Pneumopathies interstitielles associées à la ScS

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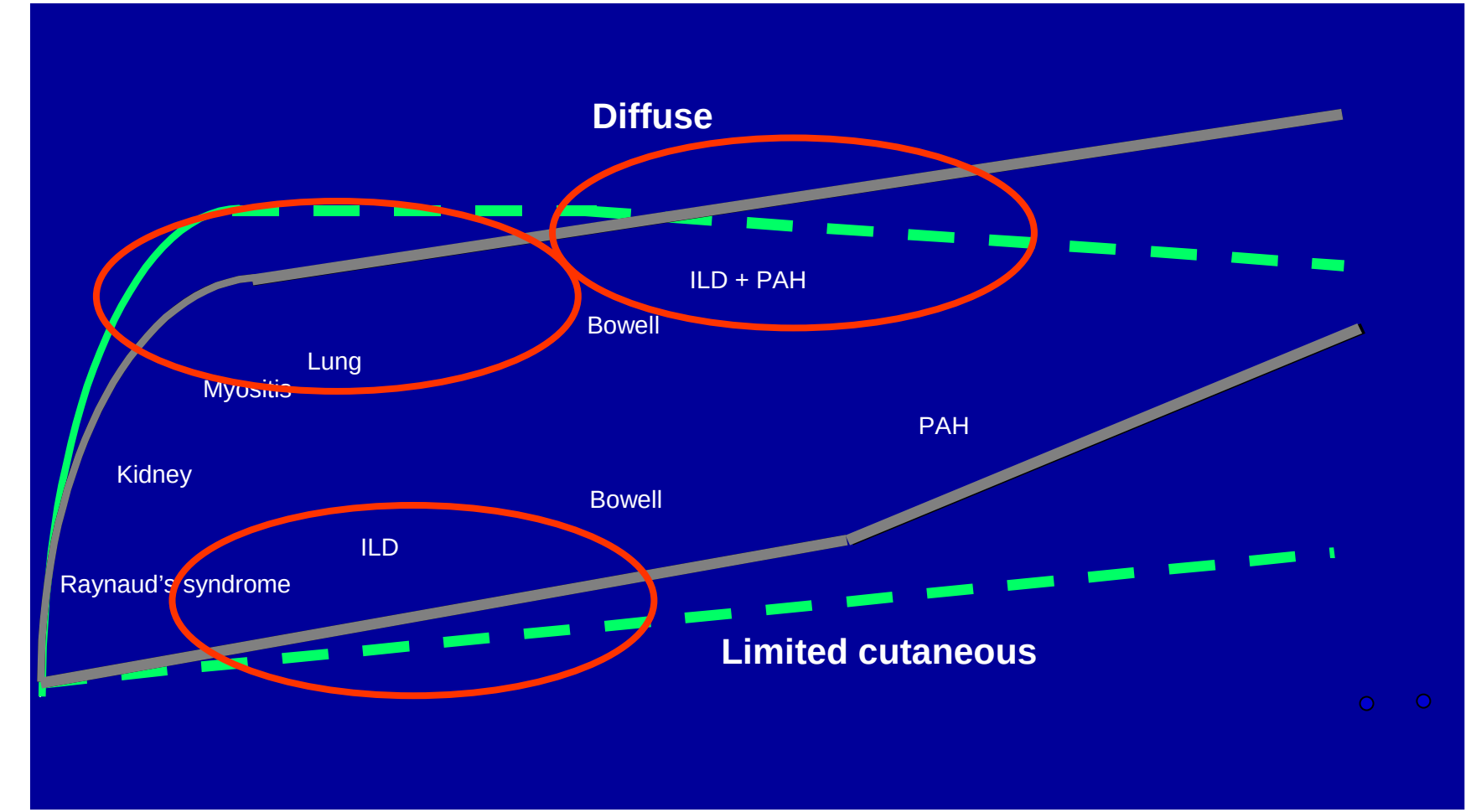
COCHIN BROCA HÔTEL-DIEU

Conflits d’intérêt LM

- Consultant**: Actelion, CSL Behring, Cytheris, GSK, LFB Biotechnologies, Lilly, Pfizer**
  - **Subventions ARMIIC**
- Investigateur**: Actelion, CSL Behring, Pfizer**
- Soutien financier (projets de recherche)**: Actelion, CSL Behring, GSK, LFB Biotechnologies, Pfizer**

SYSTEMIC SCLEROSIS : EVOLUTION



Prevalence of visceral involvement in SSc

	Total	Missing data	lcSSc	dcSSc
Number of patients, *n* (%)	1483 (100)	0 (0)	674 (45.5)	484 (32.7)
Percentage of organ involvement by SSc subsets				
RP	94.4	0.1	96.3	94.2
Skin involvement	87.8	0.3	91.5	97.6
PAH	15.8	0.1	14.9	18.5
Pulmonary fibrosis	34.5	0.1	20.8	56.1
Oesophagus	60	0.1	59.2	69.3
Stomach	14.2	0.2	15.3	15.6
Intestine	5.7	0.2	6.1	5.3
Kidney	10.5	0.2	9.1	15.9
Heart	14.6	0.2	12	23
Musculoskeletal system	47.5	1.4	44.9	56.6
Nervous system	6.4	2.2	4.1	7.1
Sicca-symptoms	39.5	2.5	43.5	39.7
Masticatory organ	24.1	7.2	23.7	34.1

Hunzelmann N, *et al.* *Rheumatology* 2008; 47:1185-92.

Atteinte pulmonaire au cours de la sclérodermie: manifestations cliniques

Signes cliniques souvent modestes.

Symptômes
- **Toux sèche**
- **Dyspnée**

Signes cliniques
- **Diminution de l'expansion thoracique**
- **Crépitants des bases pulmonaires**
- **Signes droits (HTAP)**
- **Pas d 'hippocratisme digital**

Examens complémentaires

- Le mauvais pronostic de la PID au cours de la ScS impose son **dépistage systématique**.
- Pas de recommandations consensuelles sur les examens de dépistage et la fréquence à laquelle les renouveler.
- Le bilan doit comporter:
  - tomodensitométrie thoracique haute résolution (TDMHR)
  - épreuves fonctionnelles respiratoires (EFR) avec mesure du coefficient de transfert du monoxyde de carbone (DLCO)
  - test de marche de 6 min avec mesure de la saturation en oxygène et l'estimation de la dyspnée à l'aide de l'indice de Borg.

