DES Pneumologie Ile de France

09/12/2016

Pneumopathie interstitielle diffuse associée à la Sclérodermie

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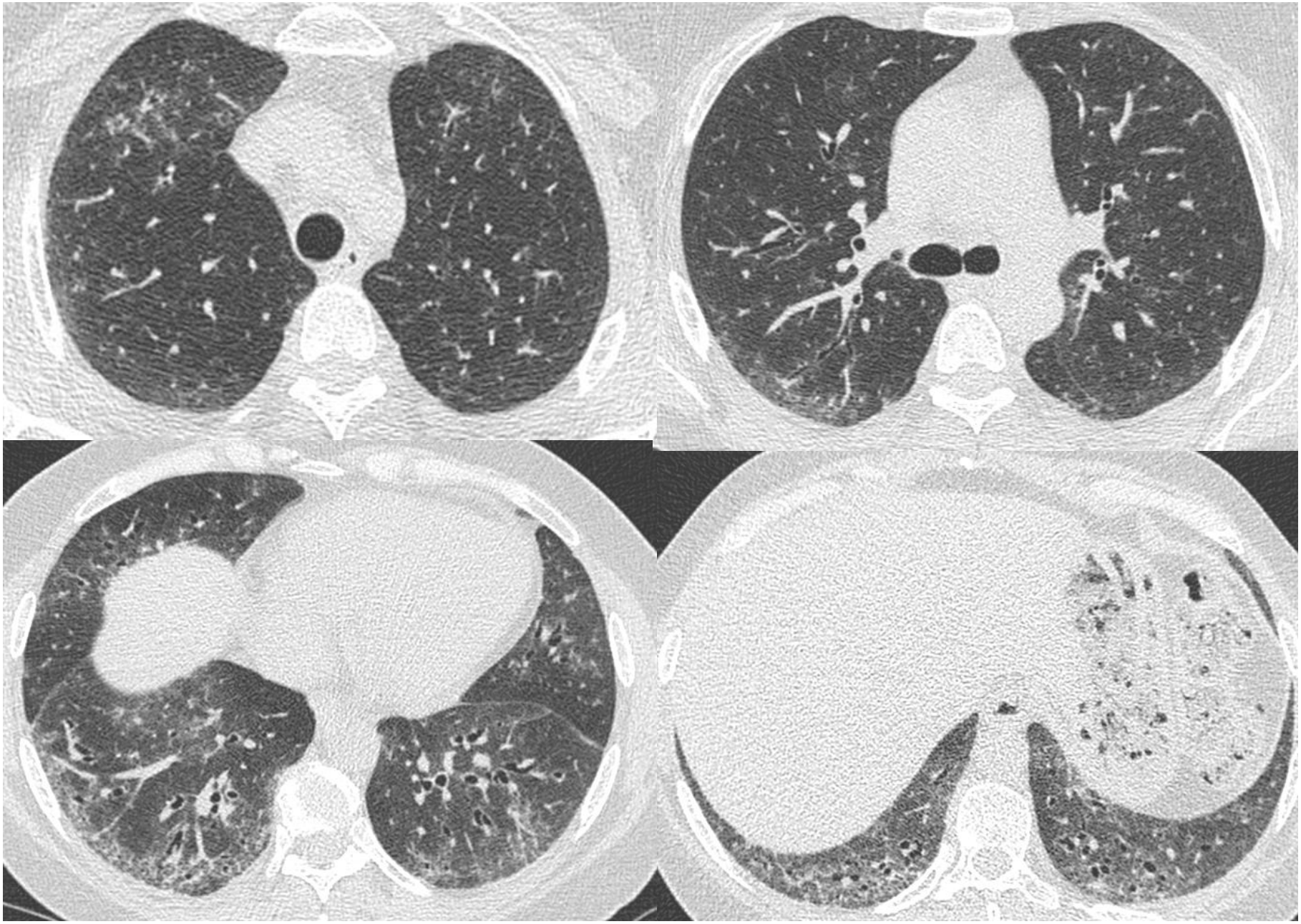
Observation 1 – Mme P. 53 ans

- **Motif de Consultation: PID**

- **Mode de Vie**
  - Secrétaire commerciale
  - Pavillon sain – 1 canari
  - Non fumeuse
- **ATCD**
  - Pas de notion de PID dans la famille ni de connectivite
  - 1992: Hémianopsie latérale homonyme droite sous oestro-progestatifs
  - 2000: Coelioscopie pour Endométriose
  - Canal carpien bilatéral opéré en 1999 à droite et en 2002 à gauche

- **HDLM**
  - Asthénie d'installation lentement progressive avec arthralgies des mains, toux sèche

EFR : CVF 2, 600 L (92 %) CPT 3,660 L (79%), VEMS 2,140 L (86%) DLCO 40%

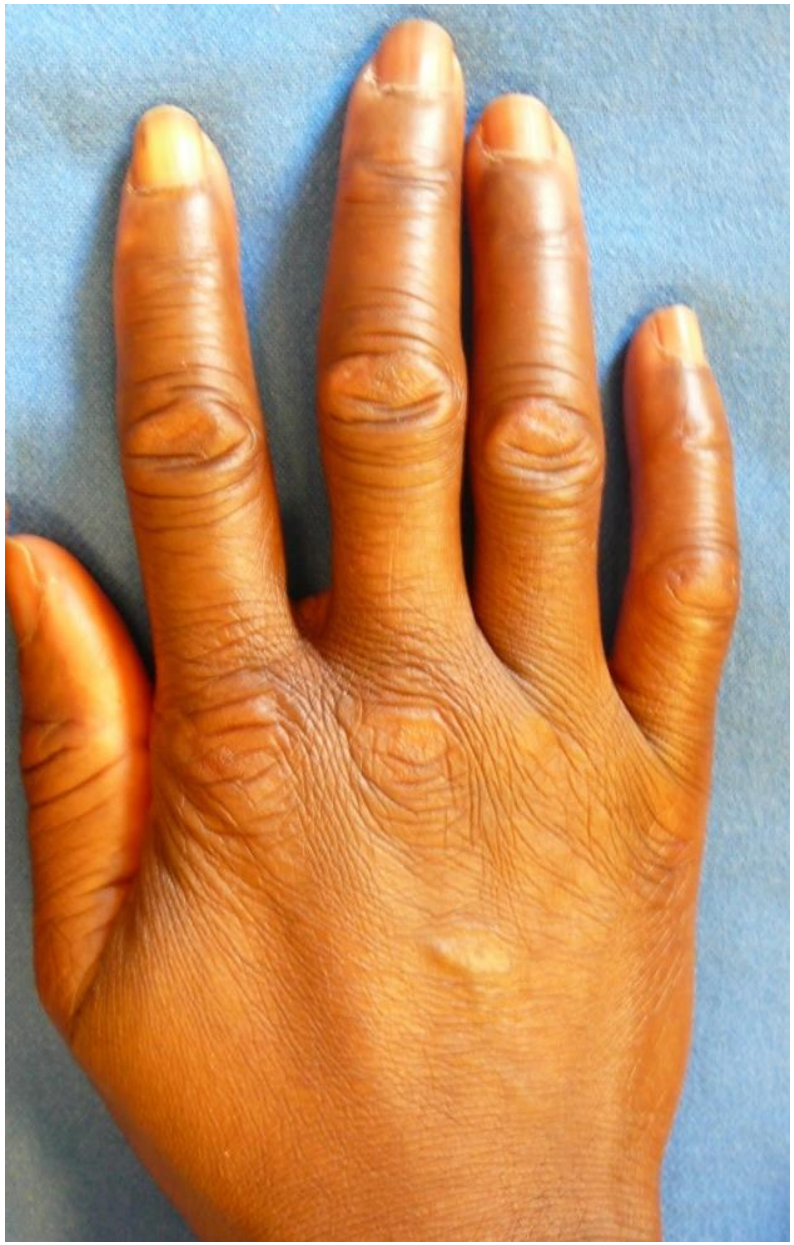


2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative

Table 1 The American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis*

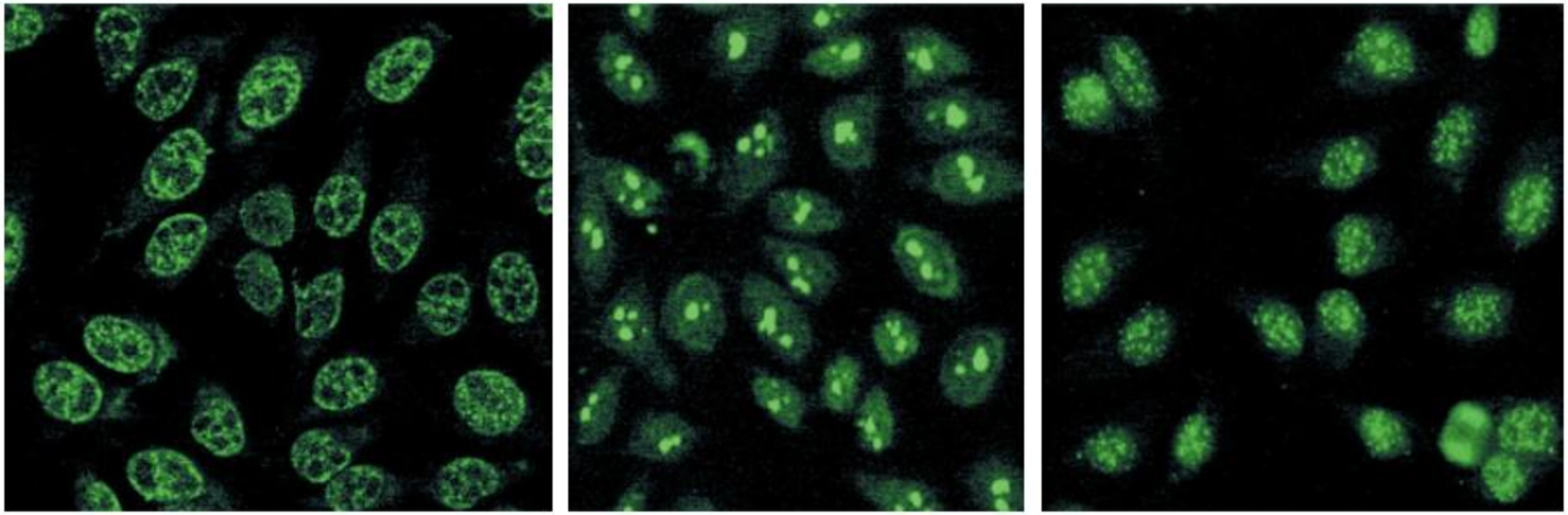
Item	Sub-item(s)	Weight/ score†
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints *(sufficient criterion)*	–	9
Skin thickening of the fingers *(only count the higher score)*	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions *(only count the higher score)*	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	–	2
Abnormal nailfold capillaries	–	2
Pulmonary arterial hypertension and/or interstitial lung disease *(maximum score is 2)*	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	–	3
SSc-related autoantibodies (anticentromere, anti–topoisomerase I [anti–Scl-70], anti–RNA polymerase III) *(maximum score is 3)*	Anticentromere Anti–topoisomerase I Anti–RNA polymerase III	3

van den Hoogen F, *et al*. *Ann Rheum Dis* 2013;**72**:1747–1755.



