Pneumopathie interstitielle diffuse et ScS: Traitement

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XXIV^{èmes} Ateliers francophones de la sclérodermie systémique – Cochin – 22 et 23 mai 2019

Conflicts of interest

- **Consultant**: Actelion, CSL Behring, LFB Biotechnologies, Lilly, Pfizer, Octapharma
  - Financial support to ARMIIC
- **Investigator**: Actelion, CSL Behring, Pfizer
- **Financial support (grants to ARMIIC)**: Actelion, CSL Behring, GSK, LFB Biotechnologies, Pfizer
- **Invited conference**: SOBI, Roche, Actelion, CSL Behring, Octapharma, GSK, LFB Biotechnologies, Pfizer, Lilly, UCB pharma

Pneumopathie interstitielle diffuse et ScS
Qui traiter et combien de temps ?

1. Traitements disponibles
2. Quel traitement ?
3. Qui traiter ?
4. Combien de temps ?
5. Conclusions

Traitements disponibles

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

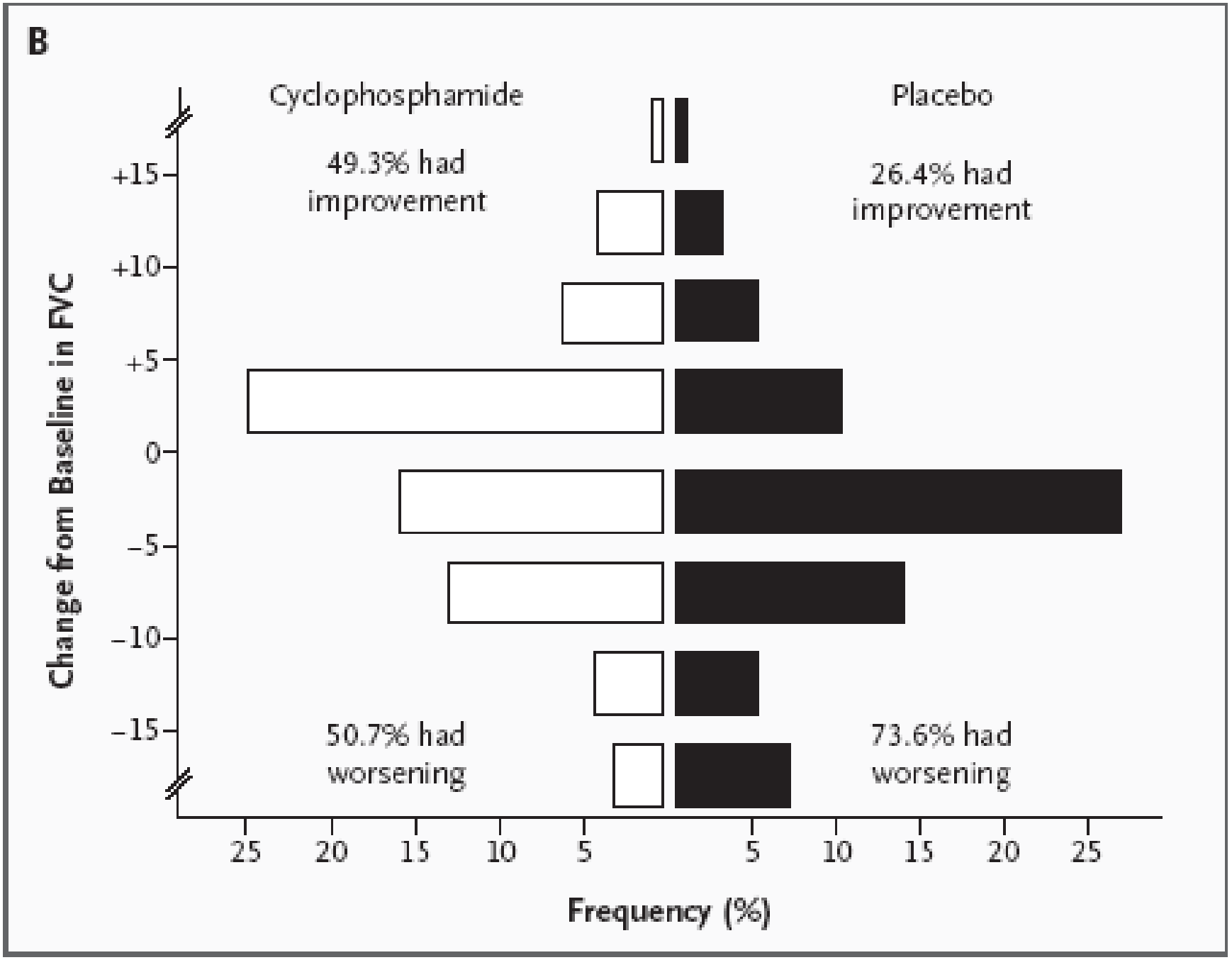
Carlotta Nannini[1], Colin P West[2,3], Patricia J Erwin[4] and Eric L Matteson[1]

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 (%)

Research article

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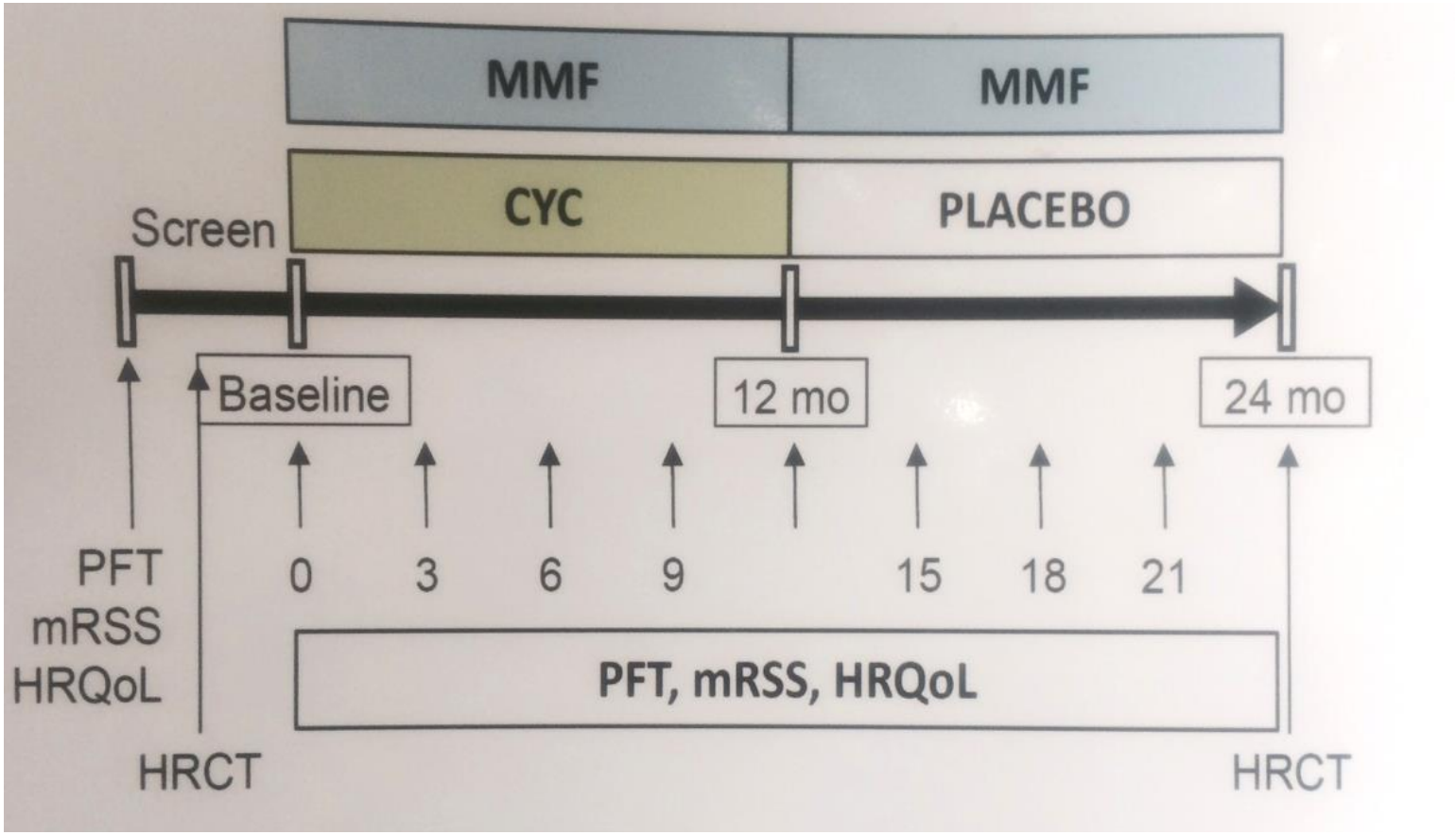
Results