Sclérodermie et PID

- Explorations fonctionnelles respiratoires

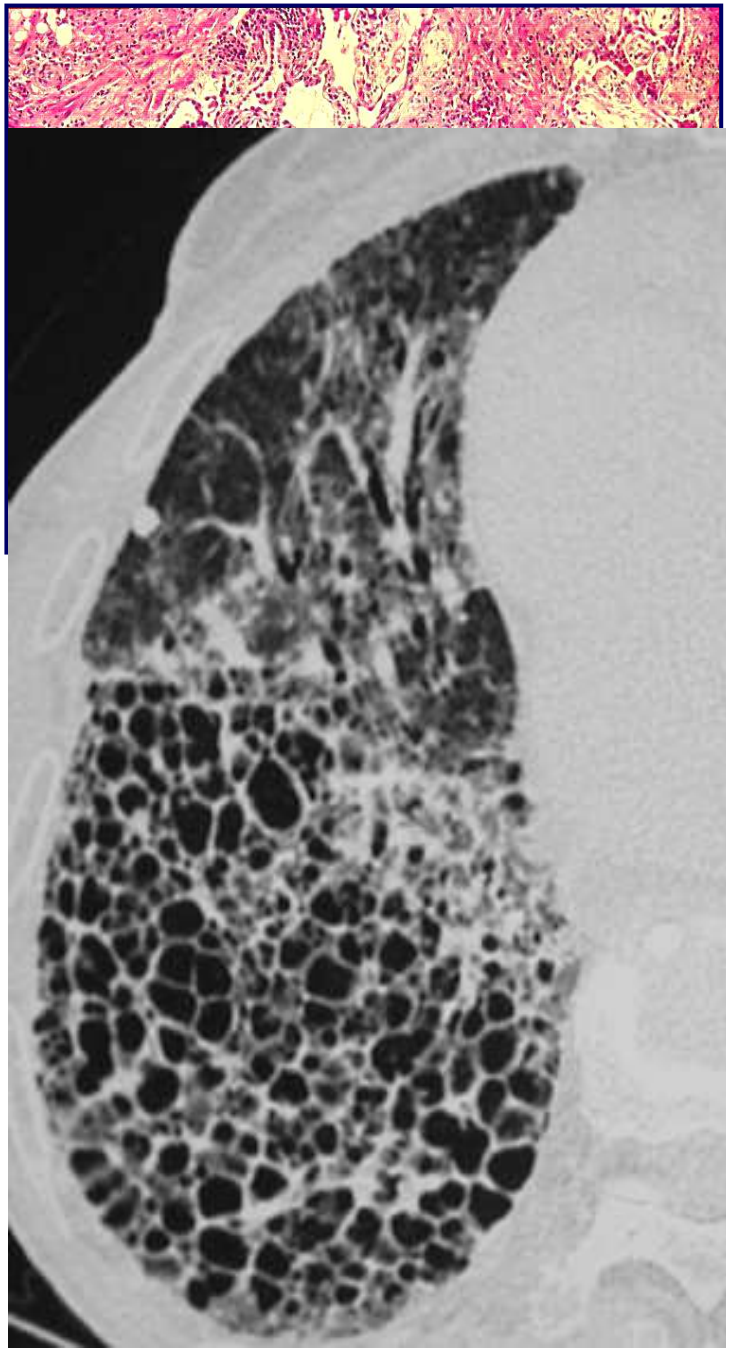
  peuvent être normales

  – syndrome restrictif, le + souvent

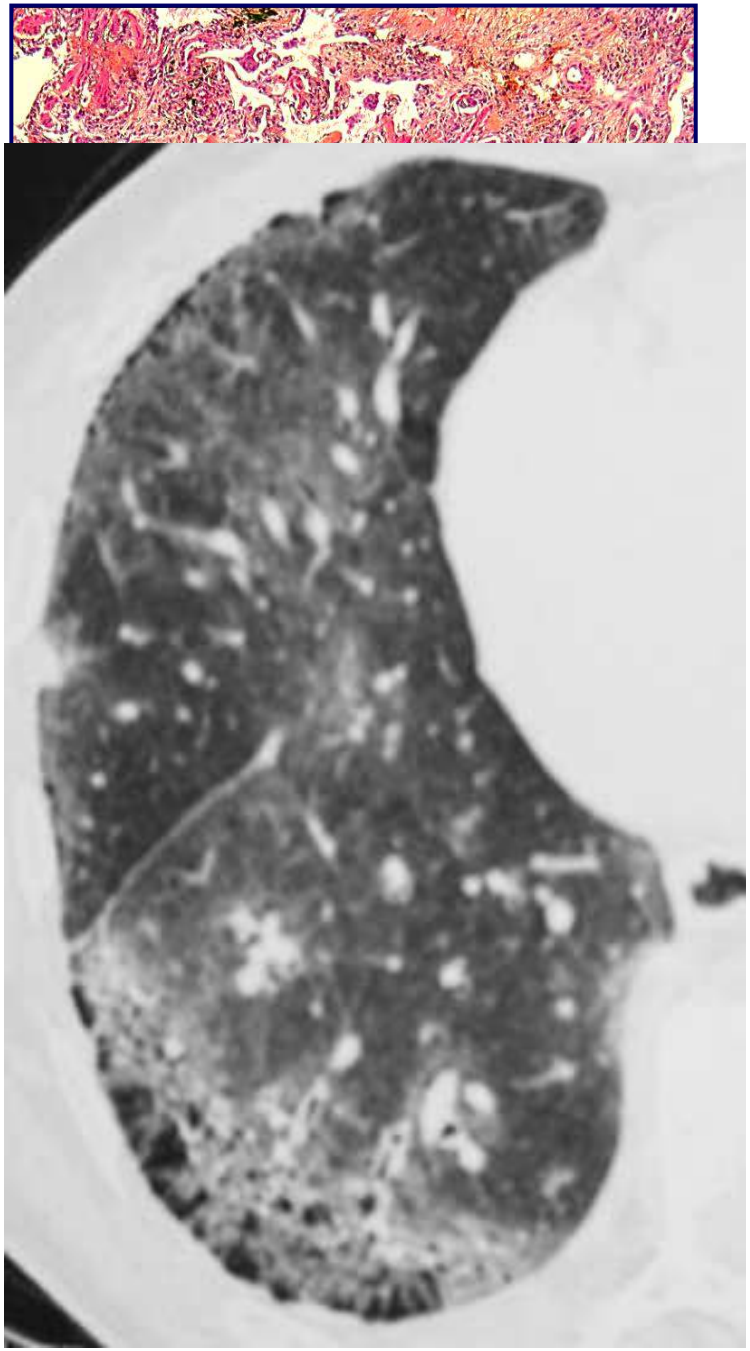
  – anomalie de la DLCO, désaturation à l'effort