A

30% des SSc diffuses | 25-50% des SSc -Myosites | 70-80% des SSc limitées



Topoisomérases | PM-Scl ; Th/To | Centromères

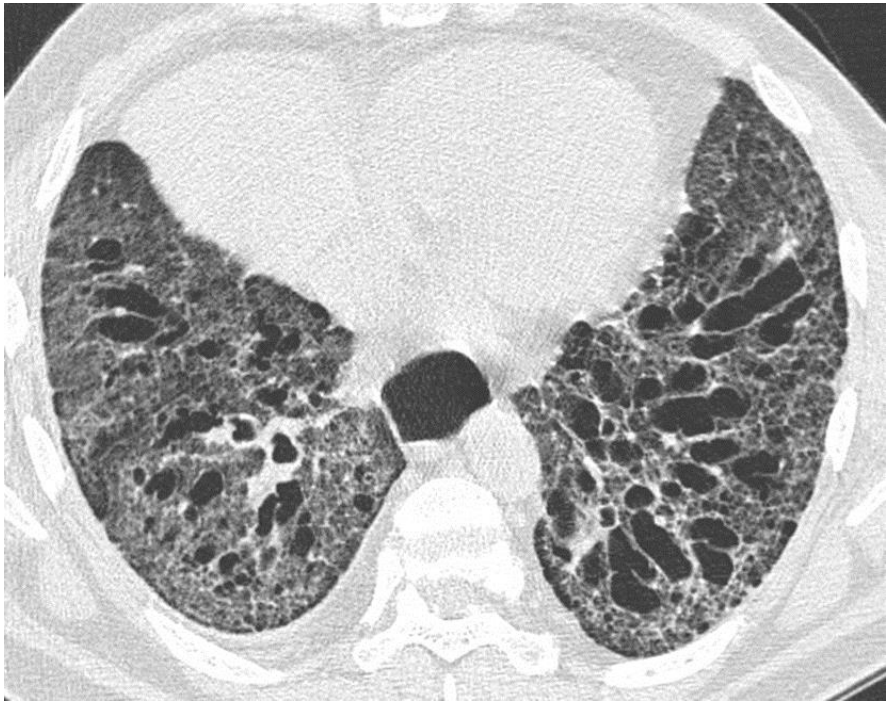
B

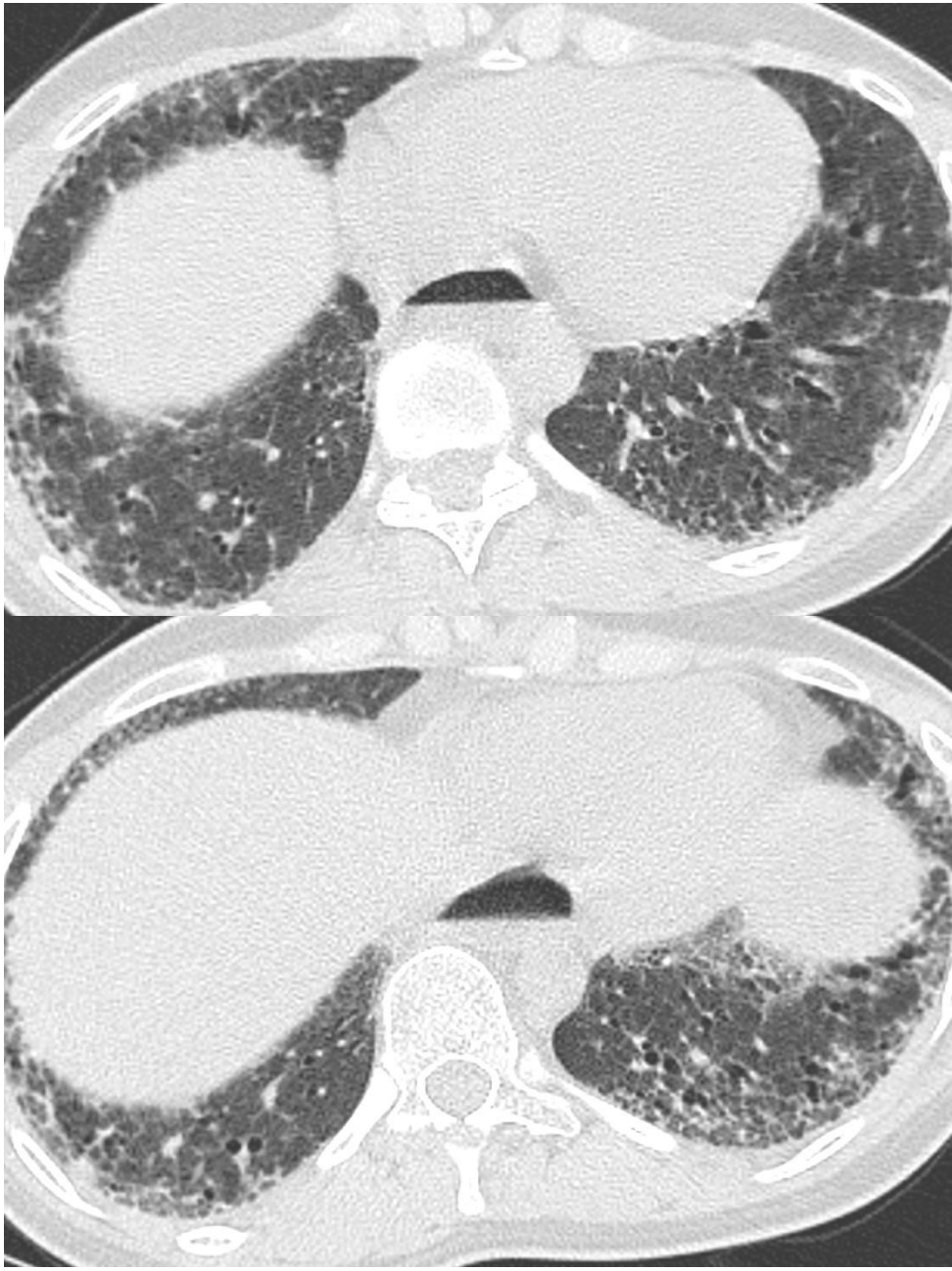
Classic Autoantibodies	Clinical Features	New Autoantibodies	Role
Anti–topoisomerase I	Diffuse cutaneous scleroderma	Anti–endothelial cell	Induce apoptosis of endothelial cells
Anticentromere proteins	Limited cutaneous scleroderma, pulmonary hypertension	Anti–FBN 1	Activate normal human fibroblasts
Anti–RNA polymerase I/II	Diffuse cutaneous scleroderma, renal involvement	Anti–MMP 1 and 3	Prevent degradation of ECM proteins
Antipolymyositis, sclerosis	Polymyositis, calcinosis	Anti-PDGFR	Stimulate normal human fibroblasts through Ha-Ras-ERK1/2-ROS
Antifibrillarin (U3RNP)	Diffuse cutaneous scleroderma, internal-organ involvement	Anti–Nag-2	Induce endothelial-cell apoptosis
Anti-Th/To	Limited cutaneous scleroderma, pulmonary fibrosis		

Gabrielli et al. *N Engl J Med* 2009

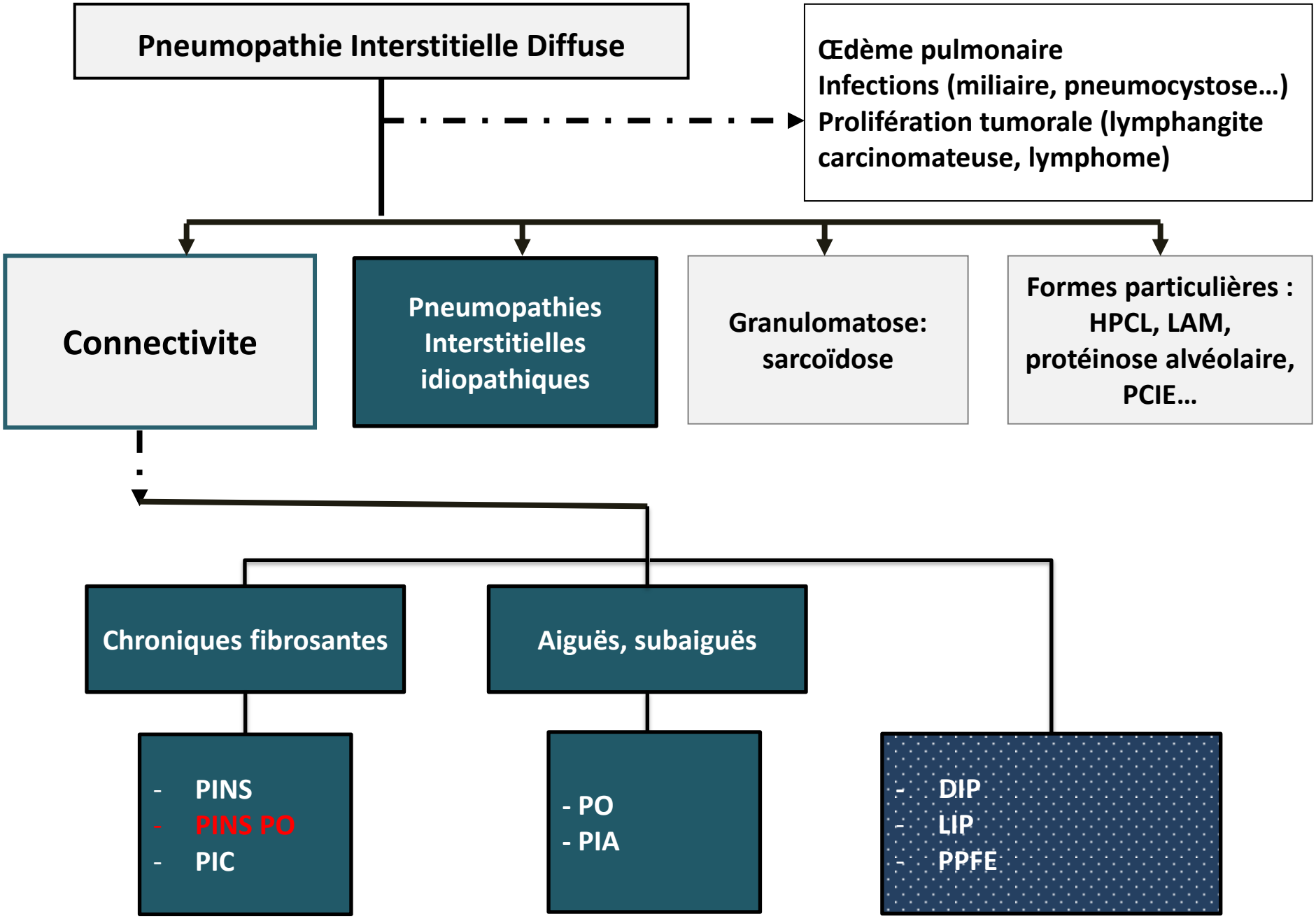
Atteinte oesophagienne

- Diamètre coronal de la lumière ≥ 9 mm sous-aortique
- Niveau hydro-aérique





Diapo H. Nunes


Pneumopathie Interstitielle Diffuse
Œdème pulmonaire
Infections (miliaire, pneumocystose…)
Prolifération tumorale (lymphangite carcinomateuse, lymphome)
Connectivite
Pneumopathies Interstitielles idiopathiques
Granulomatose: sarcoïdose
Formes particulières : HPCL, LAM, protéinose alvéolaire, PCIE…
Chroniques fibrosantes
Aiguës, subaiguës
- PINS
- PINS PO
- PIC
- PO
- PIA
- DIP
- LIP
- PPFE

LBA

- Résultats variables en fonction du territoire lavé.
- Données du LBA non corrélées au pattern histologique de la PID-SSc.
- Résultats corrélés à la sévérité de la PID, mais impact pronostique propre controversé.

Goh et al. *Arthritis Rheum* 2007
Strange et al. *Am J Respir Crit Care Med* 2008
Kowal-Bielecka et al. *Semin Arthritis Rheum* 2010

- Pas de valeur prédictive d'une progression de la maladie ou d'une réponse au traitement.

Goh et al. *Arthritis Rheum* 2007
Strange et al. *Am J Respir Crit Care Med* 2008

Traitement

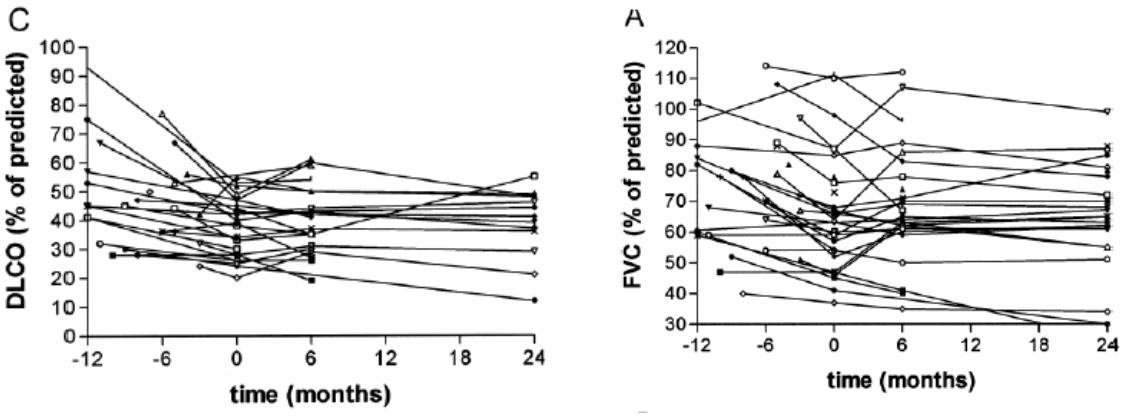
- Qui ?
- Quand ?
- Comment ?
- Combien de temps?

