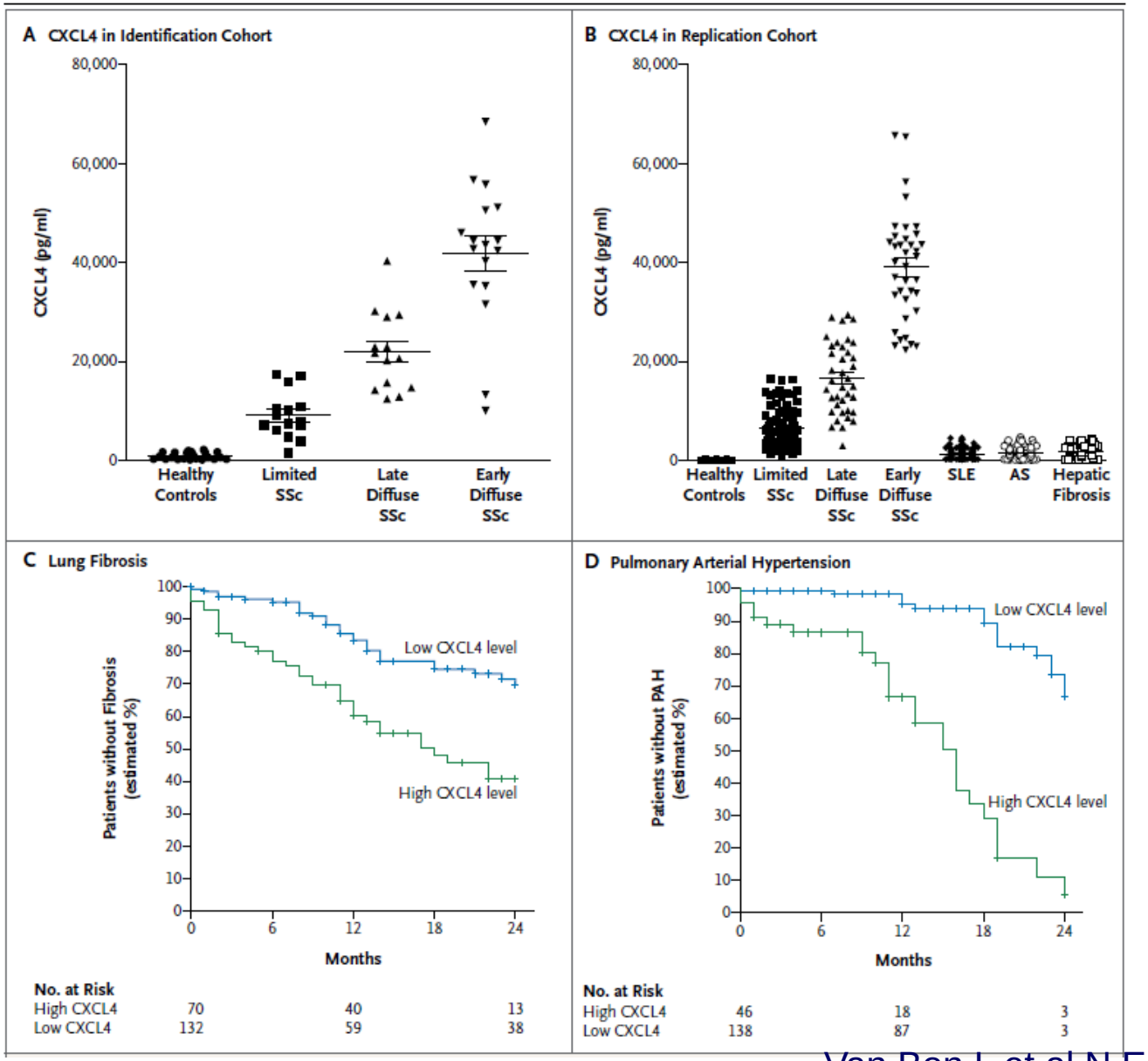

Schachna L. et al. Arthritis Rheum 2006

# One-Year Survival of Adults with Systemic Sclerosis Following Lung Transplantation: A Nationwide Cohort Study.

- A total of 3763 adults were transplanted during the study period and met inclusion criteria: 229 with SSc, 201 with PAH, and 3333 with ILD
- The 1-year unadjusted mortality rate following LTx per 100 person-years was 21.4 among adults with SSc, 19.0 among adults with PAH, and 17.8 among adults with ILD.
- Adults with SSc had a 48% increased risk of death at 1 year following LTx compared to adults with ILD, but no increase in risk of death at 1 year compared to adults with PAH.

Abstract 1797. ACR Boston 2014

# Increased Levels of Circulating CXCL4 in Systemic Sclerosis and the Association with Lung Fibrosis and PAH




Van Bon L et al N Engl J Med 2014

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

- Comparison of Therapeutic Regimens for Scleroderma Interstitial Lung Disease (The Scleroderma Lung Study II)
- Cyclophosphamide systemic sclerosis associated ILD
- A trial of Taladafil in ILD of Scleroderma
- Study of pomalidomide in SSc with ILD
- Safety and Tolerability of Pirfenidone in Patients With SSc-ILD (LOTUSS)
- Rituximab Versus Cyclophosphamide in Connective Tissue Disease-ILD
- Imatinib in Systemic Sclerosis
- Low-Dose Oral Imatinib for Scleroderma Pulmonary Involvement
- Safety Evaluation of Dasatinib in Subjects With Scleroderma Pulmonary Fibrosis
- Nintedanib in systemic sclerosis
- Evaluating N-acetylcysteine in CTD-ILD treatment
- Autologous stem cell SSc immune suppression trial

# Safety and Tolerability of Pirfenidone in Patients with SSc Interstitial Lung Disease

**Khanna D et al.**

- 40 patients (63.5%) on MMF and others (36.5%): no immunosuppressant. Mean (SD) mRSS, %FVC and %$DL_{CO}$ at baseline: 11.4 (9.6), 76.0 (14.2) and 59.7 (16.5), respectively.
- Frequency and type of TEAEs were similar for both titration groups.
- No clinically significant changes in vital signs, ECGs, or laboratory tests.
- At week 16, the median change from baseline in %FVC was -0.5% (range -42% to 12%); the median change from baseline in %$DL_{CO}$ was 1.5% (range -24.0% to 40.0%); minor changes (mean±SD) were observed in Mahler TDI (1.0±3.41) and mRSS (-0.4±3.71).
- **Conclusion:** pirfenidone was safe and generally well-tolerated in SSc-ILD patients, despite pre-existing co-morbidities, and concomitant use of MMF.

Abstract Number: 3134

# Treatment of SSc-ILD

- **PPI (± prokinetics)**
- **Cyclophosphamide/MMF (if worsening)**
- **Low dose corticosteroids (10 mg/j)**
- **Oxygen**
- **Rituximab**
- **Lung transplantation**

- **Rehabilitation**

# Conclusions

- ILD is the first cause of mortality in SSc patients
- Only a minority of patients with SSc-ILD will develop end stage respiratory insufficiency
- There is no validated treatment of SSc-ILD
- Cyclophosphamide remains the best candidate, possibly in patients with worsening ILD
- MMF might represent an interesting perspective.
- There is a need for new molecules
- In case of failure patients fulfilling criteria should be proposed for lung transplantation

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