- Rôle majeur dans le suivi et le traitement

UIP



NSIP



Sclérodermie et PID

TABLE 1. HISTOPATHOLOGIC DIAGNOSIS, ACCORDING TO TYPE OF SCLERODERMA AND DURATION OF EXTERNAL DYSPNEA

Histologic Subset	No. of Subjects	Type of Scleroderma (Limited/Diffuse)	Mean Duration of Dyspnea at Biopsy (*mo*)
NSIP	62 (77.5%)	43/19	11
UIP	6 (7.5%)	4/2	28
ESL	6 (7.5%)	5/1	24
Miscellaneous*	6 (7.5%)	4/2	12

Definition of abbreviations: NSIP = nonspecific interstitial pneumonia; ESL = end-stage lung disease; UIP = usual interstitial pneumonia.

* Miscellaneous: respiratory bronchiolitis interstitial lung disease (n = 4), sarcoidosis (n = 1), organizing pneumonia (n = 1).

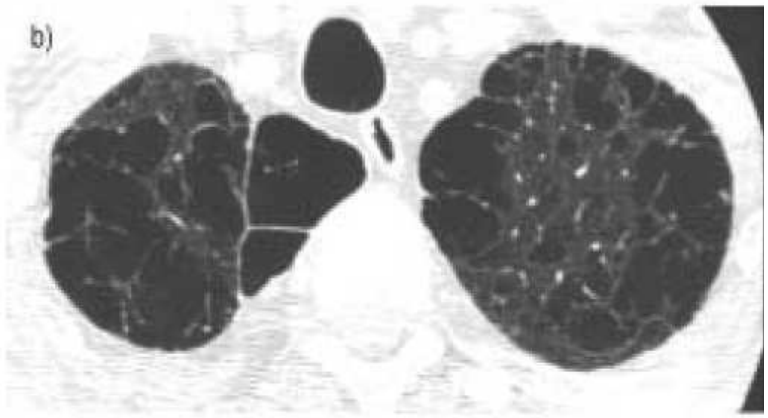
Bouros D, AJRCCM 2005, 165:1581

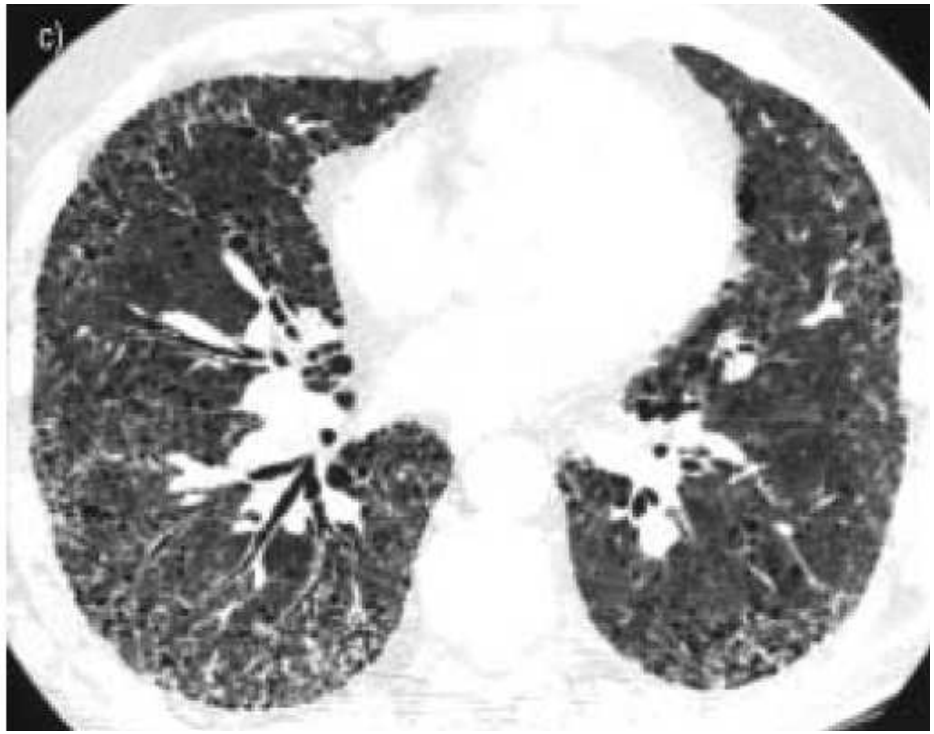
Eur Respir J 2005; 26: 586–593
DOI: 10.1183/09031936.05.00021005