3 essais thérapeutiques avec le Cyclophosphamide

- Amélioration modeste voire non significative

Tashkin *et al.* N Engl J Med. 2006
Hoyles *et al.* Arthritis Rheum. 2006

- Bénéfice sur les formes aggravatives



Berezne *et al.* J Rheumatol. 2008

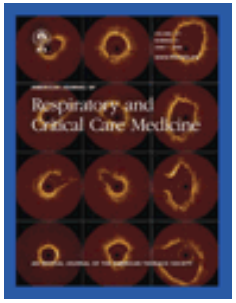
Mais attendre 6 mois = retard au traitement

Important de déterminer des facteurs pronostiques au diagnostic de la PID

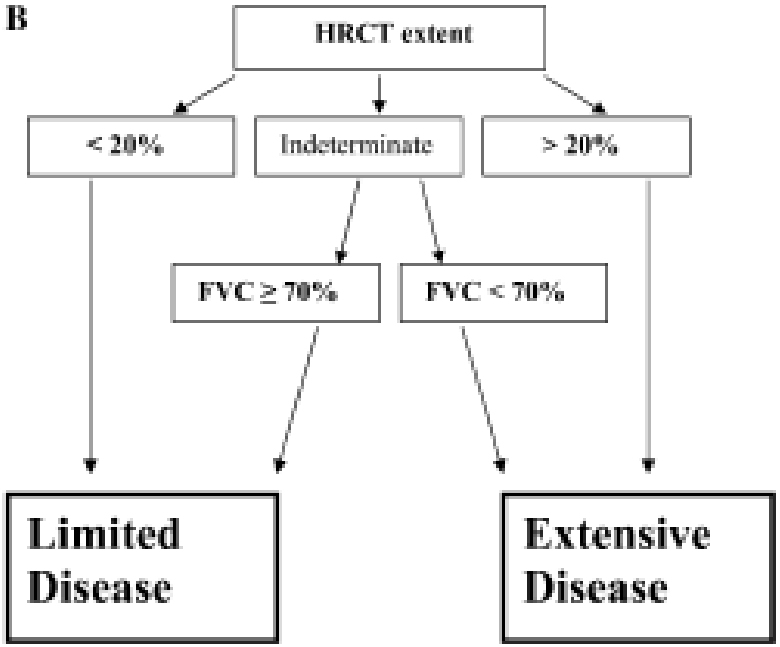
Interstitial Lung Disease in Systemic Sclerosis

A Simple Staging System

Nicole S. L. Goh[1], Sujal R. Desai[2], Srihari Veeraraghavan[1], David M. Hansell[1], Susan J. Copley[3], Toby M. Maher[1], Tamera J. Corte[1], Clare R. Sander[1], Jonathan Ratoff[1], Anand Devaraj[1], Gracijela Bozovic[1], Christopher P. Denton[4], Carol M. Black[4], Roland M. du Bois[1], and Athol U. Wells[1]



Algorithme pronostique



- 215 patients with SSc-ILD
- 2 radiologists, 2 physicians with > 18 mo of experience in ILD and 4 trainees (2 radiologists and 2 physicians, with 6 mo experience in ILD).
- Analysis required 1.49 ± 0.93 minutes/scan.
- Interobserver agreement was good for practitioners (k = 0.64), and fair to moderate for trainees (k = 0.41).

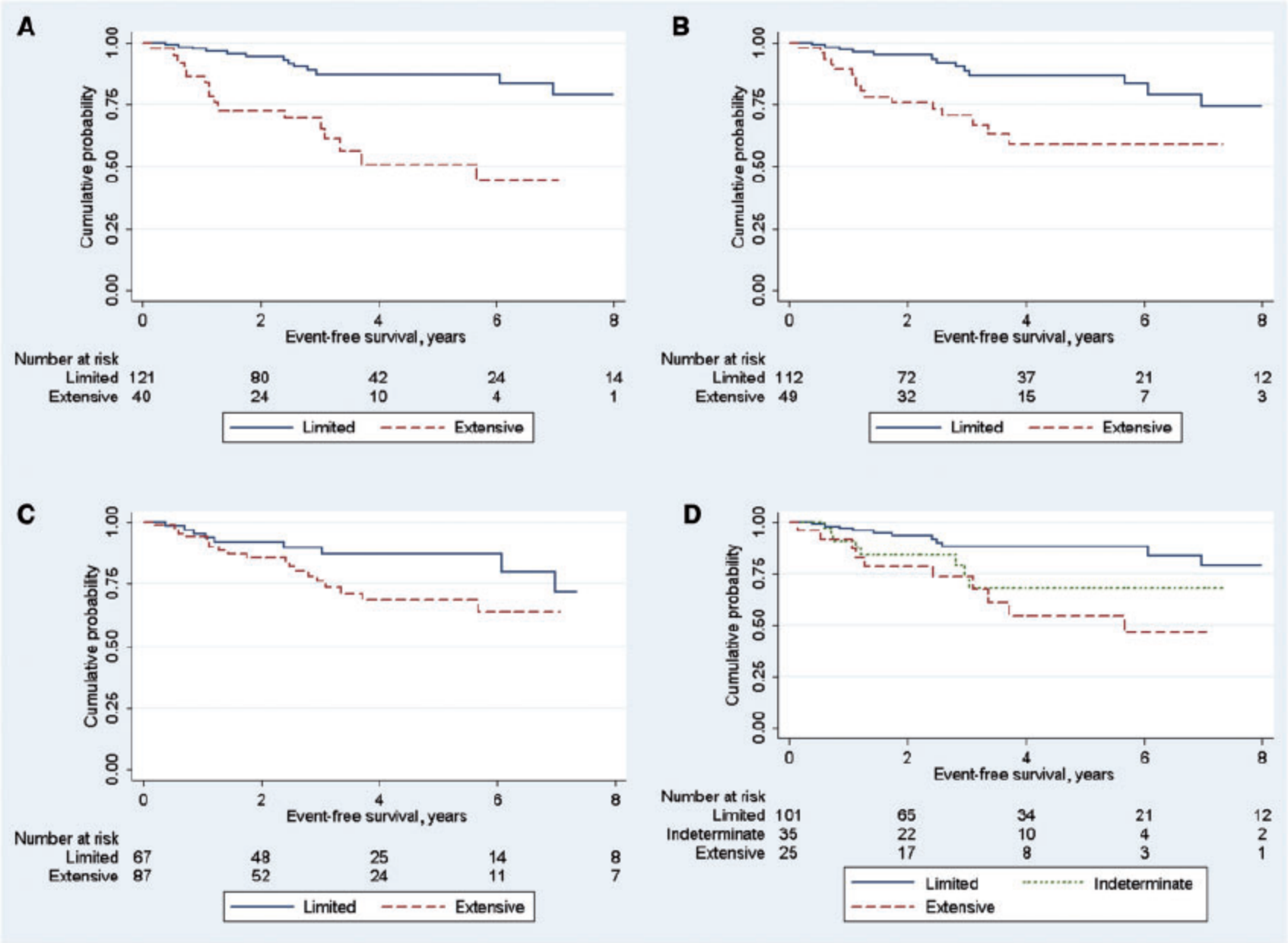
RHEUMATOLOGY

Rheumatology 2013;52:155–160
doi:10.1093/rheumatology/kes289
Advance Access publication 13 October 2012

Concise report

Extent of disease on high-resolution computed tomography lung is a predictor of decline and mortality in systemic sclerosis-related interstitial lung disease

Owen A. Moore[1], Nicole Goh[2,3], Tamera Corte[4], Hannah Rouse[5], Oliver Hennessy[5], Vivek Thakkar[1], Jillian Byron[1], Joanne Sahhar[6], Janet Roddy[7], Eli Gabbay[8], Peter Youssef[9], Peter Nash[10], Jane Zochling[11], Susanna M. Proudman[12,13], Wendy Stevens[1] and Mandana Nikpour[1,14]



Moore et al. *Rheumatology* 2013

Predictors of Mortality and Progression in Scleroderma-Associated Interstitial Lung Disease

A Systematic Review

Tiffany A. Winstone, MD; Deborah Assayag, MD; Pearce G. Wilcox, MD; James V. Dunne, MD; Cameron J. Hague, MD; Jonathon Leipsic, MD; Harold R. Collard, MD, FCCP; and Christopher J. Ryerson, MD

Predictors of mortality in SSc-ILD

Patient-specific variables

Age
Male gender

ILD-specific variables

SSc-specific variables

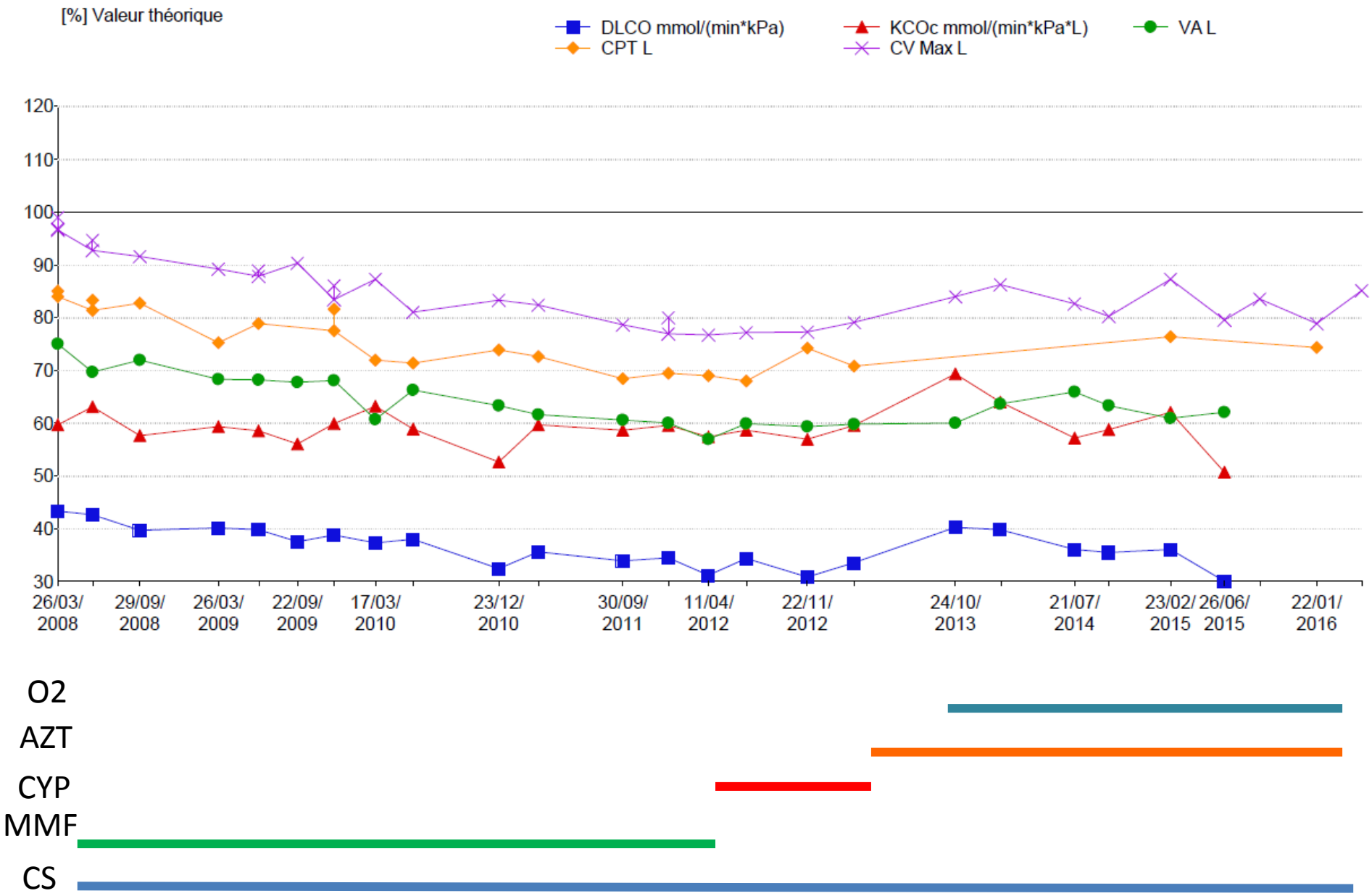
Anticentromere antibody
dSSc
LVEF
PAH/PH*
Pericardial effusion

Physiological variables
DLCO*
Δ DLCO at 3 yrs
End-stage lung disease
FEV_1
FVC*
FVC/DLCO
SpO_2

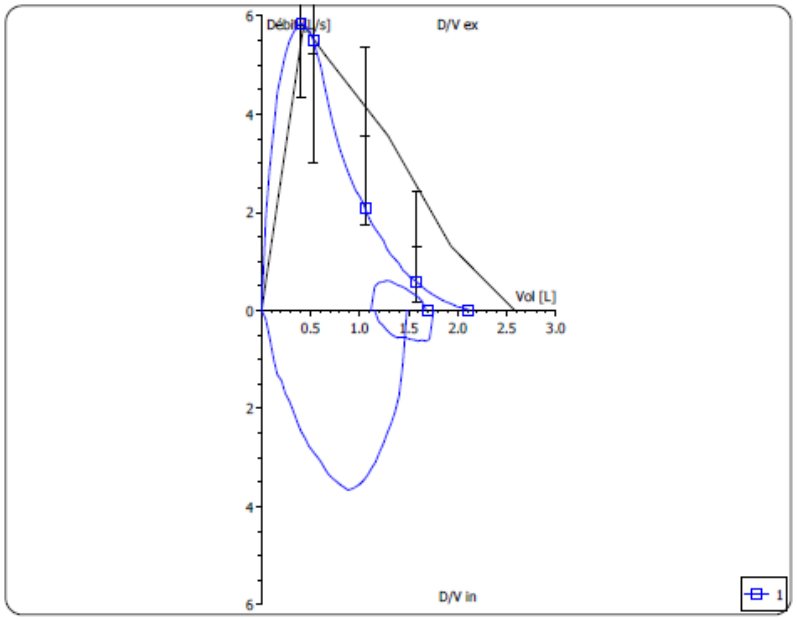
Radiological variables
Alveolar score
Extent of disease*
Presence of honeycombing
Proportion of ground glass
Reticulation