- 3 randomized clinical trials and 6 prospective observational studies were included for analysis. In the pooled analysis, the FVC and the DLCO after 12 months of therapy were unchanged (mean changes of 2.83% (95% confidence interval = 0.35 to 5.31) and 4.56% (95% confidence interval = -0.21 to 9.33), respectively).

Conclusions

- Cyclophosphamide treatment in patients with systemic sclerosis-related interstitial lung disease does not result in clinically significant improvement of pulmonary function.

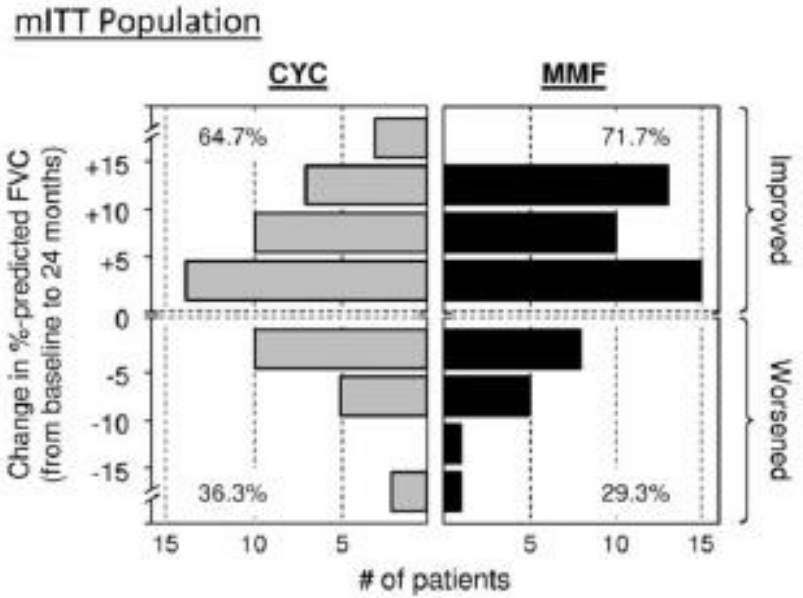
SCLERODERMA LUNG STUDY II

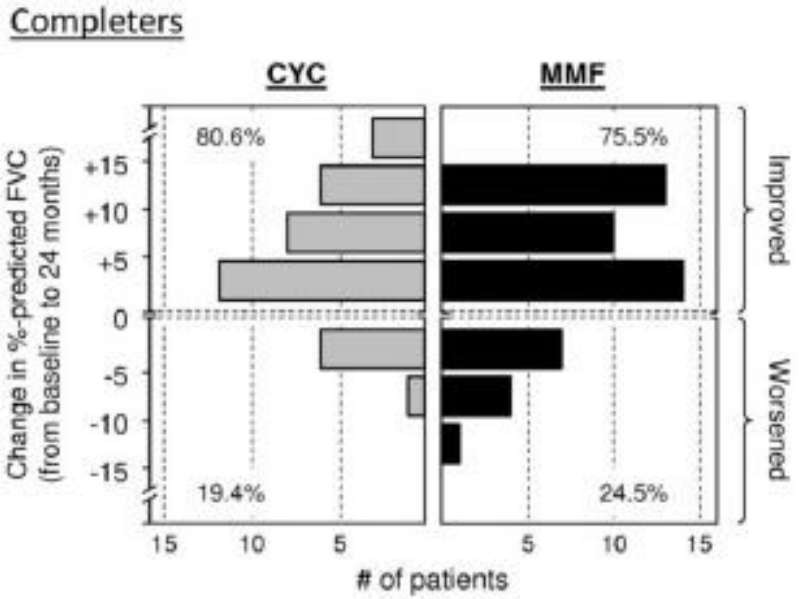


142 patients with SSc-ILD were randomized in the SLS II
Patients received MMF (≤3 g daily) for two years or oral CYC (≤2 mg /kg

EULAR 2016; FRI0252 - D. Khanna

SCLERODERMA LUNG STUDY II





Tashkin et al. Lancet Respir Med 2016

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.

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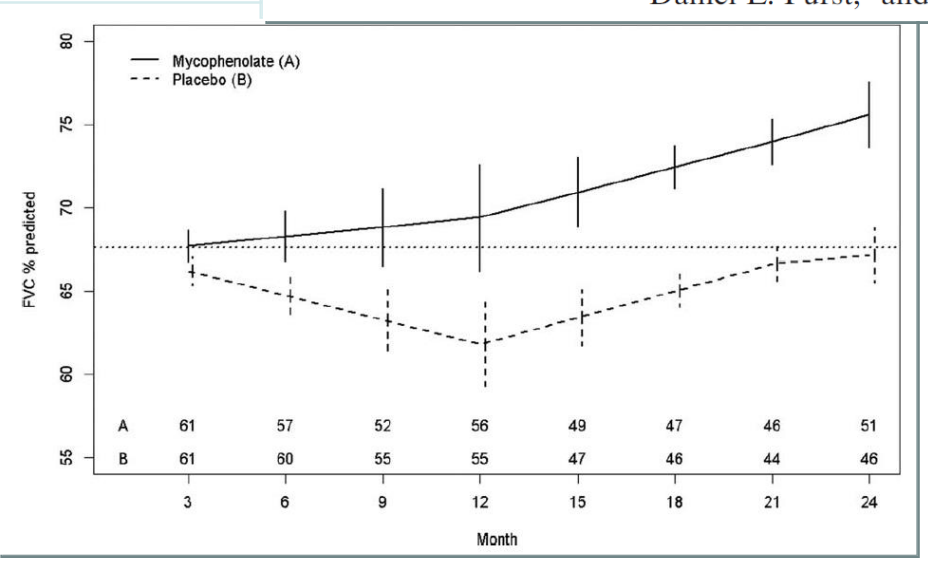
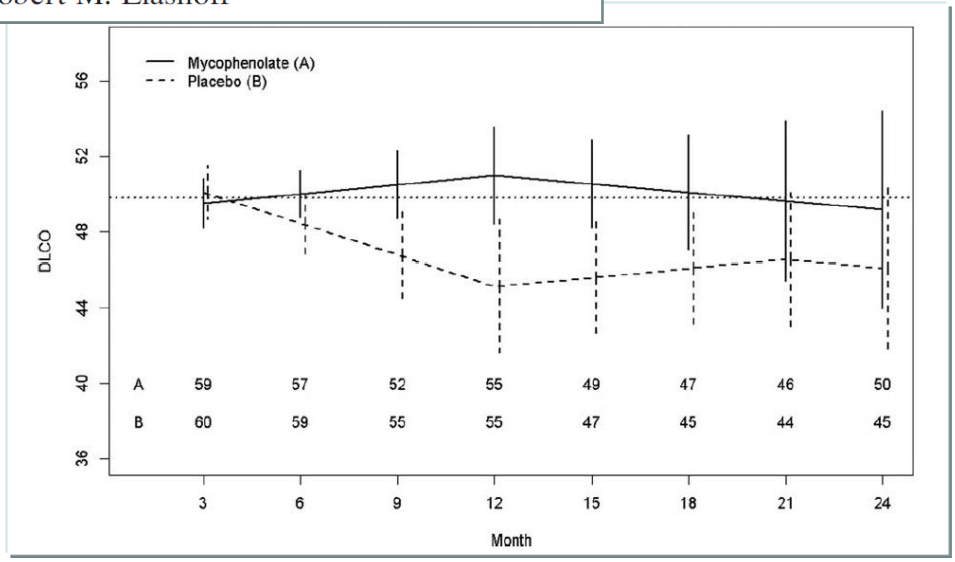
Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis–Related Interstitial Lung Disease