CLINICAL FORUM

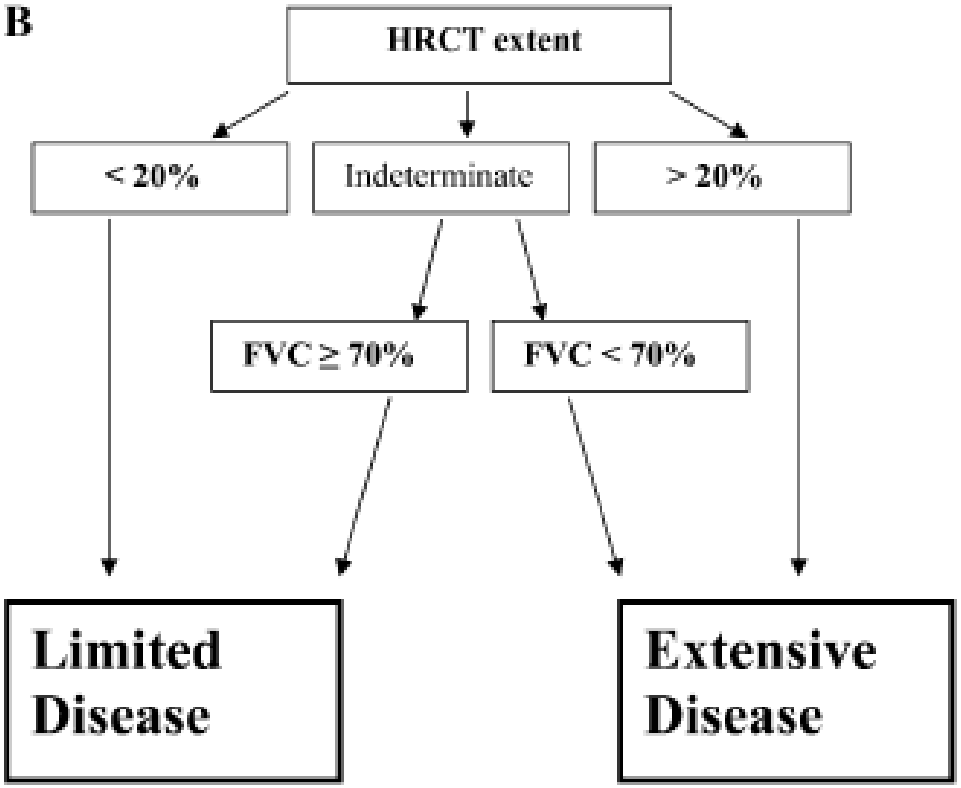
Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity

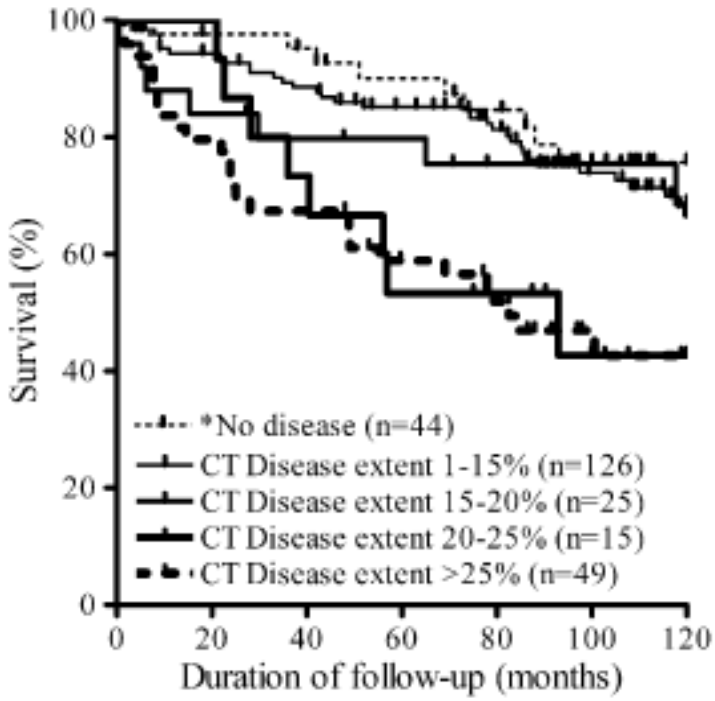
V. Cottin*, H. Nunes[#], P-Y. Brillet[¶], P. Delaval[+], G. Devouassoux[§], I. Tillie-Leblond[ƒ], D. Israel-Biet, I. Court-Fortune[##], D. Valeyre[#], J-F. Cordier* and the Groupe d'Etude et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P)**





Interstitial Lung Disease in Systemic Sclerosis
A Simple Staging System
Goh NSL, AJRCCM 2008