Bronchoscopic variables
Eosinophils >2%
Neutrophils >4%

Laboratory/Other variables
C-reactive protein
Elevated KL-6
Hemoglobin level
Rapid DTPA pulmonary clearanc

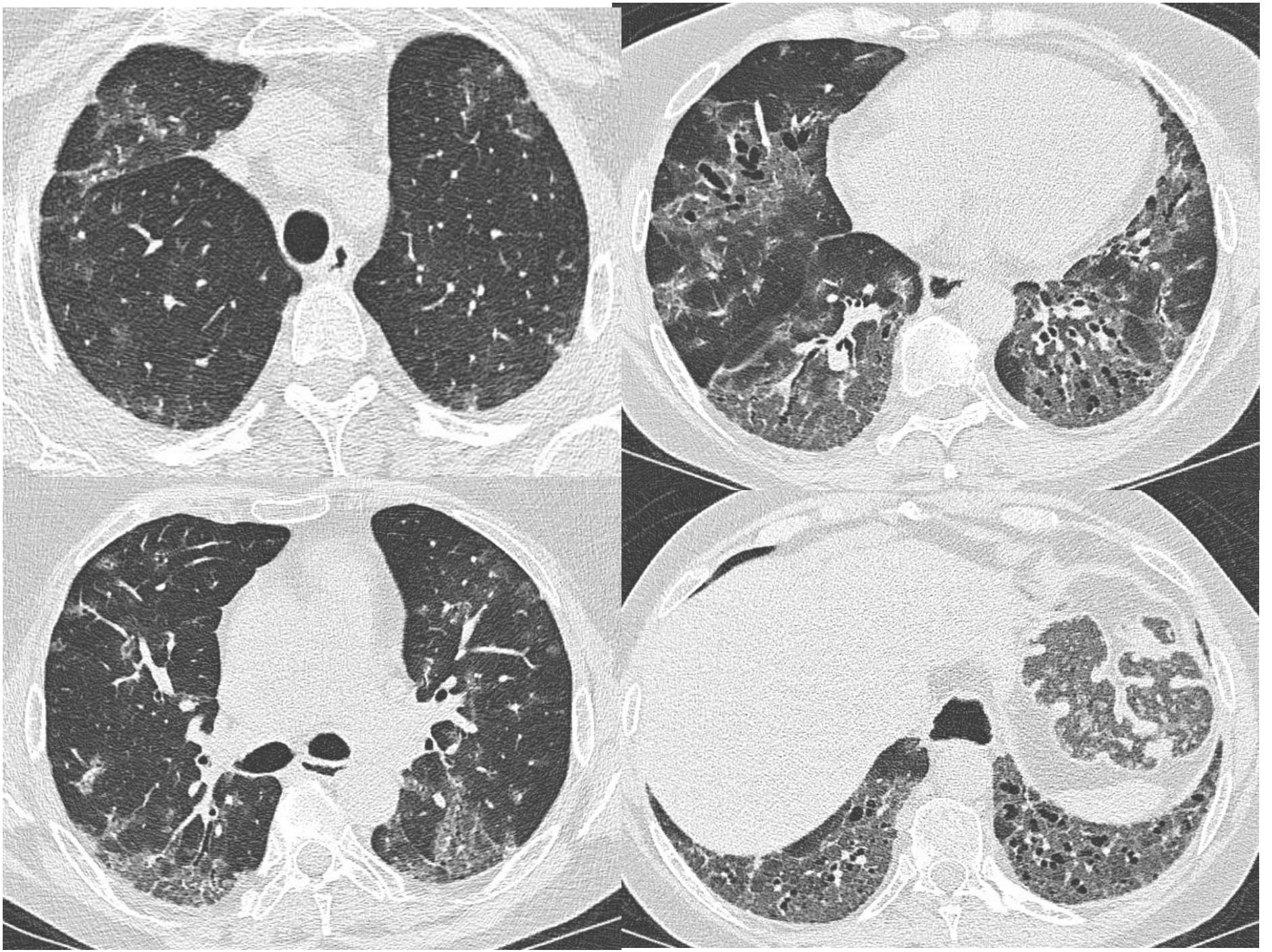

[%] Valeur théorique
DLCO mmol/(min*kPa)
KCOc mmol/(min*kPa*L)
VA L
CPT L
CV Max L
120
110
100
90
80
70
60
50
40
30
26/03/ 2008
29/09/ 2008
26/03/ 2009
22/09/ 2009
17/03/ 2010
23/12/ 2010
30/09/ 2011
11/04/ 2012
22/11/ 2012
24/10/ 2013
21/07/ 2014
23/02/ 2015
26/06/ 2015
22/01/ 2016
O2
AZT
CYP
MMF
CS

Basal 22/01/16 08:52:13 V



		Théo	Théo bas	Basal	%Théo
Date				22/01/16	
Heure				08:52:13	
Laboratoire				V	
Capacité Vitale plet	[L]	2.67	1.98	2.10	79
VR Pléthysmo.	[L]	1.80	1.23	1.34	74
Capacité totale pleth	[L]	4.64	3.65	3.44	74
VR % CPT	[%]	39.02	29.46	38.95	100
CRF pléthysmo.	[L]	2.60	1.78	1.76	68
VGT % CPT	[%]	54.54	44.81	51.11	94
R 0.5 IN	[kPa*s/L]	0.30	0.30	0.23	78
Cond spécif VA	[1/(KPA*S)]	1.04	1.04	1.22	117
CV Maximale	[L]	2.67	1.98	2.10	79
Capacité Inspiratoire	[L]	1.87	1.87	1.68	90
Volume Réserve Expi	[L]	0.79	0.79	0.42	53
CV Forcée	[L]	2.58	1.87	2.10	82
VEMS	[L]	2.17	1.54	1.69	78
VEMS % CV MAX	[%]	77.89	67.21	80.52	103
DEMM 25/75	[L/s]	2.89	1.49	1.59	55
Débit de pointe Expi	[L/s]	5.81	4.33	5.85	101
DEM 75	[L/s]	5.21	3.00	5.51	106
DEM 50	[L/s]	3.56	1.75	2.10	59
DEM 25	[L/s]	1.29	0.16	0.58	45

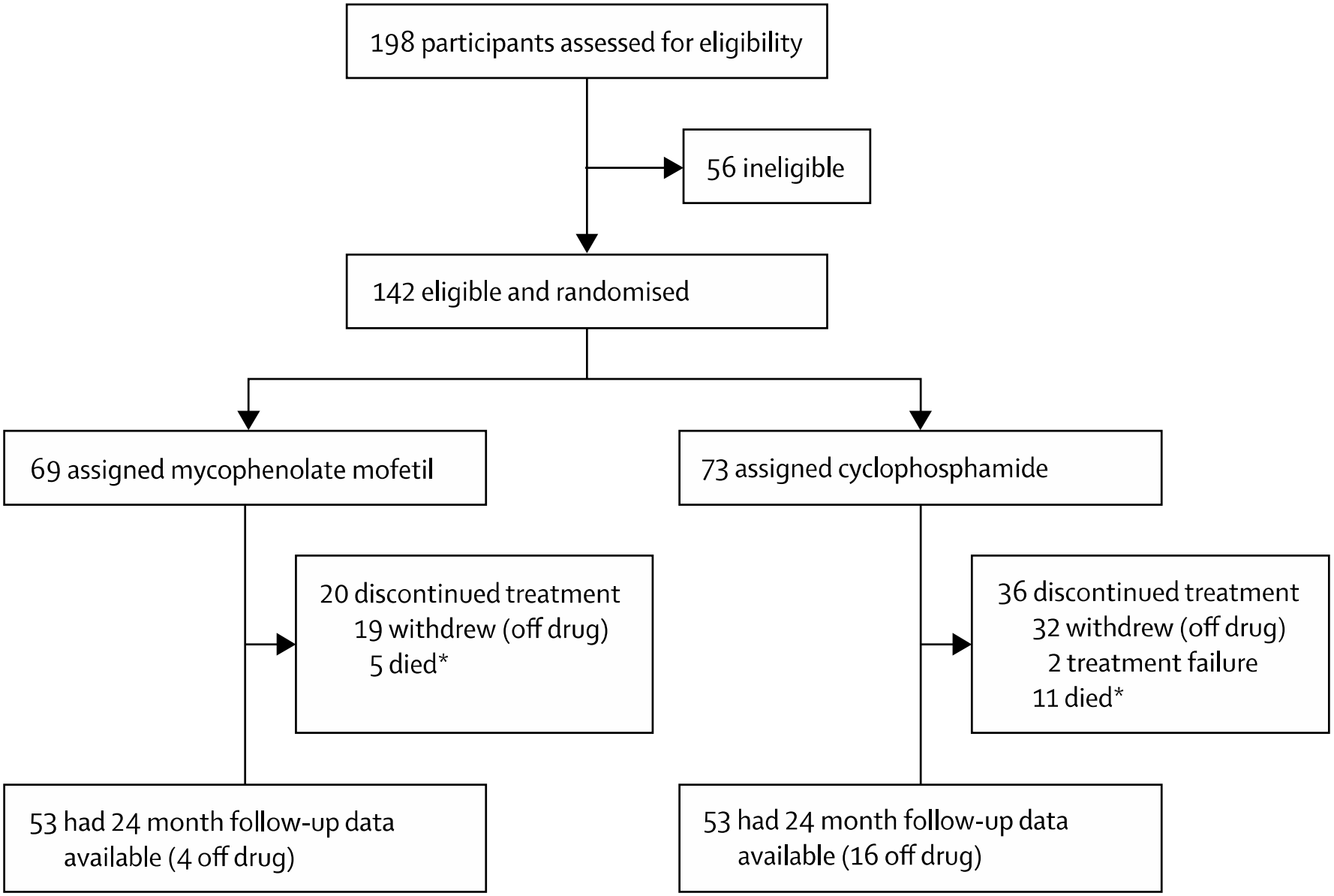
DLCOSB	7.29	2.62	36.0
KCO	1.57	0.96	61.4
Hb		12.2	
DLCOc	7.29	2.73	37.4
KCOc	1.57	1.00	63.8
VIN	2.67	2.09	78.5
CV MAX	2.67	2.27	85.1
VA-SB	4.49	2.72	60.6
TA		5.05	
DLNOSB	31.1	12.8	41.2
KNO		4.72	
Dm	14.10	6.51	46.2
Vc	56.5	19.6	34.8
NO/CO		4.89	