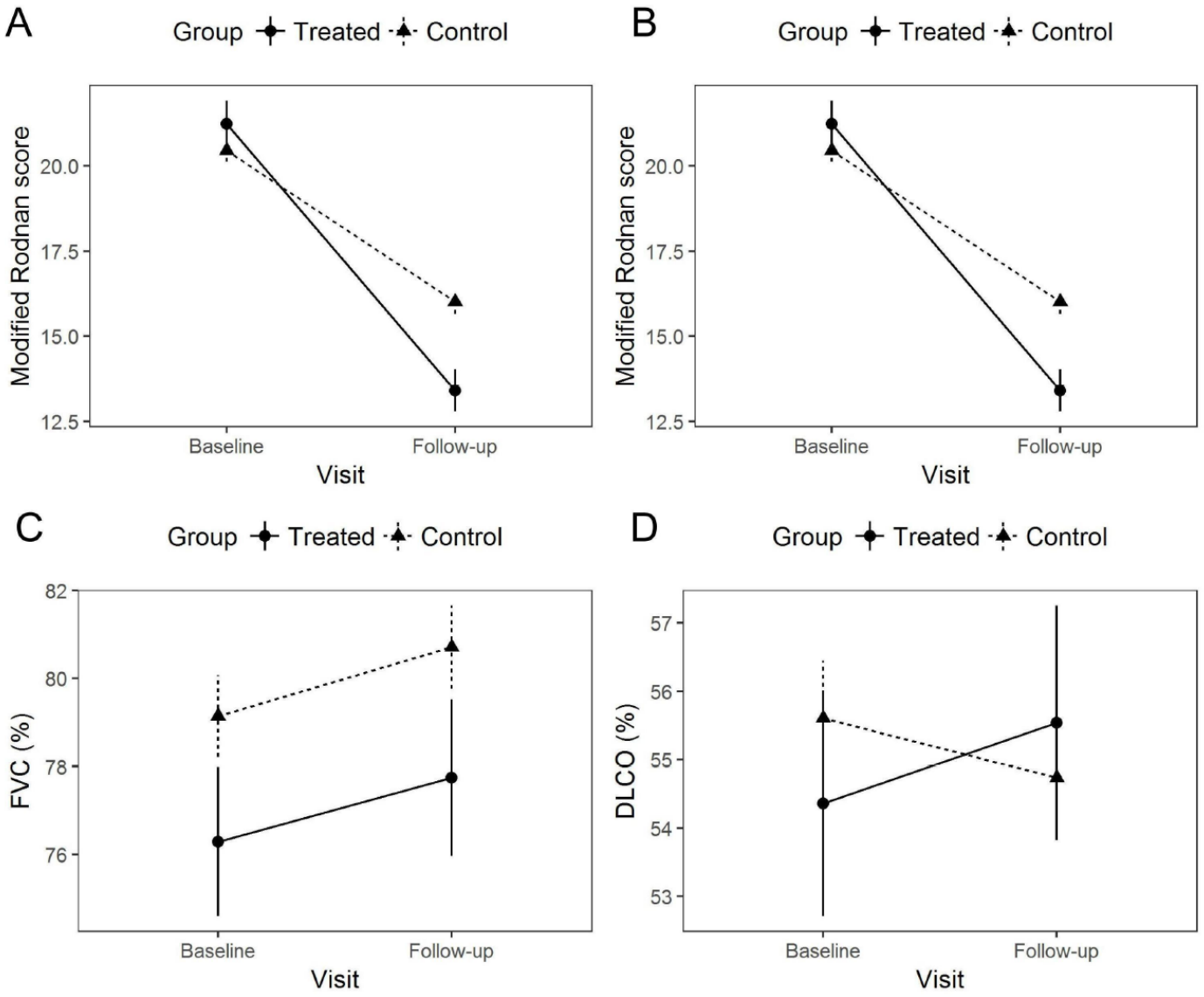
An Analysis of Scleroderma Lung Studies I and II

Elizabeth R. Volkmann,[1] Donald P. Tashkin,[1] Ning Li,[1] Michael D. Roth,[1] Dinesh Khanna,[2] Anna-Maria Hoffmann-Vold,[3] Grace Kim,[1] Jonathan Goldin,[1] Philip J. Clements,[1] Daniel E. Furst,[1] and Robert M. Elashoff[1]