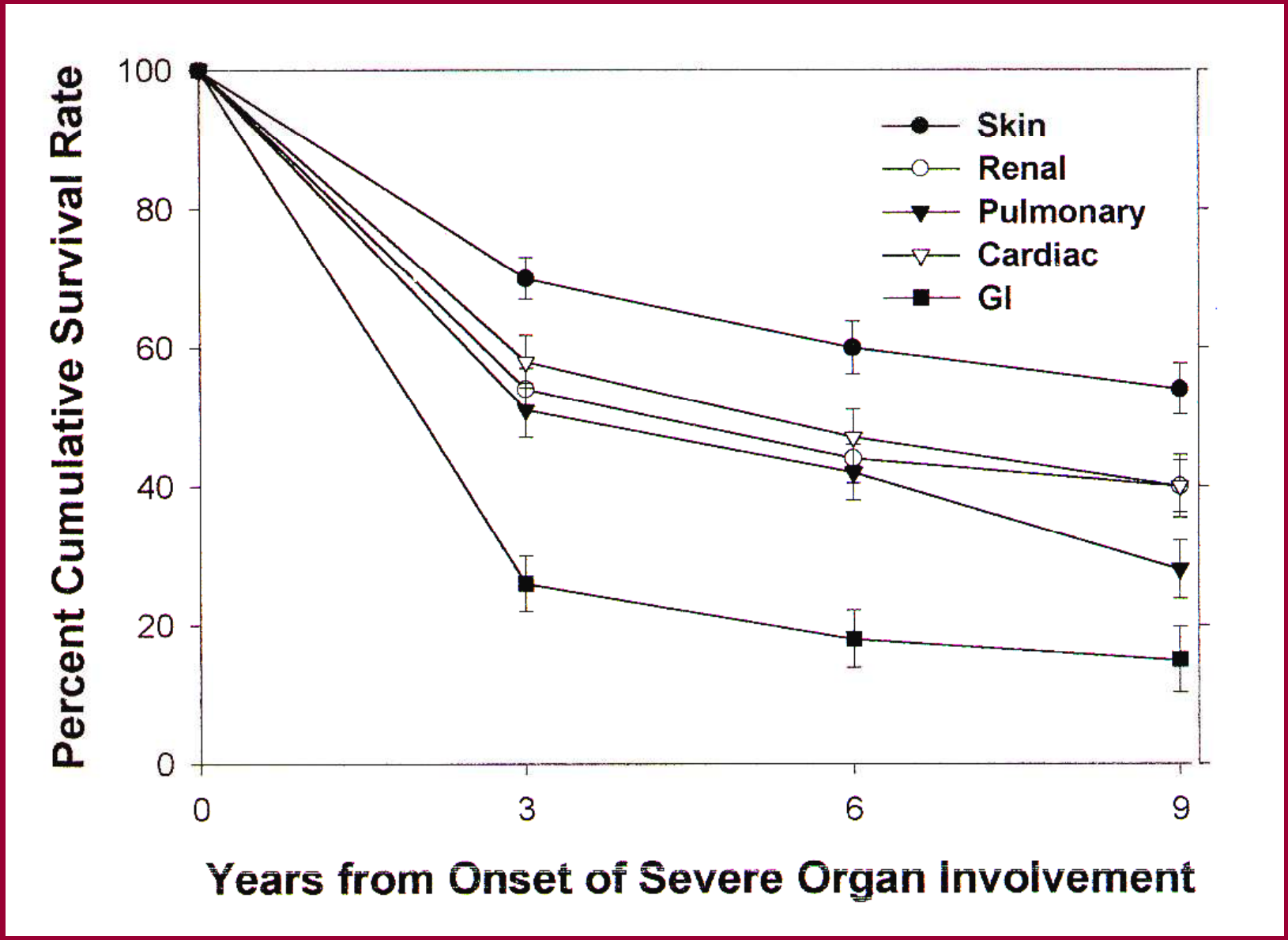




SSc-ILD Prognosis (II)

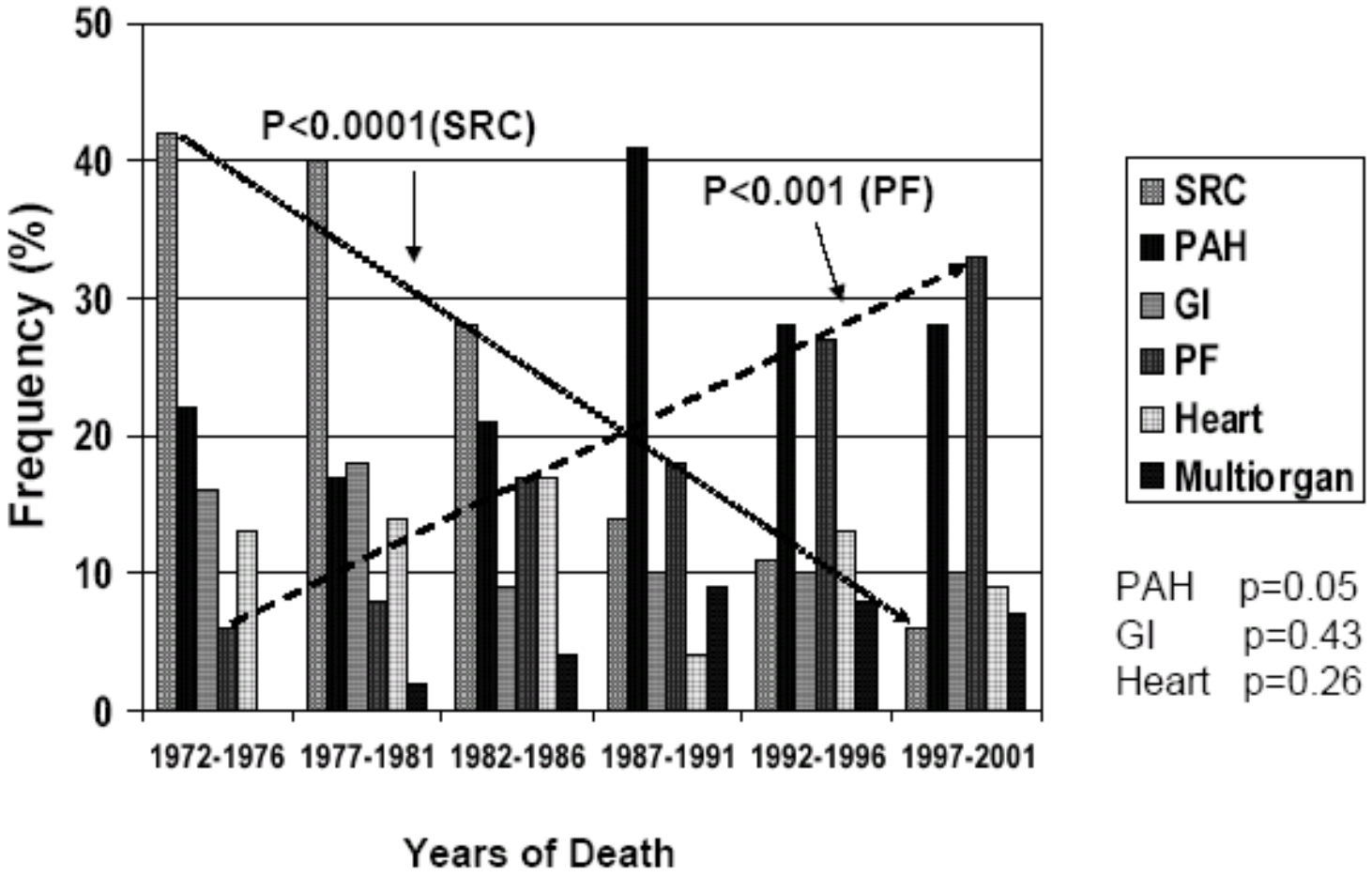
- Main parameters of prognostic value in SSc-ILD:
  - Severe ILD at diagnosis
    - Clinical symptoms: dyspnea, crackles
    - PFTs (DLCO and/of FVC<70%)
    - HRCT (extended lesions with a dominant ground glass pattern)
  - Rapidly worsening ILD defined by a loss of 10% FVC or 15% DLCO during the last 12 months.
  - BAL data do not influence any more therapeutic decision

Severe organ involvement in SSc with diffuse scleroderma



Steen VD, Medsger T, Arthr Rheum 2000; 43: 2437-2444

Changes in causes of systemic sclerosis related deaths between 1972 and 2001



Steen VD, Medsger T, Ann Rheum Dis 2007, Feb 28 EPub

Treatment of SSc-ILD

- **PPI**
- **Cyclophosphamide**
- **Low dose corticosteroids (10 mg/j)**
- **Oxygen**
- **Lung transplantation**

- **Rehabilitation**

Systemic sclerosis and corticosteroids

No documented efficacy of CS alone in SSc in RCT

- Edematous scleroderma
- polyarthritis
- Inflammatory myopathy
- pericarditis
- alveolitis

Induction of scleroderma renal crisis ?