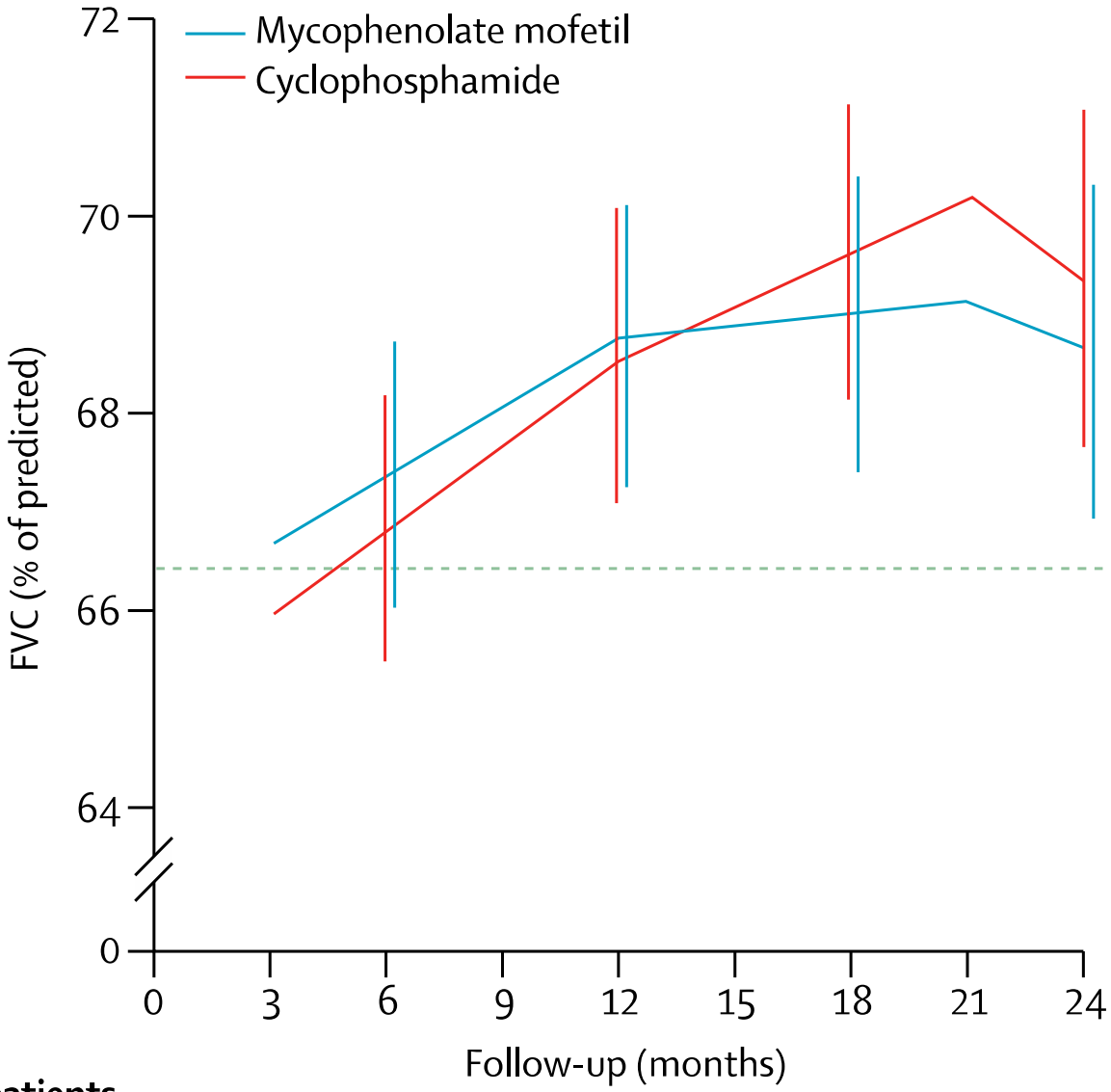
Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial

*Donald P Tashkin, Michael D Roth, Philip J Clements, Daniel E Furst, Dinesh Khanna, Eric C Kleerup, Jonathan Goldin, Edgar Arriola, Elizabeth R Volkmann, Suzanne Kafaja, Richard Silver, Virginia Steen, Charlie Strange, Robert Wise, Fredrick Wigley, Maureen Mayes, David J Riley, Sabiha Hussain, Shervin Assassi, Vivien M Hsu, Bela Patel, Kristine Phillips, Fernando Martinez, Jeffrey Golden, M Kari Connolly, John Varga, Jane Dematte, Monique E Hinchcliff, Aryeh Fischer, Jeffrey Swigris, Richard Meehan, Arthur Theodore, Robert Simms, Suncica Volkov, Dean E Schraufnagel, Mary Beth Scholand, Tracy Frech, Jerry A Molitor, Kristin Highland, Charles A Read, Marvin J Fritzler, Grace Hyun J Kim, Chi-Hong Tseng, Robert M Elashoff, for the Sclerodema Lung Study II Investigators**

www.thelancet.com/respiratory **Vol 4 September 2016**



Lancet Respir Med 2016; 4: 708–19



Number of patients

Mycophenolate mofetil	69	64	60	54	59	51	49	47	53
Cyclophosphamide	72	62	56	51	51	44	46	40	51

Lancet Respir Med 2016; 4: 708–19

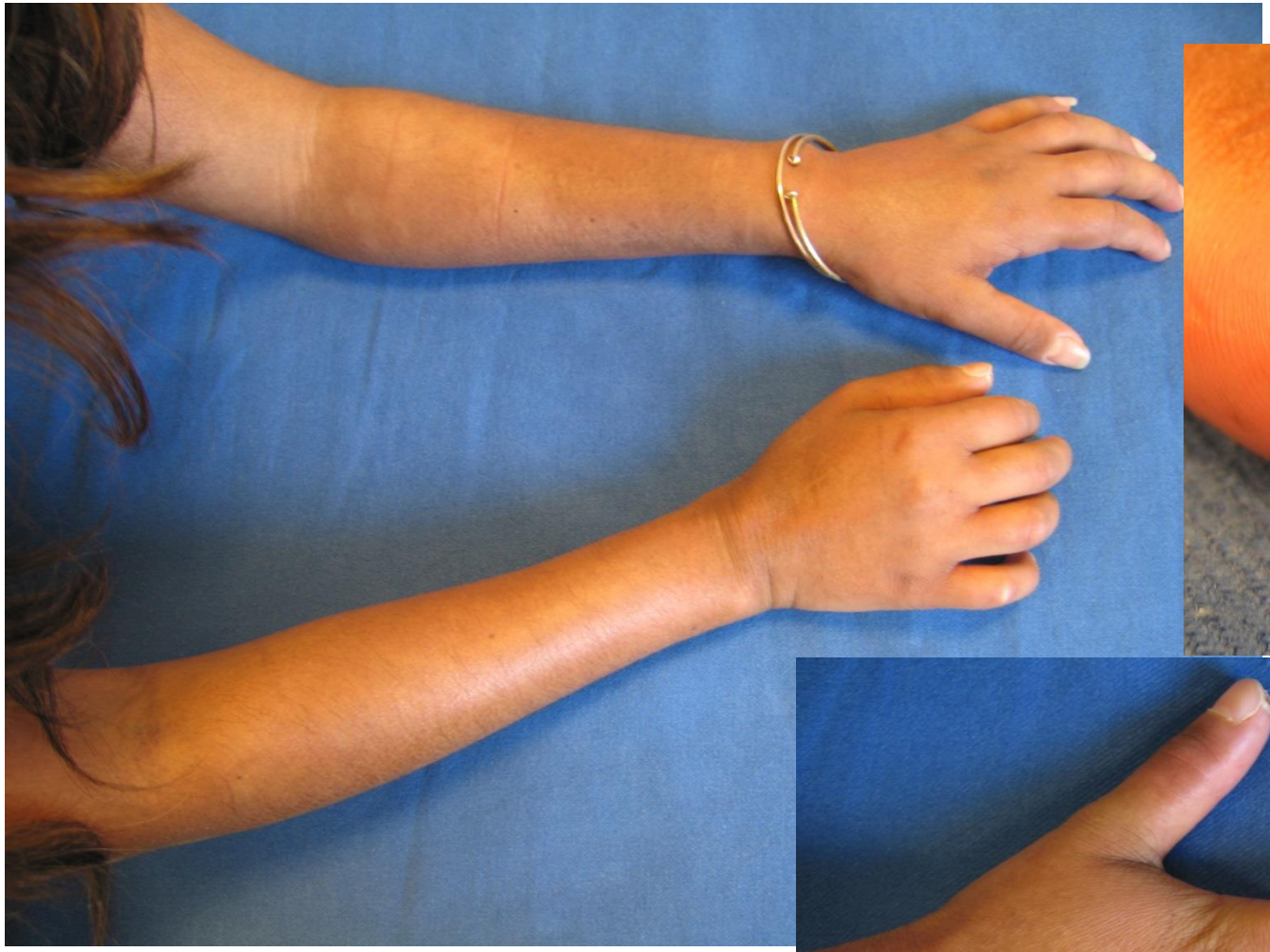
	Mycophenolate mofetil		Cyclophosphamide	
	Adverse events	Patients (n=69)	Adverse events	Patients (n=73)
Adverse events*				
Leucopenia†	5	4 (6%)	51	30 (41%)
Neutropenia	3	3 (4%)	7	5 (7%)
Anaemia	18	8 (12%)	26	13 (18%)
Thrombocytopenia	0	0	7	4 (6%)
Haematuria	3	3 (4%)	2	2 (3%)
Pneumonia	6	5 (7%)	4	4 (6%)
Serious adverse events‡				
Total	42	27 (39%)	36	22 (30%)
Related to treatment§	3	3 (4%)	8	7 (10%)
Related to underlying disease§	16	9 (13%)	16	13 (18%)
Due to other causes§¶	22	14 (20%)	11	6 (8%)
Unknown cause§	3	3 (4%)	3	3 (4%)
Death	..	5 (7%)	..	11 (15%)

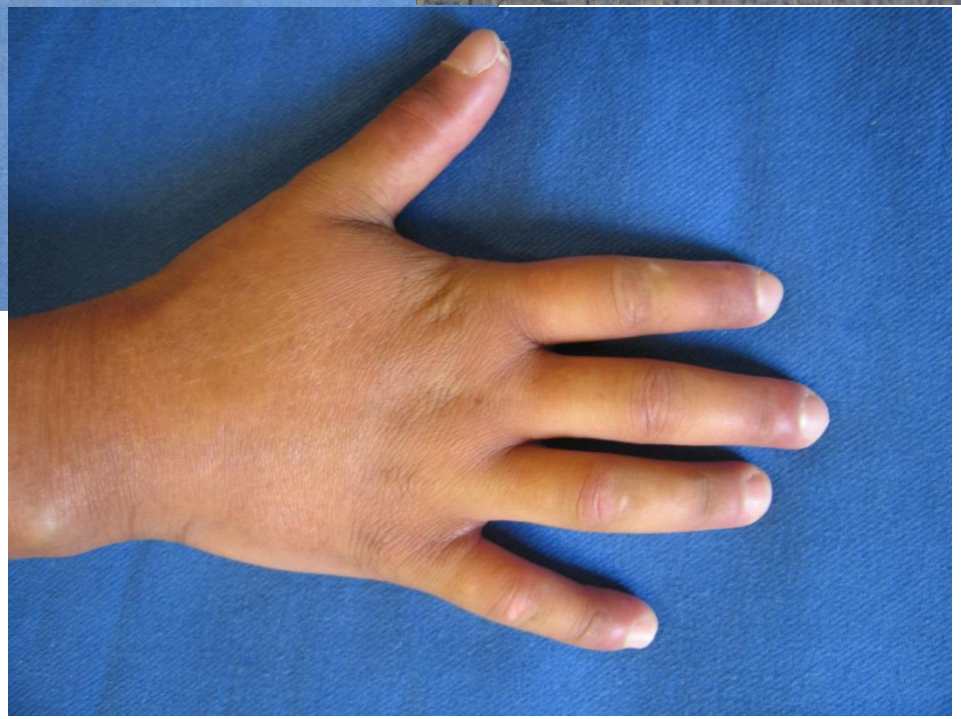
Lancet Respir Med 2016; 4: 708–19

Observation 2 – Mme R. née en 1983

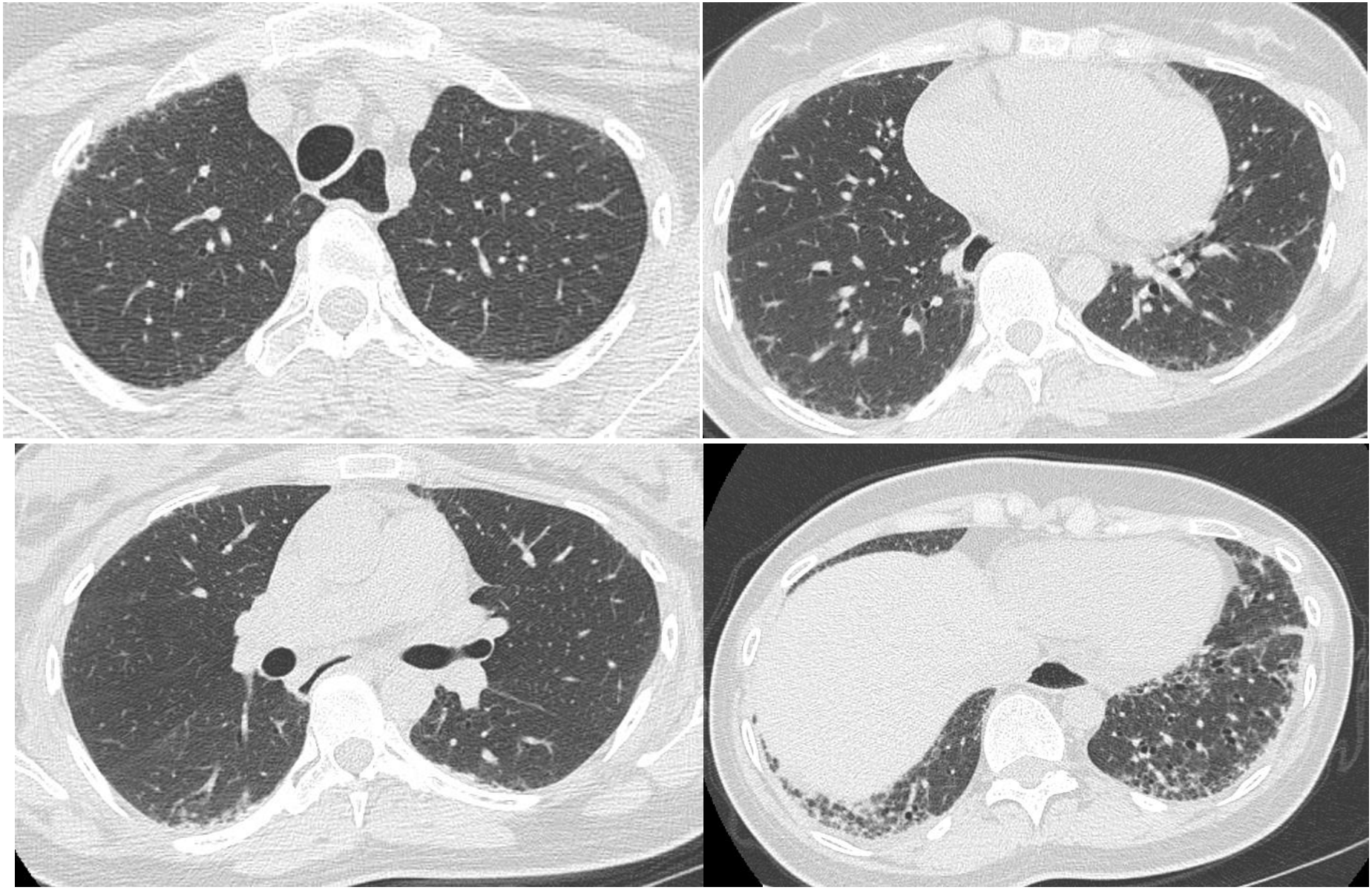
- **Motif de Consultation: adressée par le service de dermatologie pour sclérodermie avec PID**