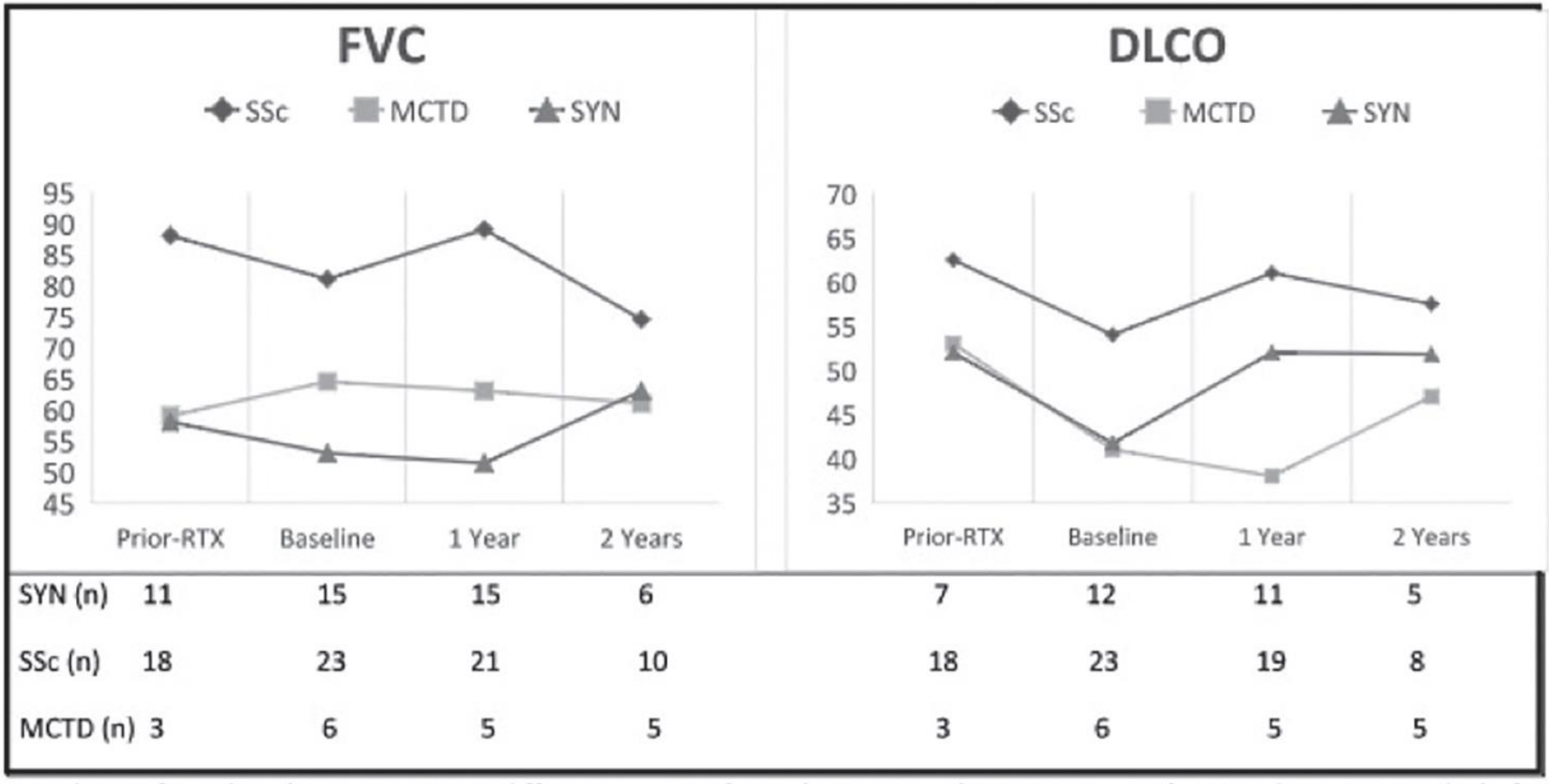


Outcomes of patients with systemic sclerosis treated with rituximab in contemporary practice: a prospective cohort study



Elahi M et al. ARD 2019

Effects of rituximab in connective tissue disorders related interstitial lung disease



SYN (n)	11	15	15	6	7	12	11	5
SSc (n)	18	23	21	10	18	23	19	8
MCTD (n)	3	6	5	5	3	6	5	5

A trend of improvement of PFTs was observed in SYN patients although not reaching significance, while SSc and MCTD patients were stabilised.

LEPRI G et al. Clin Exp Rheumatol 2016

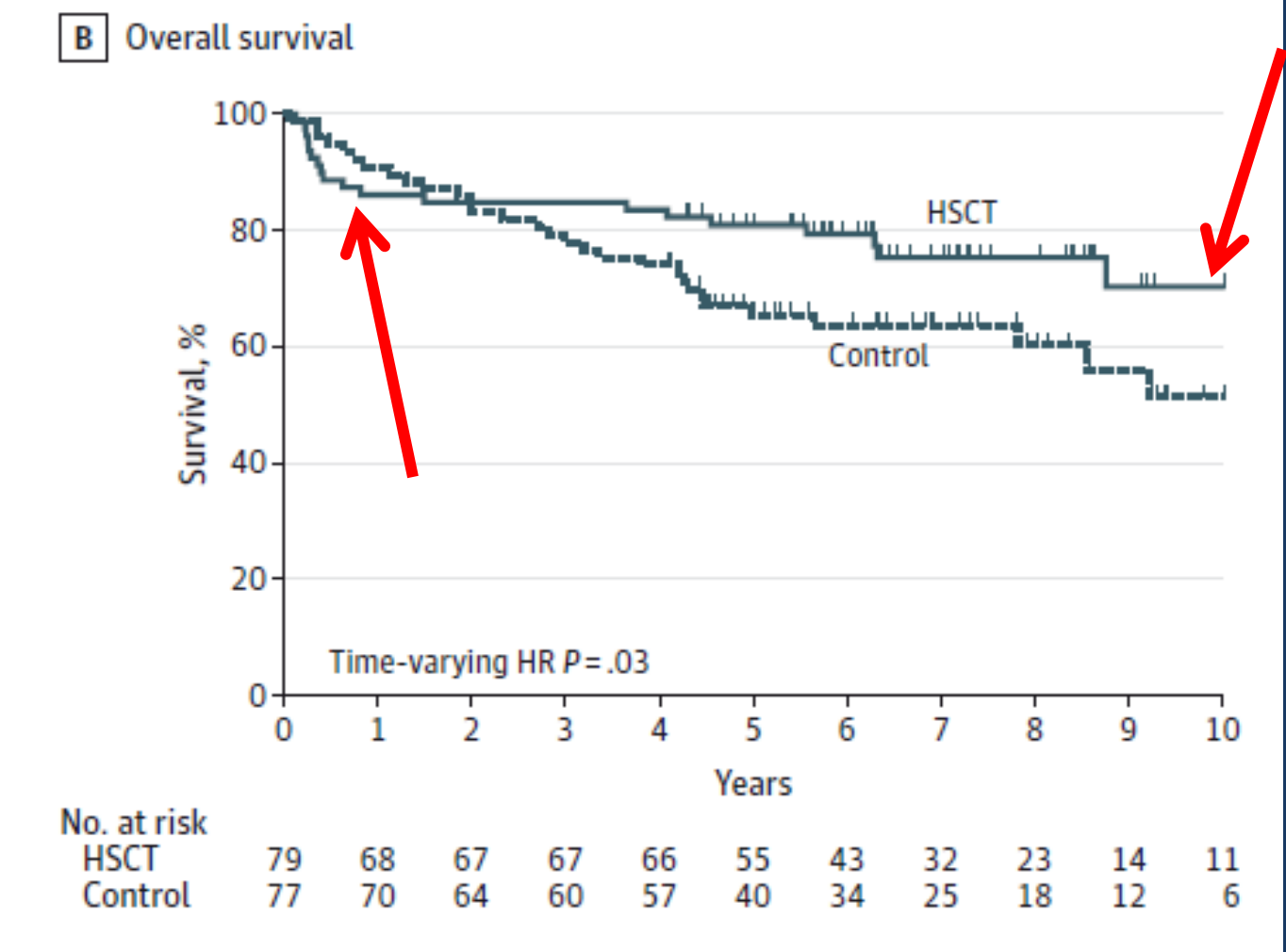
Safety and Tolerability of Pirfenidone in Patients with SSc Interstitial Lung Disease

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.

Khanna D et al. J Rheumatol 2016

Stem cell transplantation: The ASTIS Trial



van Laar JM, *et al. JAMA* 2014; 311:2490-98.

The updated EULAR recommendations for treatment of systemic sclerosis, according to the organ involvement: Skin and lung disease

Two RCTs and their re-analysis have shown that *methotrexate* improves skin score in early diffuse SSc. Positive effects on other organ manifestations have not been established. Methotrexate may be considered for treatment of skin manifestations of early diffuse SSc.	A
In view of the results from two high-quality RCTs and despite its known toxicity, *cyclophosphamide* should be considered for treatment of SSc-ILD, in particular for patients with SSc with progressive ILD.	A
Regarding *HSCT*, two RCTs have shown improvement of skin involvement and stabilisation of lung function in patients with SSc and one large RCT reports improvement in event-free survival in patients with SSc as compared with cyclophosphamide in both trials. HSCT should be considered for treatment of selected patients with rapidly progressive SSc at risk of organ failure. In view of the high risk of treatment-related side effects and of early treatment-related mortality, careful selection of patients with SSc for this kind of treatment and the experience of the medical team are of key importance.	A

Kowal-Bielecka O, *et al*. *Ann Rheum Dis* 2017;**76**:1327–1339.