Steen et al, 1998; DeMarco et al, 2002; Teixeira et al, 2008; Guillevin et al, 2011, submitted

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. • The SLS and FAST study are the only 2 high quality RCTs conducted so far. • 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

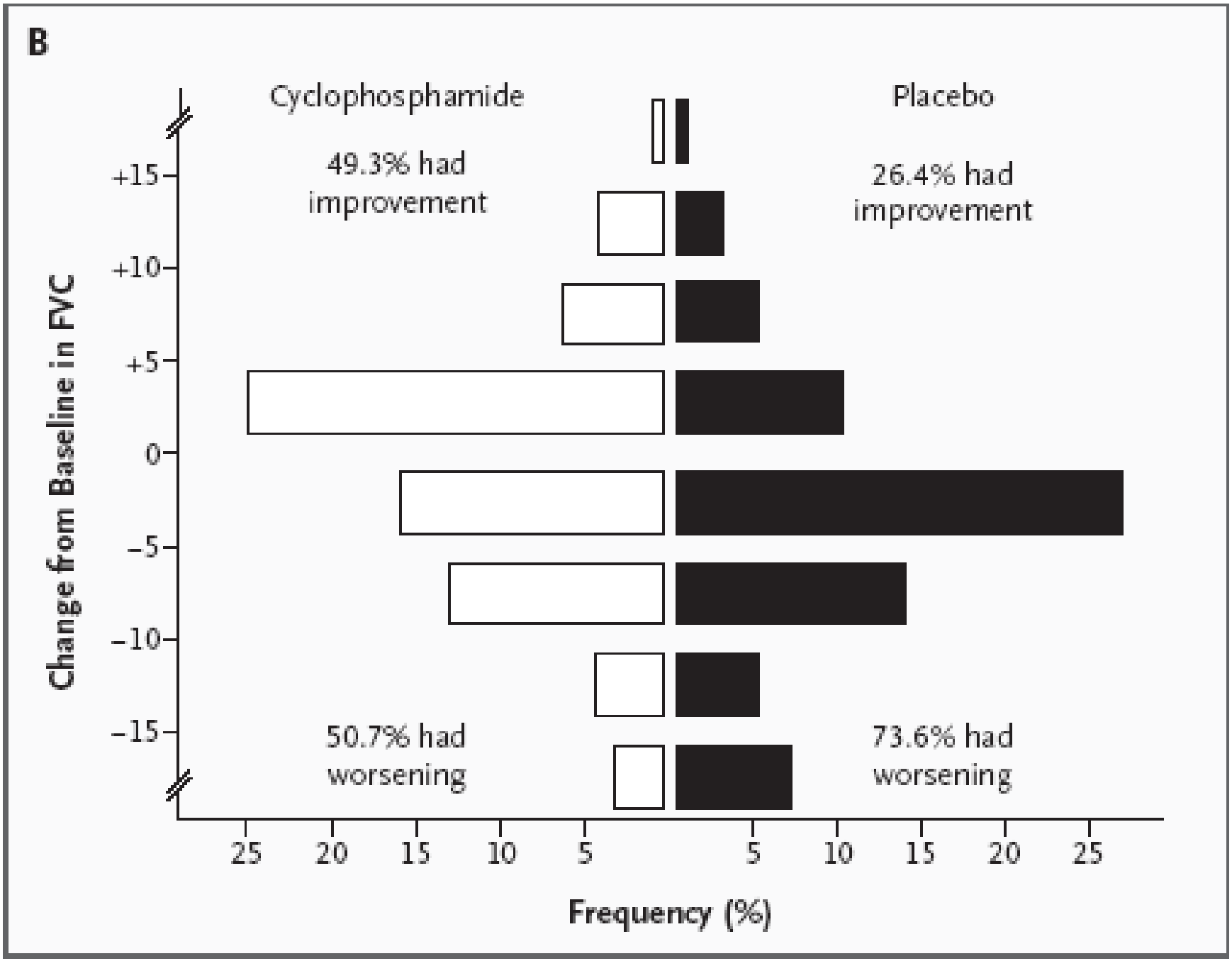
Carlotta Nannini[1], Colin P West[2,3], Patricia J Erwin[4] and Eric L Matteson[1]

Table 2

Randomized clinical trial study characteristics

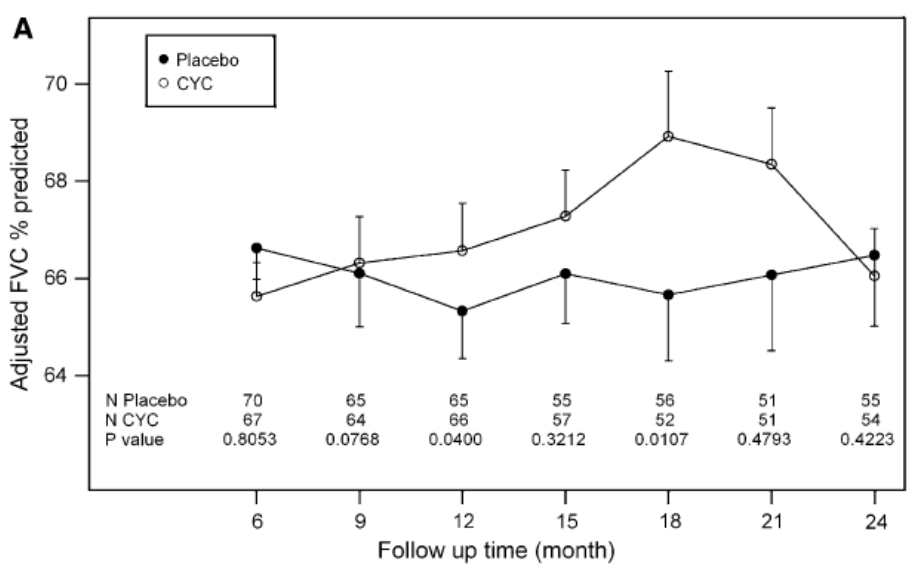
Study	Number of patients	Mean age (years)	Outcome measure[a]	CYC treatment	Placebo/ alternative treatment	Corticosteroid	Length of follow-up (months)
Hoyles and colleagues [10]	45	55	FVC, 80.1 ± 10.3	Intravenous, 600 mg/m^2 monthly	Placebo	Prednisone 20 mg alternate days	12
			DLCO, 52.9 ± 1.6				
Nadashkevich 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				