- **Mode de Vie**
  - Née en Guyane, secrétaire, tabac 0, 6 canaris
- **ATCD**
  - Pas de notion de PID dans la famille ni de connectivite
- **HDLM**
  - 2007 Sclérodermie systémique cutanée diffuse
    - Atteinte cutanée diffuse
    - Raynaud
    - Atteinte oesophagienne
    - Atteinte musculaire prouvée
    - AAN 1/160ème moucheté type centromères





EFR 2007: CVF 1670 ml (49 %), CPT 2470 ml (54%), TLCO à 44%



05 / 2008

- **TM6 :** distance parcourue 472 m désaturation de 97 à 92 %
- **EFR :** stabilité des volumes pulmonaires, amélioration de la DLCO
  CVF à 1100 ml (31 % Theo)
  CPT à 1720 ml (38 %)
  CVF à 1080 ml (34 %)
  DLCO à 29 %

- **Echographie cardiaque:** normale, notamment PAPs estimée à 21 mmHg

- **Traitement :**
  - Cellcept : 2 g par jour
  - Cortancyl : 16 mg par jour
  - Bitildiem 120 : 1 cp x 2 par jour.
  - Fonzilane 300 : 1 cp x 2/jour
  - Triatec 1,25 : 1 cp par jour
  - Cacit D3 : 1 sachet par jour
  - Inexium 40 : 1 cp par jour
  - Motilium : 1 cp x 3 par jour.
- consultation dans un centre de transplantation pulmonaire

Crise rénale sclérodermique

5 % des patients ayant une Sclérodermie systémique

Anticorps anti-RNApolymerase III (10% des SSc ; 15% SSc cutanées diffuses)

CS > 15 mg/j dans les 3 mois

Table 1. Main clinical and biological manifestations of scleroderma renal crisis from the literature.

	Steen, et al[2]	Walker, et al[6]	DeMarco, et al[5]	Penn, et al[8]	Teixeira, et al[7]	Guillevin, et al[72]	Hudson, et al[70]
Type of study	R	R	R	R	R	R	P
No. patients	195	16	18	110	50	91	75
Age, yrs	50	54	45	51	53	53	52.5
Sex, % males	25	31	17	21	26	22	33.3
Symptoms < 4 years, %	76	69	100	66 (< 1 y)	86	79 (< 3 y)	32 (< 1 y)
Diffuse SSc, %	83	100	100	78	86	85.7	74.7
Antitopoisomerase 1 antibodies, %	20	6	ND	17.2	32	31	25.3
Anticentromere antibodies, %	1	ND	ND	1.8	0	3.4	4
Hypertension, %	90	94	ND	ND	88	85.7	93.3
Systolic/diastolic BP, mmHg	184/108	203/113	130/76	193/114	189/111	184/107	ND/ND
Pericarditis, %	53	ND	ND	ND	6	ND	33.3
Left ventricular insufficiency, %	25	56	39	31	46	46	ND
Arrhythmia, %	ND	ND	ND	ND	18	ND	ND
Seizures, %	8	12	ND	ND	10	ND	ND
Hypertensive encephalopathy, %	ND	ND	ND	ND	34	58	ND
Intracerebral hemorrhage, %	ND	ND	ND	ND	10	ND	ND
Thrombotic microangiopathy, %	30	81	ND	59	46	56	ND
Platelet count < 150,000/mm^3, %	39	ND	ND	50	ND	ND	ND
Hematuria, %	38	ND	ND	ND	42*	42*	ND
Proteinuria, %	63 (> 0.25 g/d)	ND	ND	ND	53 (> 0.5 g/d)	68	ND

* Hematuria documented with dipstick measurement or urinalysis. SSc: systemic sclerosis; BP: blood pressure; ND: not documented; P: prospective; R: retrospective.

Mouthon et al. *J Rheumatol.* 2015

Table 2. Prognosis of scleroderma renal crisis from the literature.

	Steen, et al[2]	Walker, et al[6]	DeMarco, et al[5]	Penn, et al[8]	Teixeira, et al[7]	Guillevin, et al[72]	Hudson, et al[70]
No. patients	195	16	18	110	50	91	75
Patients under dialysis, %	43	31	ND	64	56	54	53
Temporarily	23	6	ND	23	16	14	ND
Permanently	19	25	ND	42	22	39	25 (at 1 yr)
Died while under dialysis	ND	ND	ND	18	18	26	ND
Dead at 5 yrs, %	19*	31	50	41	31	40	36**

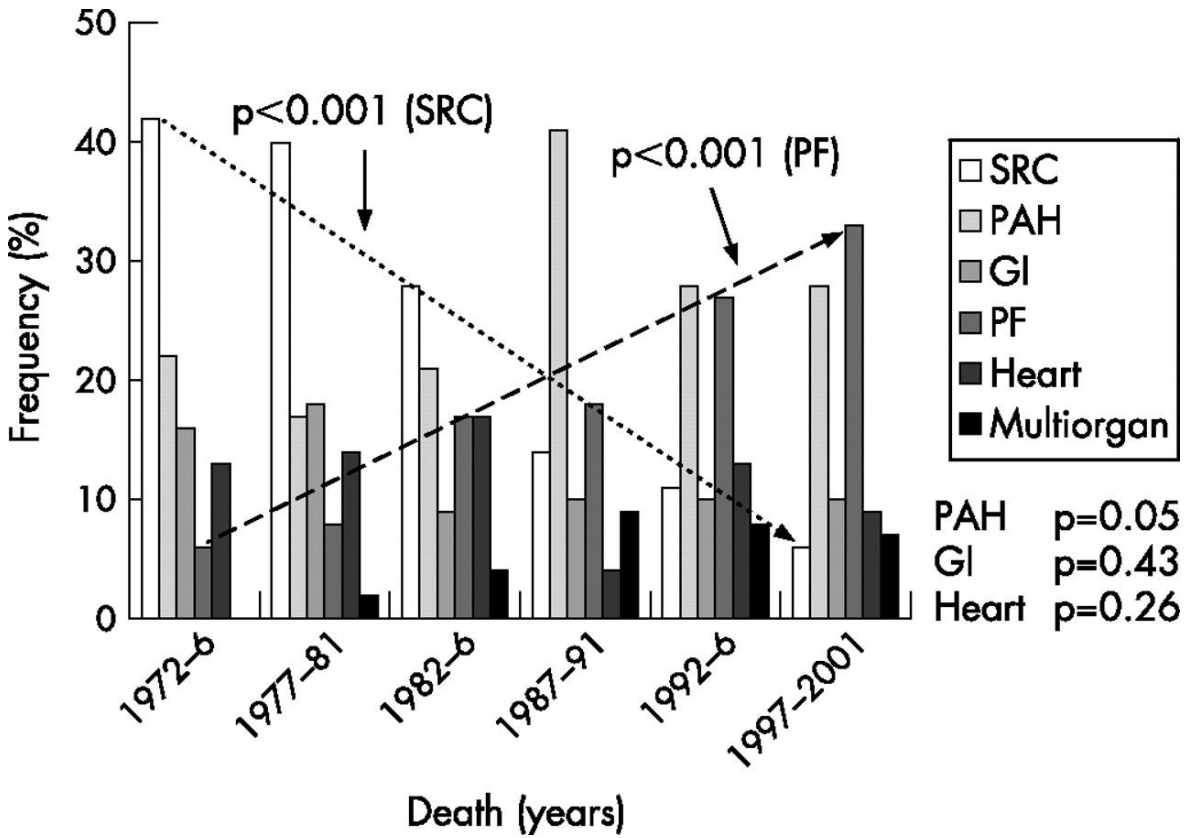
Scleroderma renal crisis (SRC):

- HTA maligne & I rénale aiguë oligo-anurique
- Plus fréquent chez les patients sous CS
- Déclenché par nephrotoxiques ou depletion vasculaire
- PBR non indispensable mais élément pronostique
- Pronostic (5-year survival 65%) amélioré avec introduction des IEC

Changes in causes of death in systemic sclerosis, 1972–2002

Virginia D Steen, Thomas A Medsger

Ann Rheum Dis 2007;**66**:940–944. doi: 10.1136/ard.2006.066068



PID: cause directe de 40% des DC et facteur contributif majeur dans 27% des autres cas

Outcome of Patients with Systemic Sclerosis in the Intensive Care Unit

Frédéric Pène, Tarik Hissem, Alice Bérezné, Yannick Allanore, Guillaume Geri, Julien Charpentier, Jérôme Avouac, Loïc Guillevin, Alain Cariou, Jean-Daniel Chiche, Jean-Paul Mira, and Luc Mouthon

2006 - 2012
41 patients

ICU survival
28 patients (68.2%)

Hospital survival
25 patients (61%)

6-month survival
22 patients * (53.6%)

One-year survival
16 patients ** (39%)