Current active trials investigating experimental therapeutic agents for SSc-ILD

Agent	Mechanism of Action	Primary End Point	Design	Phase
Pomalidomide	Derivative of thalidomide (antiangiogenic, immunomodulatory)	Change in FVC, mRSS at 52 wk	Double-blind RCT	II
Belimumab	BAFF inhibitor	Change in skin score (secondary outcomes: change in FVC, D_{LCO}) at 48 wk	Double-blind RCT	II
Tadalafil†	PDE5 inhibitor	Change in FVC over 6 mo	Double-blind RCT	III
Nilotinib	Tyrosine kinase inhibitor	Safety and tolerability (secondary outcomes: change in skin score, PFT) at 6 mo	Open-label pilot study	IIa
Abatacept	Selective T-cell costimulation modulator	Safety and tolerability; change in skin score (secondary outcomes: change in FVC, joint count) at 12 mo	Double-blind RCT	II
Nintedanib	Tyrosine kinase inhibitor	Annual rate of decline in FVC over 12 mo	Double-blind RCT	III
Abituzumab	Monoclonal IgG2 antibody targeting α_v-integrins	Safety and tolerability; change in FVC at 12 mo	Double-blind RCT	II
Bortezomib	TGF-signaling inhibitor	Safety and tolerability (secondary outcomes: FVC, skin score, HRQOL) at 48 wk	Double-blind RCT	II
Dabigatran	Thrombin inhibitor	Safety (secondary outcomes: skin score, lung fibroblasts) at 6 mo	Open-label single group	I

Definition of abbreviations: BAFF = B-cell activating factor belonging to the tumor necrosis factor family; D_{LCO} = diffusing capacity of the lung for carbon monoxide; HRQOL = health-related quality of life; mRSS = modified Rodnan skin (skin thickness) score; PDE5 = phosphodiesterase-5; PFT = pulmonary function test; RCT = randomized controlled trial; TGF = transforming growth factor.

*According to clinicaltrials.gov as of May 2016.

†Study has been completed; awaiting results.

Volkmann & Tashkin, Ann Am Thorac Soc 2016

Lung transplantation

- 3763 adults were transplanted during the study period and met inclusion criteria: 229 with SSc, 201 with PAH, and 3333 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.

- If medical treatment fails, lung transpantation can be proposed to SSc patients in the absence of contra-indication

Bernstein EJ et al. Arthritis Rheumatol. 2015

SSc-PAH: Any place for lung transplantation?

Proposed SSc specific contraindications

- Muscles
  - Uncontrolled active inflammatory myopathy
  - Myopathy with diaphragm involvement
- DU: 1 severe episode of DU per year despite optimal treatment
- Gastrointestinal
  - Oesophageal stricture
  - Active and and severe GI ulcerations despite optimal treatment
  - High grade dysplasia in a Barett's oesophagus
  - Gastroparesis
- Heart
  - Conduction abnormalities and/or rhythm disturbances (not a CI if HLT is considered)
- Kidneys

Launay D, *et al. Presse Med* 2014; 43:e345-e363.

Quel traitement ?

Treatment of SSc-ILD

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

- **Rehabilitation**

Qui traiter ?

Cas clinique

- Femme 60 ans
- SSc évoluant depuis 8 ans
- Rodnan 12, arthralgies, RGO
- CV 60% théorique, DLCO 40% théorique
- Absence HTAP (PAP systolique 36 mm Hg)
- CT scan: PID, verre dépoli, fibrose
- Traitement de fond ?

MICO therapy
(A Wells)

Qui ne pas traiter (I) ?

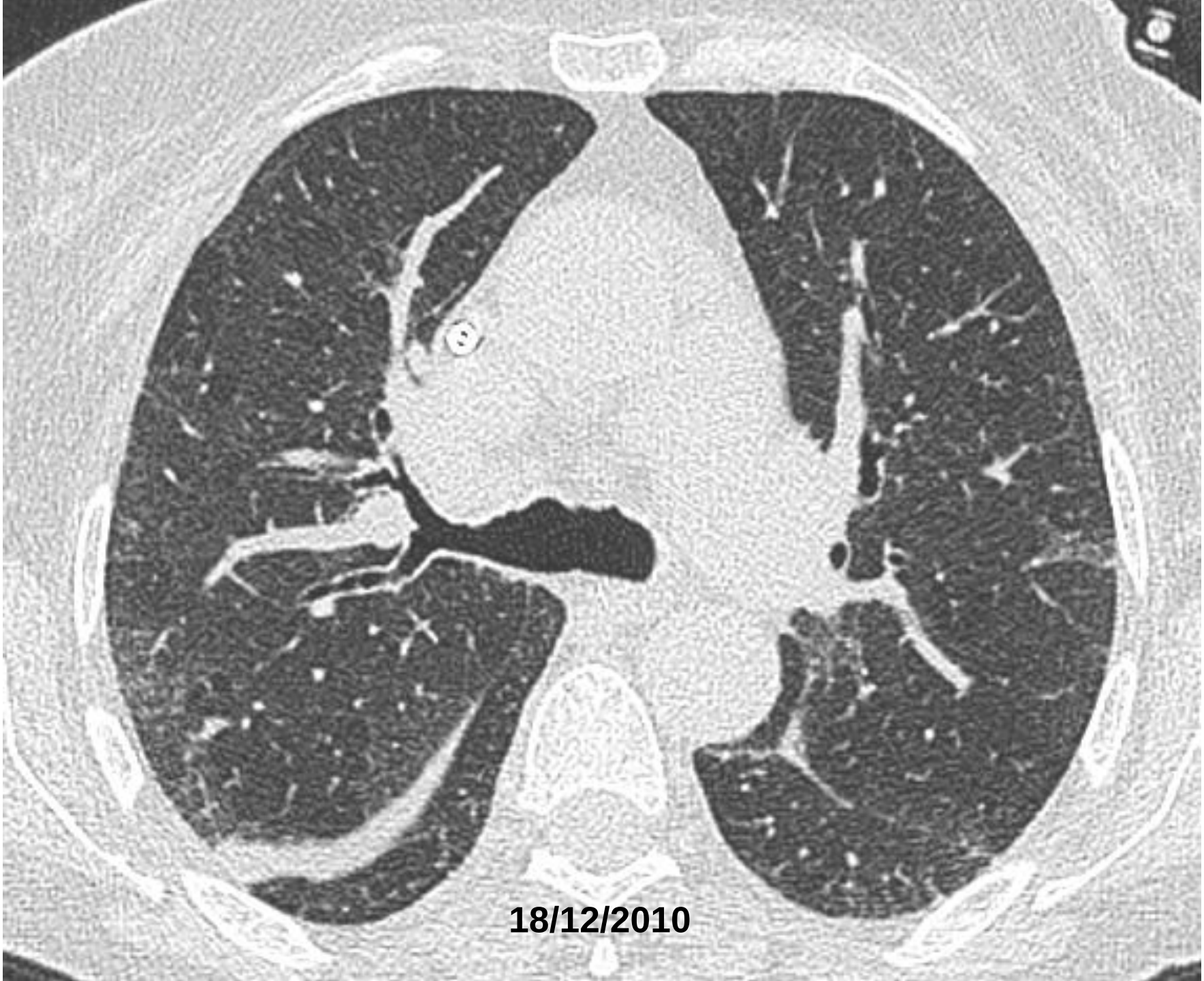
Les grands classiques (I)

I. Insuffisance ventriculaire gauche:

- Scanner thoracique en décubitus ventral/discret épanchement pleural
- Si non disponible: échographie cardiaque avec etude de la relaxation en diastole
- Si nécessaire/réalisable: épreuve d'effort