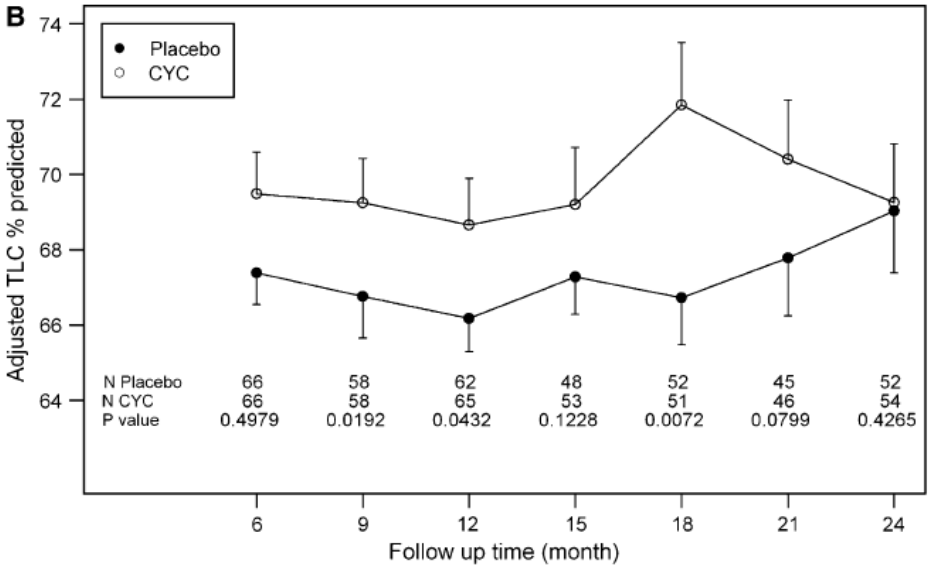
Data presented as mean ± standard deviation. AZA, azathioprine; CYC, cyclophosphamide; DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity. [a]Percentage predicted value at baseline.


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

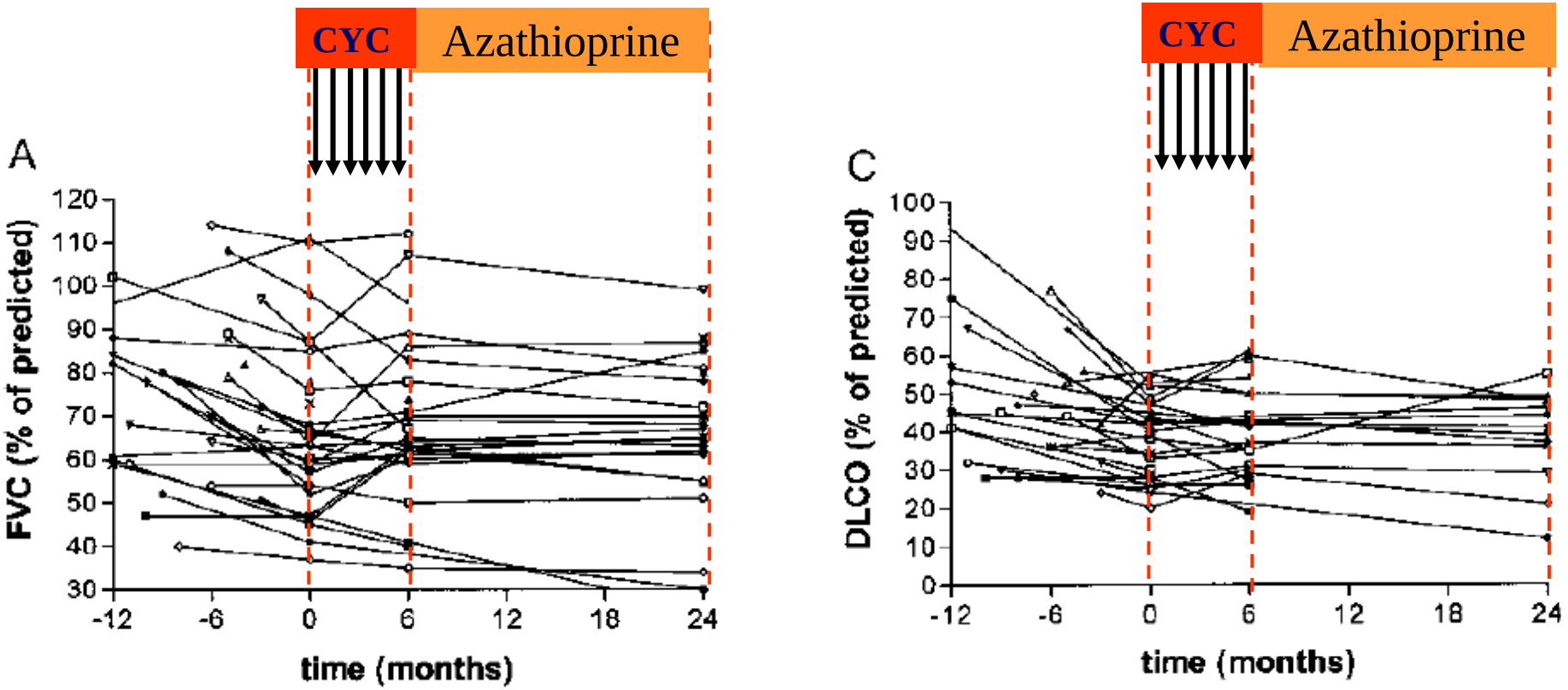
A Multicenter, Prospective, Randomized, Double-Blind, Placebo-Controlled Trial of Corticosteroids and Intravenous Cyclophosphamide Followed by Oral Azathioprine for the Treatment of Pulmonary Fibrosis in Scleroderma

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]

Mycophenolate mofetil in diffuse cutaneous SSc a retrospective analysis

- 109 patients treated with MMF and 63 control subjects receiving other immunosuppressive drugs
- 12% of patients experienced adverse reactions (gastrointestinal (GI) tract disturbances, infections).
- MMF was discontinued due to disease stabilization in 9%, side effects in 8% and no effect on the disease activity in 14% of the patients.
- Significantly lower frequency of clinically significant pulmonary fibrosis in the MMF-treated cohort (P=0.037) and significantly better 5-yr survival from disease onset and from commencement of treatment (P=0.027 and P=0.012, respectively).
- No significant difference between the two groups (modified Rodnan skin score and FVC).