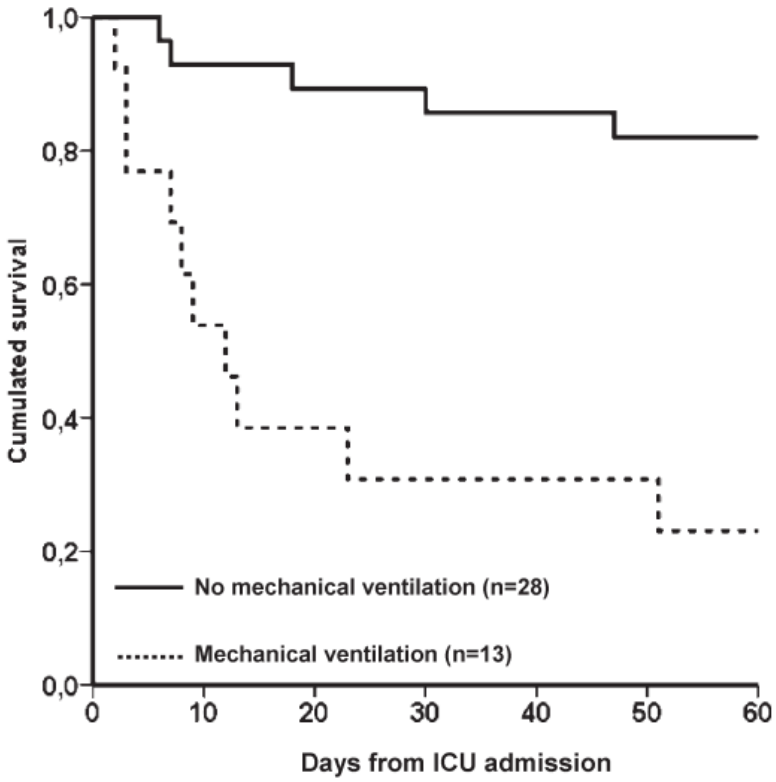
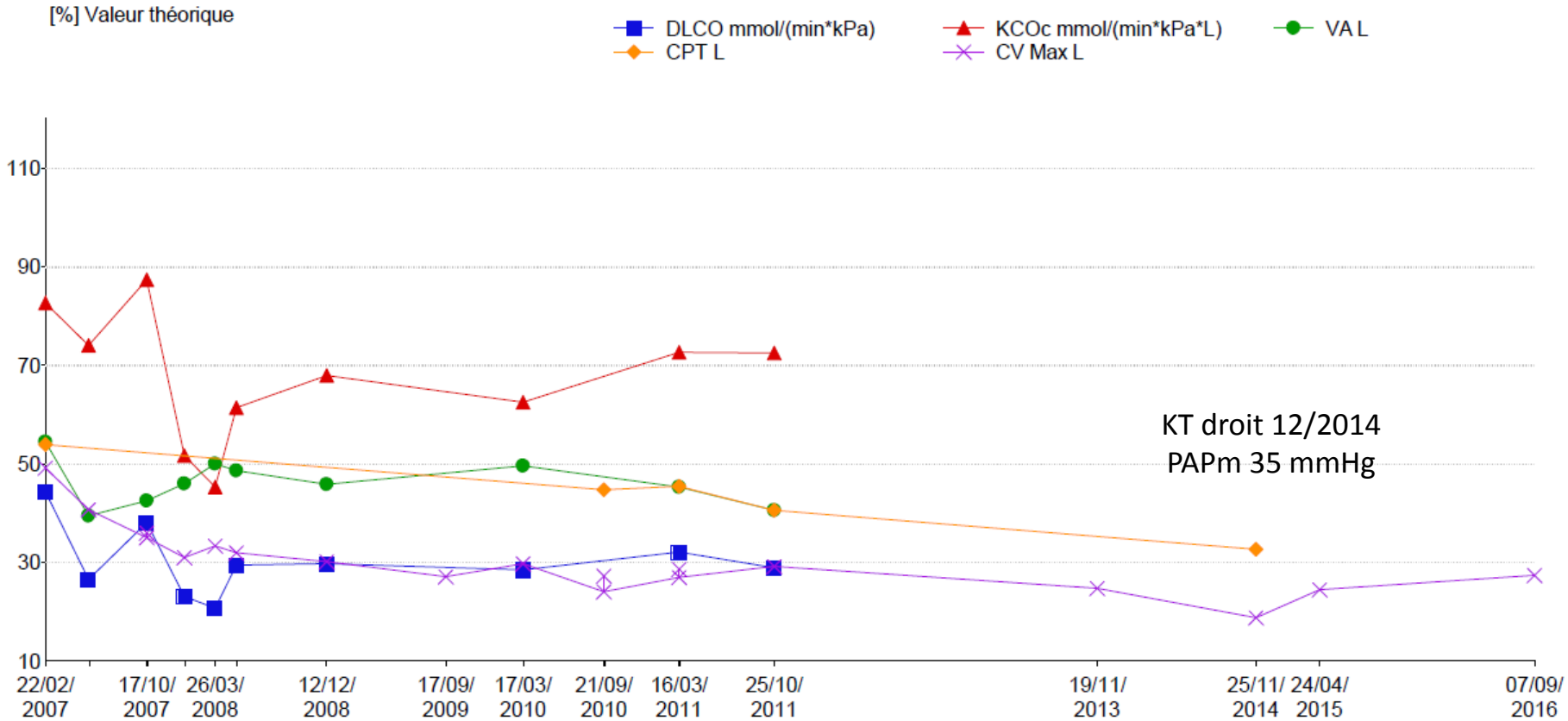
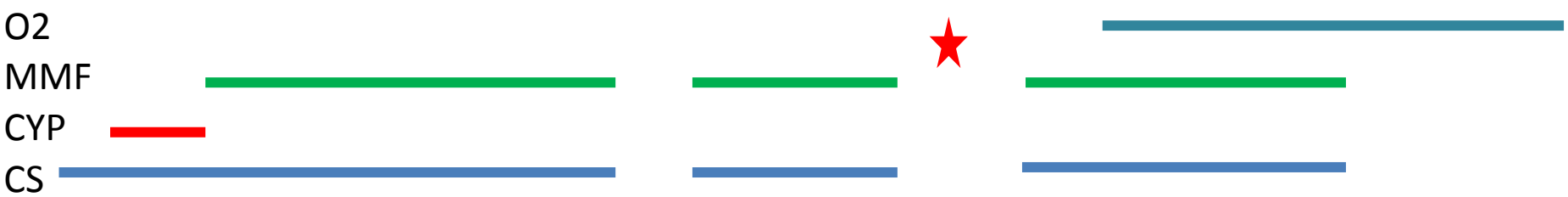


Figure 2. Survival according to the requirement of endotracheal intubation and mechanical ventilation. Log-rank test $p < 0.001$. ICU: intensive care unit.

The Journal of Rheumatology 2015; 42:8; doi:10.3899/jrheum.141617


[%] Valeur théorique
DLCO mmol/(min*kPa)
KCOc mmol/(min*kPa*L)
VA L
CPT L
CV Max L
110
90
70
50
30
10
22/02/ 2007
17/10/ 2007
26/03/ 2008
12/12/ 2008
17/09/ 2009
17/03/ 2010
21/09/ 2010
16/03/ 2011
25/10/ 2011
19/11/ 2013
25/11/ 2014
24/04/ 2015
07/09/ 2016
KT droit 12/2014
PAPm 35 mmHg


O2
MMF
CYP
CS

10/2016 : CVF=1.03L (29%), VEMS=980mL (33%);
GDS sous 2L/min: pH 7.37, PaOC2= 49, PaO2= 74 ; TM6: 210m (29%) Nadir 78%.

Transplantation Pulmonaire au cours de la Sclérodermie

Table 1 Demographic characteristics of systemic sclerosis patients who have undergone lung transplantation.

Reference	*N*	Mean age	Sex female:male	PAH (%)	ILD (%)	Type of lung transplant
Massad 2005	47	46	27:20	NA	NA	27 SLT 20 DLT
Schachna 2006	29	46.6	16:13	11	15	9 DLT 18 SLT 2 HLT
Shitrit 2009	7	52	5:2	6 (84)	7 (100)	7 SLT
Saggar 2010	15	53.2	4:11	2	6	1 SLT 14 DLT
Crespo 2011	67	49	NR	NR	NR	NR
Sottile 2011	22	NR	NR	NR	22 (100)	NR
Pakhale 2002	9	NR	5:4	NR	NR	7 DLT 2 SLT

PAH Pulmonary arterial hypertension, ILD Interstitial lung disease, SLT Single lung transplant, DLT Double lung transplant, HLT Heart lung transplant.

Khan et al. *Respir Med* 2013

Table 2 Survival post-lung transplantation in systemic sclerosis.

Reference	*N*	30 day survival		6-month survival		1-year survival		2-year survival		3-year survival	
		SSc	Non-SSc	SSc	Non SSc	SSc	Non-SSc	SSc	Non-SSc	SSc	Non-SSc
Pakhale 2002	9	88.9%	NA	NR	NA	NR	NA	NR	NA	NR	NA
Massad 2005	47	85%	NR	NR	NR	67.6%	75.5%	58%	66.5%	45.9%	58.8%
Schachna 2006	29	69%	80% ILD 79% IPAH	69%	80% ILD 79% IPAH	59%	59% ILD 74% IPAH	52%	37% ILD 58% IPAH	NR	NR
Shitrit 2009	7	NR	NR	NR	NR	88%	84%	NR	NR	73%	NR
Saggar 2010	15	NR	NR	NR	NR	93.4%	86.9%	80%	71.1%	NR	NR
Crespo 2011	67	91%	95%	NR	NR	73%	86%	NR	NR	NR	NR
Sottile 2011	22	NR	NR	85%	90% ILD 90% IPAH	79%	83% ILD 90% IPAH	NR	NR	68%	69% ILD 90% IPAH

SSc Systemic sclerosis, Non-SSc Non systemic sclerosis, ILD Interstitial lung disease, IPAH Idiopathic pulmonary arterial hypertension, NA Not applicable, NR Not reported.

Khan et al. *Respir Med* 2013

Presse Med. 2014; 43: e345–e363
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on line on
www.em-consulte.com/revue/lpm
www.sciencedirect.com

SYSTEMIC SCLEROSIS

Quarterly Medical Review

Lung and heart-lung transplantation for systemic sclerosis patients. A monocentric experience of 13 patients, review of the literature and position paper of a multidisciplinary Working Group

David Launay[1,2,3], Laurent Savale[4,5,6], Alice Berezne[7,17], Jérôme Le Pavec[4,6,8,17], Eric Hachulla[1,2,3], Luc Mouthon[7], Olivier Sitbon[4,5,6], Benoit Lambert[9], Marianne Gaudric[10], Xavier Jais[4,5,6], Francois Stephan[11], Pierre-Yves Hatron[1,2], Nicolas Lamblin[1,12], Olivier Vignaux[13], Vincent Cottin[14], Dominique Farge[15], Benoît Wallaert[1,16], Loic Guillevin[7], Gerald Simonneau[4,5,6], Olaf Mercier[4,6,8], Elie Fadel[4,6,8], Philippe Dartevelle[4,6,8], Marc Humbert[4,5,6], Sacha Mussot[4,6,8], On behalf of the Working Group on Heart/Lung transplantation in systemic sclerosis of the French Network on Pulmonary Hypertension

TABLE II

Outcome of our 13 SSc patients undergoing lung or heart-lung transplantation

Patients No	Date of transplantation	Time of follow-up	Outcome	Cause of death
1	Feb. 1993	74 months	Dead	Faecal peritonitis
2	May 1994	83 months	Dead	BOS
3	Dec. 2000	133 months	Alive	–
4	Oct. 2003	44 months	Dead	Renal insufficiency
5	May 2008	45 months	Alive	–
6	Jan. 2009	5 months	Dead	Septicaemia *S. aureus*
7	Jul. 2009	7 months	Dead	Multifactorial cause
8	Oct. 2009	28 months	Alive	–
9	Sep. 2010	21 days	Dead	Primary graft dysfunction
10	Dec. 2010	20 days	Dead	*S. aureus* pneumoniae, septic shock with acute renal insufficiency
11	Feb. 2012	5 months	Alive	–
12	Jun. 2012	1 months	Alive	–
13	Jul. 2012	3 days	Dead	Acute cerebellar infarction

Launay et al. PressMed 2014

Absolute contraindications

- Untreatable organ failure other than lung (especially creatinine clearance < 50 mL/min/1.73 m^2 using the modification of diet in renal disease formula, liver);
- Non-curable chronic extrapulmonary infection including chronic active viral hepatitis B, hepatitis C, HIV;
- Active or recent neoplasia (less than 2 years), except for basal cell or squamous cutaneous tumours and fully resected carcinomas in situ. A waiting period of 5 years is recommended for high grade tumours of the colon, breast and kidney and for melanomas of stage III or above;
- Active smoking or other substance addiction within the last 6 months;
- Uncontrolled psychiatric or psychological disorders associated with the inability to cooperate or comply with medical therapy;
- Major spinal/thoracic deformity and degenerative neuromuscular diseases likely to seriously impair ventilation mechanics;
- Documented non-adherence with medical therapy or follow-up;
- Body mass index (BMI) < 15 kg/m^2.

Relative contraindications

- Age > 65 years for single or bilateral LT, and > 55 years for HLT;
- Severe or symptomatic osteoporosis;
- Previous thoracic surgery;
- Under nutrition ($15 <$ BMI < 17 kg/m^2) or obesity (BMI > 30 kg/m^2);
- Invasive mechanical ventilation;
- Colonisation with resistant bacteria, fungi or mycobacteria;
- Severe loss of autonomy with poor rehabilitation potential;
- Uncontrolled comorbidities (systemic hypertension, diabetes mellitus).

Proposed systemic sclerosis specific contraindications

- Uncontrolled active inflammatory myopathy; progressive myopathy; myopathy with diaphragm involvement;
- Digital ulcers:
  - > 1 severe episode/year despite optimal treatment;
  - active digital ulcer: temporary contraindication.
- gastrointestinal:
  - oesophageal stricture;
  - active and severe upper gastrointestinal ulcerations despite optimal treatment, including proton pump inhibitors and prokinetics;
  - high grade dysplasia in a Barett's esophagus;
  - gastroparesis (abnormal gastric emptying [< 25% clearance at 90 min post-ingestion]) despite medical treatment;
  - chronic gastrointestinal bleeding with or without anaemia;
  - symptomatic involvement of the small intestine, such as malabsorption and pseudo-obstruction.
  - colorectal involvement with pseudo-obstruction, and/or diverticulitis and/or perforation.
- heart:
  - conduction abnormalities and/or rhythm disturbances (symptomatic bradycardia, ventricular and atrial tachycardia): these must be managed prior to LT (implantation of a pacemaker, where appropriate) but are not a contraindication if HLT is considered.
- kidney:
  - renal function should have been stable for 3 months except in the case of acute functional renal failure related to right ventricle dysfunction;
  - interval < 3 years between SRC and HLT/LT;
  - increased risk of scleroderma renal crisis:
    a. diffuse systemic sclerosis evolving for less than 3 years since the first non-Raynaud sign/symptom;
    b. rapidly progressive and severe cutaneous involvement: progression of the cutaneous involvement characterised by an increase of more than 25% in Rodnan score within 6 to 12 months;
    c. corticosteroids > 15 mg prednisone (or equivalent)/day.