II. Embolie pulmonaire:

- Angio-scanner thoracique >> scintigraphie de ventilation perfusion


18/12/2010

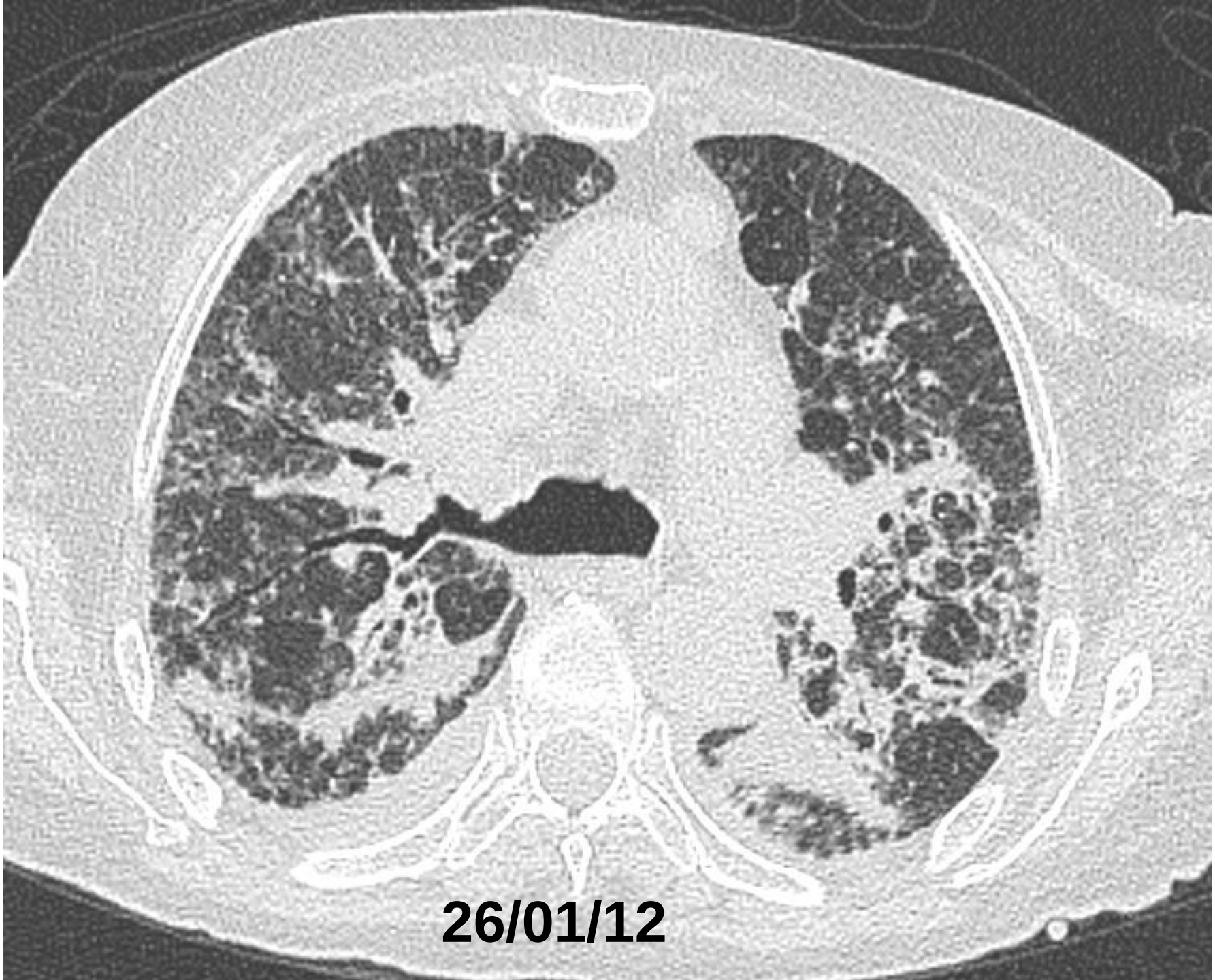
Qui ne pas traiter (II) ?

Les grands classiques (II)

III. Surinfection bronchique/pulmonaire:
Si doute pneumopathie opportuniste: LBA
Au moindre sur une surinfection bronchique, répéter les EFR après trois semaines

IV. Atteinte musculaire:
Si myopathie inflammatoire associée/syndrome de chevauchement

V. EFR « douteuses »
Discuter avec le collègues des EFR
Répéter les EFR au moindre doute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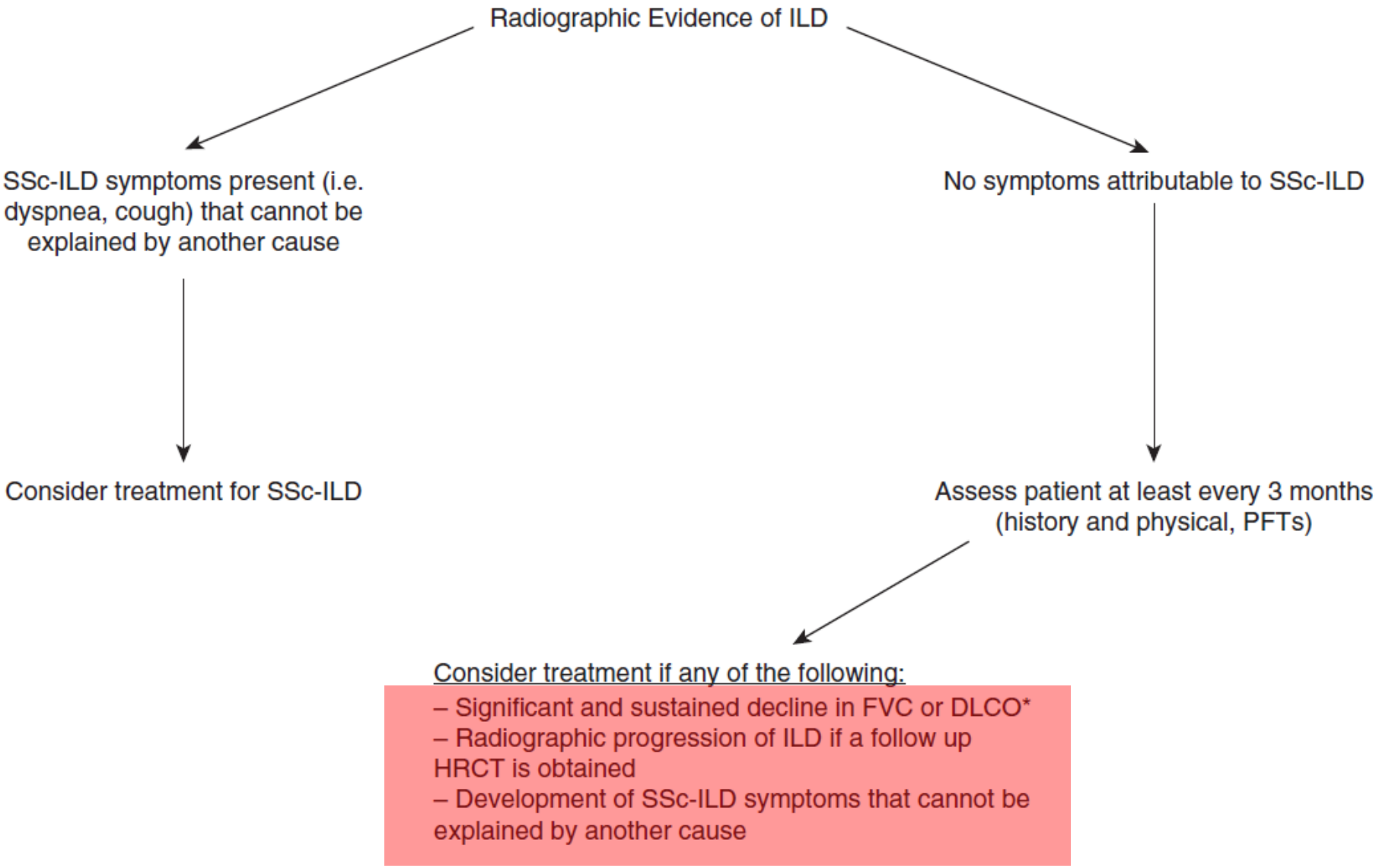
Qui ne pas traiter (III) ?