Nihtyanova SI et al. Rheumatology 2006

Proposed recommendations for future randomised trials

- Limited or diffuse SSc
- 1-year RCT
- Placebo (or active) controlled RCT
- ILD defined on HRCT
- Rigorous quality control of PFT
- Dyspnea not required as an inclusion criteria
- Primary goal: prevent disease progression
- Progression free survival is an important secondary end point
- Enhance sensitivity
  - Cohort enrichment
  - Observed progression
- Composite indices
- Biomarker signal

Khanna D Clin Exp Rheum 2010

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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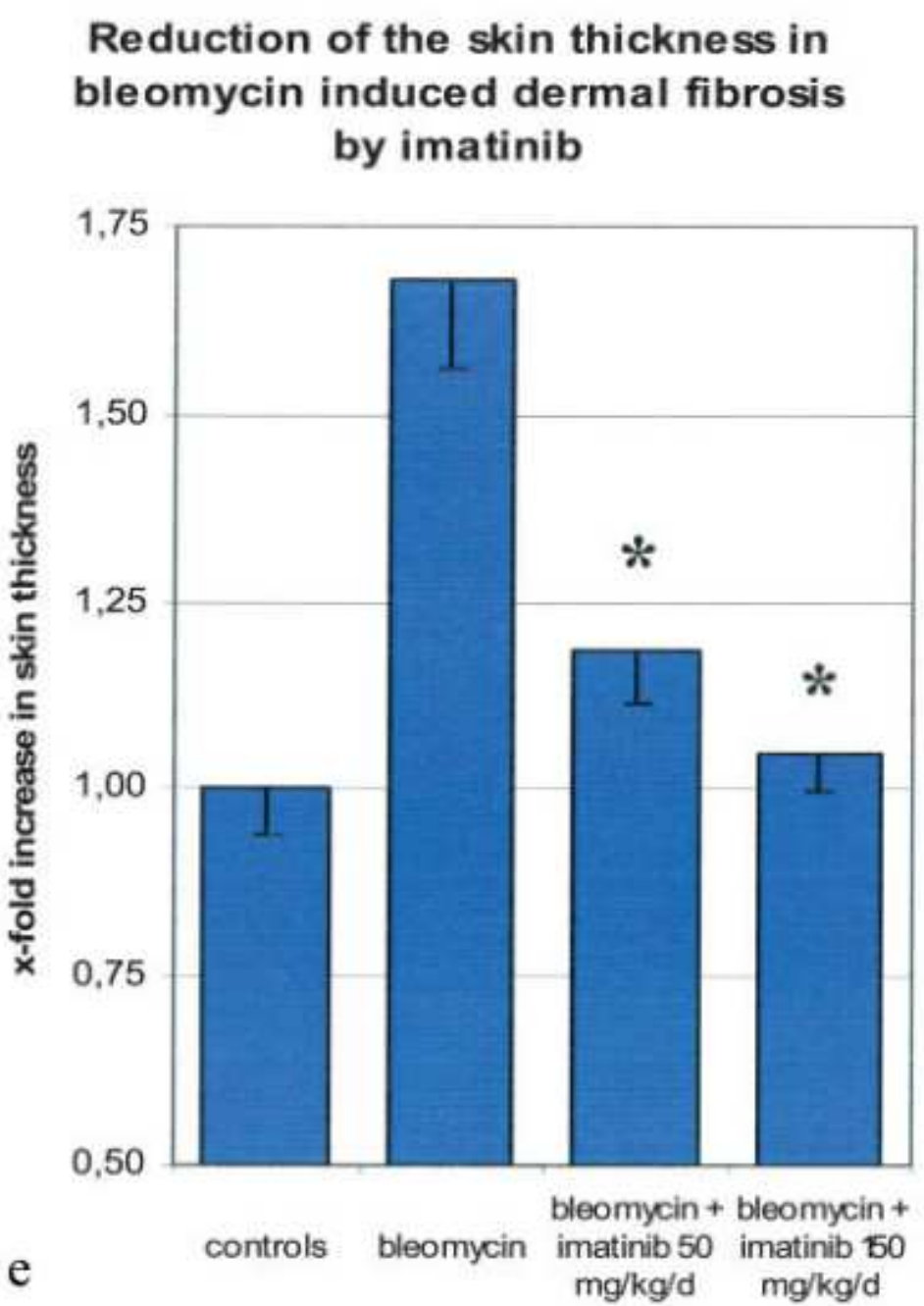
ARC : Clément Lebrun
Chef de projet : Séverine Poignant
Hôpitaux Universitaires Paris Centre
Cochin Broca Necker
Site Tarnier - Paris

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%).



Distler et al, A & R 2007

Novel therapies

Inhibition of:

- SRC kinases
- Rho associated kinases (ROCK)
- Fos related antigen-2 (Fra2)
- Histone deacetylases
- DNA methyl transferases

Distler et al, A & R 2008
Distler et al, ACR meeting 2008

SSC IN 2011

From mechanisms to medicines

Luc Mouthon

Findings from ongoing studies of imatinib in systemic sclerosis (SSc) were eagerly awaited in 2011, but results from these clinical trial have so far been disappointing. However, progress in the understanding of the mechanisms that underlie SSc pathogenesis could provide clues to novel targets for 2012 and beyond.

Mouthon, L. *Nat. Rev. Rheumatol.* advance online publication XX Month 2012; doi.10.1038/nrrheum.2011.202

Key advances

- The results of three studies show that imatinib is poorly tolerated in patients with SSc and do not enable clinicians to draw conclusions on drug efficacy[5–7]
- Tissue factor—the primary *in vivo* initiator of coagulation—interacts with endothelin-1 signaling in the activation of myofibroblasts from patients with SSc[8]
- 5-HT–5-HT$_{2B}$ receptor signaling links vascular damage and platelet activation to tissue remodeling in SSc and could be a novel therapeutic target to treat fibrotic diseases[9]

•Taken together, the results of the above studies provide evidence that imatinib at doses of 400–600 mg per day is poorly tolerated in patients with SSc.

•No conclusion can, however, be made on drug efficacy because of the heterogeneity, limited power and nonrandomized nature of the above studies, although a trend towards an improvement of FVC and MRSS was observed in patients treated with imatinib.

•Because of poor tolerance, whether testing of imatinib for SSc will progress to large prospective randomized trials is unknown, as if whether imatinib warrants further study

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.

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GFRS

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