Avant d'envisager un traitement spécifique de la PID associée à la ScS: rechercher certaines atteintes qui peuvent altérer la fonction respiratoire des patients et qui ne relèveraient pas du traitement spécifique de la fibrose

Situations particulières conditionnant le pronostic de la PID-ScS:

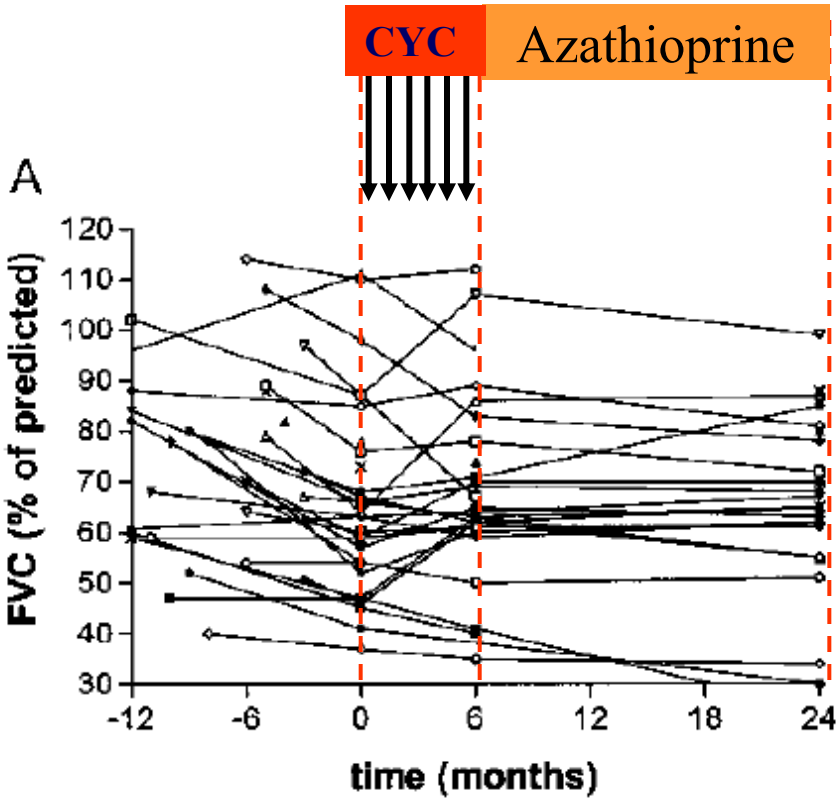
- Obésité morbide (surestimation de la perte des volumes).
- Syndrome d'apnées obstructives du sommeil.
- Syndrome emphysème et fibrose: peut sous-estimer le syndrome restrictif (DLCO plus abaissée, besoins en oxygène plus importants).
- Hypertension pulmonaire (HTP) associée

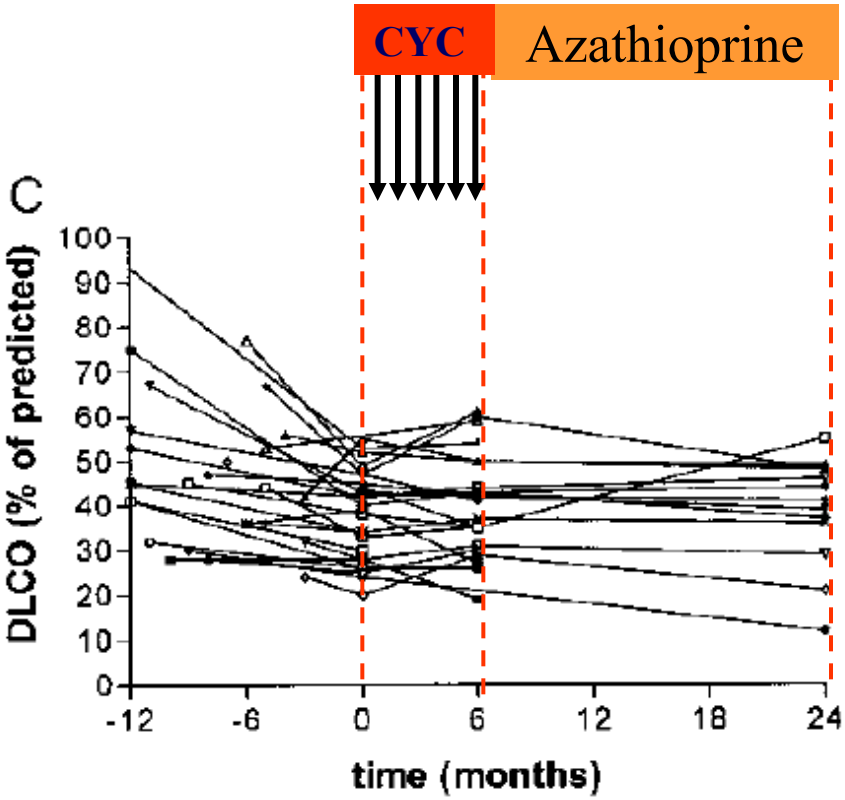
Proposed algorythm for the initiation of SSc-ILD targeted therapy



Volkmann & Tashkin, Ann Am Thorac Soc 2016

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



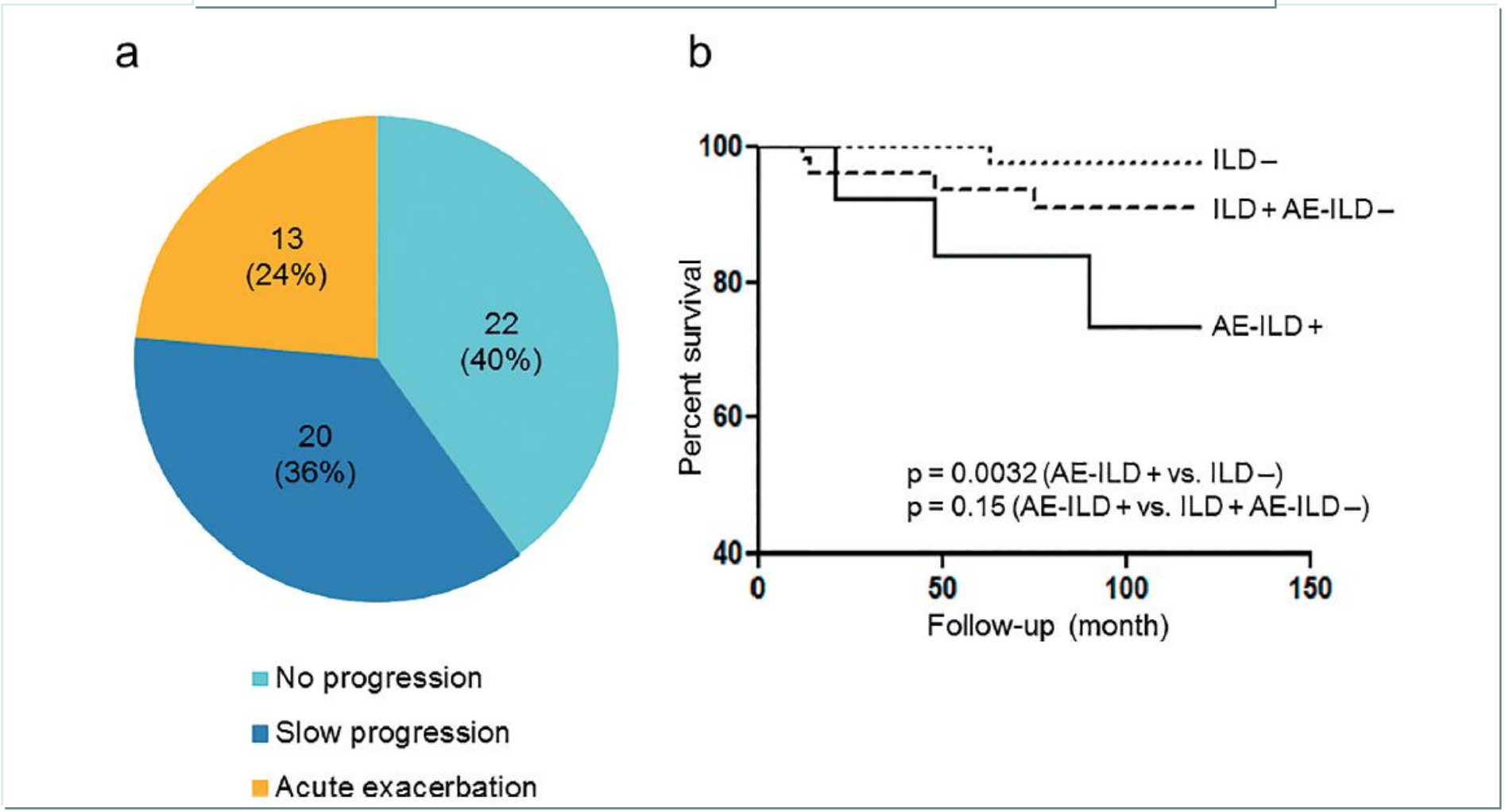


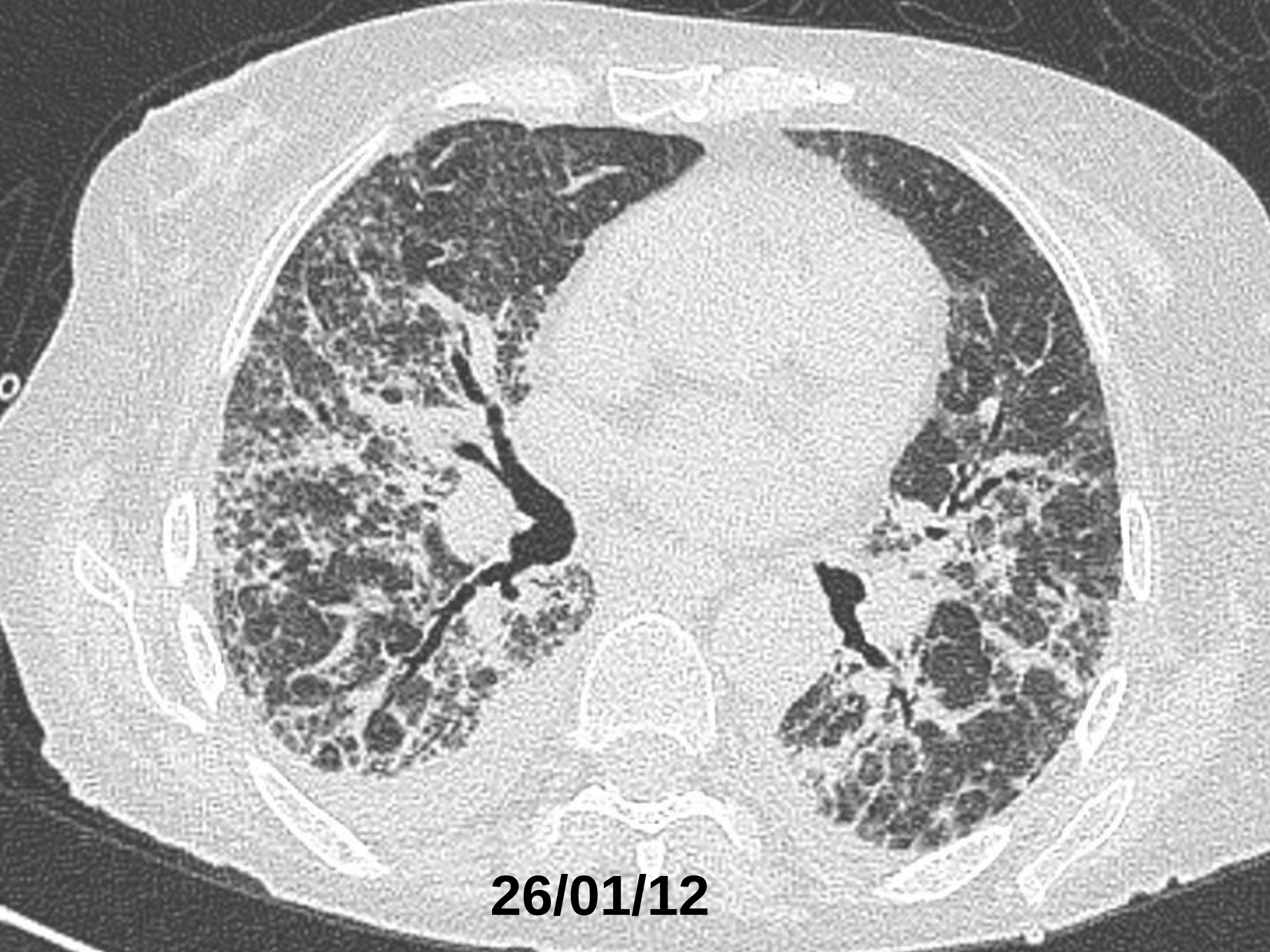
Bérezné A et al. J Rheumatol. 2008 May 1. [Epub ahead of print]

Tohoku J. Exp. Med., 2016, **239**, 297-305

High Prevalence of Acute Exacerbation of Interstitial Lung Disease in Japanese Patients with Systemic Sclerosis

Fumiko Tomiyama,[1] Ryu Watanabe,[1] Tomonori Ishii,[1] Yukiko Kamogawa,[1] Yoko Fujita,[1] Yuko Shirota,[1] Koichiro Sugimura,[2] Hiroshi Fujii[1] and Hideo Harigae[1]

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Combien de temps ?

Combien de temps ?

- Aucune données prospective randomisée sur la durée du traitement
- Traitement d'entretien indispensable
- Au moins deux ans de traitement au total si tolérance acceptable
- Traitement d'entretien de choix: MMF
- Séquence CYC – MMF ou MMF
- Données à 5 ans des essais prospectifs nécessaires
- A discuter
  - Diminution progressive
  - Arrêt brutal

Conclusions

- Traiter les malades sévères d'emblée
- Si sévère d'emblée ou aggravatif: CYC IV / MMF
- Si aggravation lente discuter MMF
- Si échec CYC/MMF: rituximab
- Si échec rituximab et éligible: transplantation pulmonaire
- A discuter dans le futur
  - Place des nouvelles thérapeutiques: pirfenidone, nintedanib, tocilizumab, HSCT
  - Intérêt des biomarqueurs: KL6, CXCL4

French Vasculitis Study Group

GFRS Groupe Francophone de Recherche sur la Sclérodermie

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