THE LANCET

Treatment of systemic sclerosis with autologous haemopoietic stem cell transplantation

A Tyndall, C Black, J Finke, J Winkler, R Mertlesmann, H H Peter, A Gratwohl

Vol 349 • January 25, 1997

EXTENDED REPORT

Autologous stem cell transplantation in the treatment of systemic sclerosis: report from the EBMT/EULAR Registry

D Farge, J Passweg, J M van Laar, Z Marjanovic, C Besenthal, J Finke, H H Peter, F C Breedveld, W E Fibbe, C Black, C Denton, I Koetter, F Locatelli, A Martini, A V N Schattenberg, F van den Hoogen, L van de Putte, F Lanza, R Arnold, P A Bacon, S Bingham, F Ciceri, B Didier, J L Diez-Martin, P Emery, W Feremans, B Hertenstein, F Hiepe, R Luosujärvi, A Leon Lara, A Marmont, A M Martinez, H Pascual Cascon, C Bocelli-Tyndall, E Gluckman, A Gratwohl, A Tyndall

Ann Rheum Dis 2004;**63**:974–981. doi: 10.1136/ard.2003.011205

ARTHRITIS & RHEUMATOLOGY
Vol. 68, No. 10, October 2016, pp 2361–2371
DOI 10.1002/art.39748
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REVIEW

Hematopoietic Stem Cell Transplantation for Scleroderma

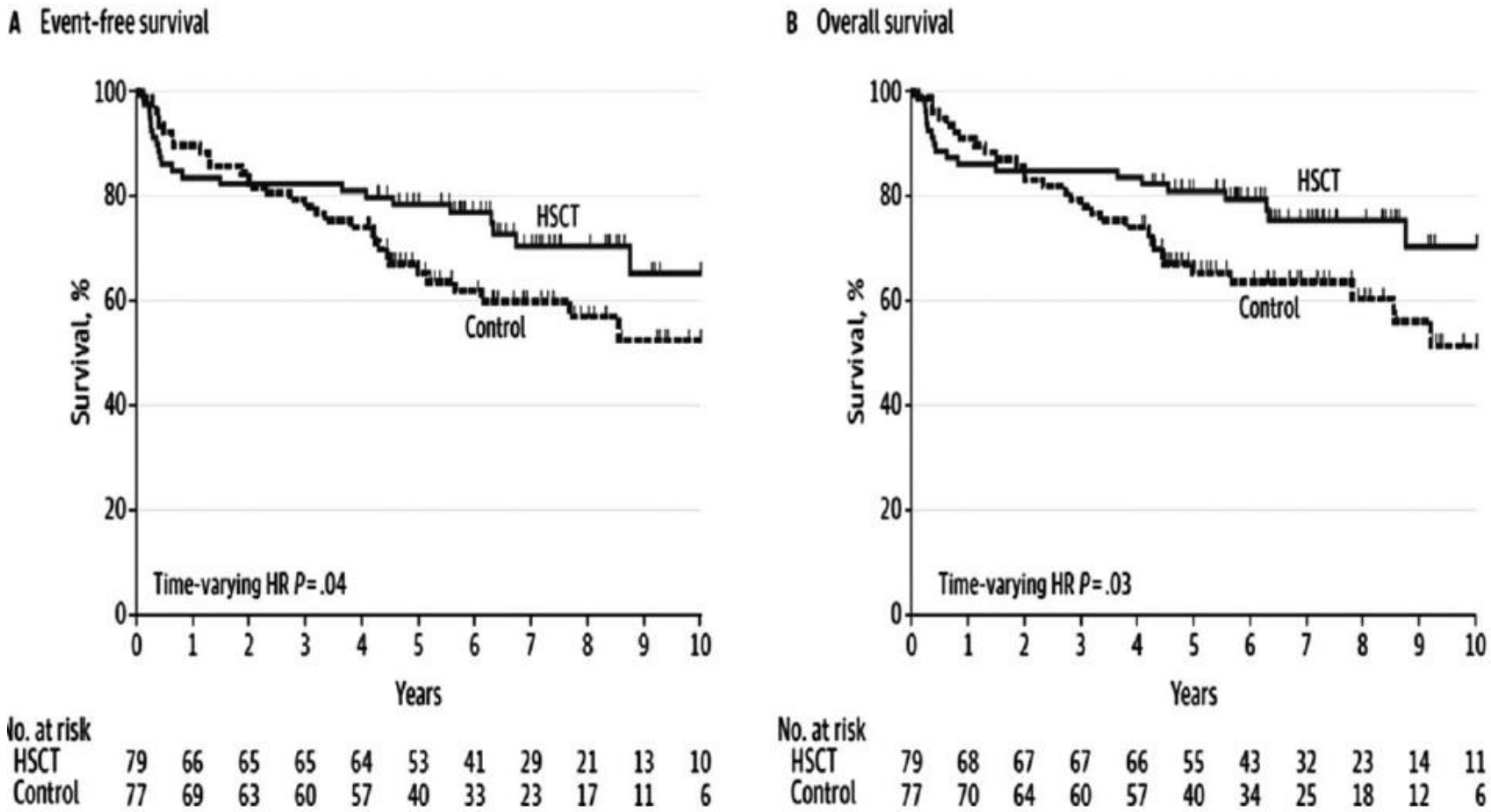
Effective Immunomodulatory Therapy for Patients With Pulmonary Involvement

Keith M. Sullivan,[1] Ankoor Shah,[1] Stefanie Sarantopoulos,[1] and Daniel E. Furst[2]

Table 1. Randomized trials of HSCT in SSc*

	ASSIST	ASTIS	SCOT
No. of centers	1	29	25†
Location of centers	US	Europe	US
Year of first randomization	2006	2001	2006
Year of last randomization	2009	2009	2011
No. of patients enrolled or screened	45	NA	205‡
No. of patients randomized	19	156	75
No. of patients randomized per year	6	19	15
Age range, years	<60	18–65	18–65
Diffuse cutaneous SSc	Yes	Yes	Yes
Primary end point	Improvement at 12 months	Organ failure–free survival at 24 months	Organ failure–free survival at 54 months
Inclusion criteria			
SSc duration, years	≤4	<2 or ≤4	≤5
MRSS	≥15	≥20 or ≥15	≥16
SSc internal disease	Yes	Yes or no	Yes
FVC, % predicted	<80 or 10% decrease	<80	70–45
DLCO, % predicted	<80	80–40	70–45
ILD§	Yes	Yes or no	Yes
Exclusion criteria			
TLC, % predicted	<45	–	–
LVEF, %	<40	<45	<50
PAP, mean mm Hg	>25	>50¶	>30
Duration of prior CYC	>6	>5	>6
Treatment regimen			
CYC arm	CYC 1,000 mg/m^2/month IV × 6 (6 gm/m^2 over 6 months)	CYC 750 mg/m^2/month IV × 12 (9 gm/m^2 over 12 months)	CYC 750 mg/m^2/month IV × 12 (9 gm/m^2 over 12 months)
HSCT arm	CYC 200 mg/kg, ATG (rabbit) 6.5 mg/kg, and methylprednisolone 5,000 mg	CYC 200 mg/kg and ATG (rabbit) 7.5 mg/kg	CYC 120 mg/kg, ATG (horse) 90 mg/kg, and TBI 800 cGy#
Autologous cells	Unselected	CD34 selected	CD34 selected
Stem cell mobilization	CYC 2 gm/m^2 and G-CSF	CYC 4 gm/m^2 and G-CSF	G-CSF only
Crossover treatment	Yes	No	No

Follow-up, years	2.6 (mean)	5.8 (median)	Ongoing (minimum 4.5)
No. with progression of SSc or no response/no. assessed			
CYC	9/9	19/77	NA
HSCT	0/10	9/79	NA
Overall mortality, no. of deaths/no. assessed			
CYC	0/9	30/77	NA
HSCT	0/10	19/79	NA



Seminars in Arthritis and Rheumatism ▮ (2016) ▮▮▮–▮▮▮

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

A multicenter, open-label, comparative study of B-cell depletion therapy with Rituximab for systemic sclerosis-associated interstitial lung disease☆

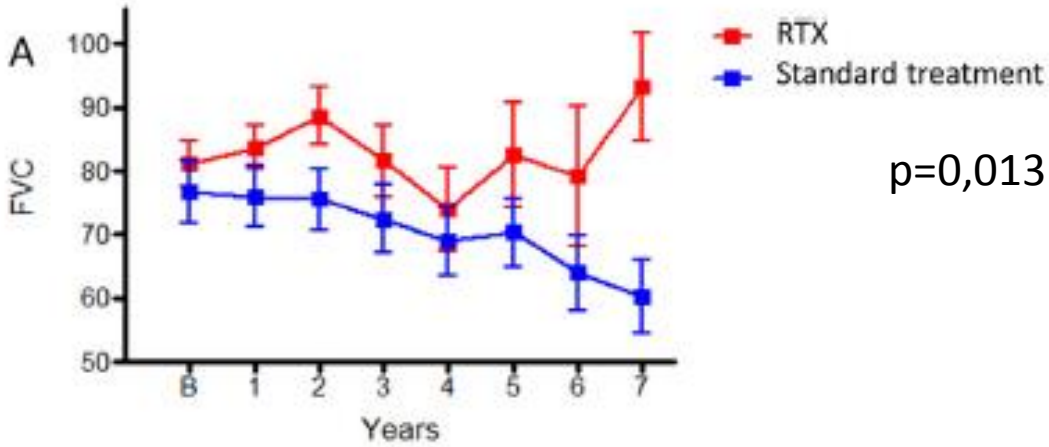
Dimitrios Daoussis, MD[a,*,1], Konstantinos Melissaropoulos, MD[a,1], Georgios Sakellaropoulos[e], Ioannis Antonopoulos, MD[a], Theodora E. Markatseli, MD[b], Theodora Simopoulou, MD[c], Panagiotis Georgiou, MD[d], Andrew P. Andonopoulos, MD[a], Alexandros A. Drosos, MD[b], Lazaros Sakkas, MD, DM, PhD(UK), FRCP(UK)[c], Stamatis-Nick Liossis, MD[a]

[a] *Division of Rheumatology, Department of Internal Medicine, Patras University Hospital, University of Patras Medical School, 26504 Rion, Patras, Greece*
[b] *Department of Rheumatology, Ioannina University Hospital, University of Ioannina Medical School, Ioannina, Greece*
[c] *Department of Rheumatology, Larissa University Hospital, University of Thessaly Medical School, Larissa, Greece*
[d] *Department of Rheumatology, Agios Andreas District Hospital, Patras, Greece*
[e] *Department of Medical Physics, University of Patras, Patras, Greece*

	RTX cohort	Control cohort	*p* Value
Patients, *n*	33	18	
Age mean, years ± SD	54.3 ± 14.33	52.11 ± 16.10	*0.62*
Female sex (%)	25/33 (75.8)	16/18 (88.9)	*0.46*
Disease duration mean in years (range)	5.73 (1–28)	2.56 (1–10)	*0.012*
Autoantibodies positive			
Scl70 (%)	25/33 (75.8)	14/18 (77.8)	*1.00*
ACA (%)	3/33 (9.1)	3/18 (16.7)	*0.65*
Other (%)	5/33 (15.1)	1/18 (5.5)	*0.40*
Disease subtype			
Diffuse (%)	30/33 (90.9)	14/18 (77.8)	*0.22*
Limited (%)	3/33 (9.1)	4/18 (22.2)	*0.22*
Pulmonary hypertension (%)[a]	6/33 (18.2)	5/18 (27.8)	*0.48*
MRSS, mean ± SD	14.72 ± 10.52	17.78 ± 9.48	*0.31*
FVC, mean ± SD	80.60 ± 21.21	77.72 ± 18.29	*0.63*
DLCO, mean ± SD	59.22 ± 18.17	64.24 ± 25.56	*0.42*
Concurrent medication			
Prednisolone(or equivalent) (%)	18/33 (54.5)	17/18 (94.4)	
Methotrexate (%)	2/33 (6.1)	6/18 (33.3)	
Mycophenolate (%)	10/33 (30.3)	10/18 (55.5)	
Azathioprine (%)	0/33 (0.0)	2/18 (11.1)	
Hydroxychloroquine (%)	1/33 (3.0)	0/18 (0.0)	

Daoussis et al. *Semin Arthr Rheum* 2016

Patients were treated with two or more cycles of RTX. Each cycle consisted of four infusions of 375 mg of RTX per m^2 of body surface area, once weekly. RTX cycles were repeated every 6 months. Thirteen patients in the RTX group received concurrent



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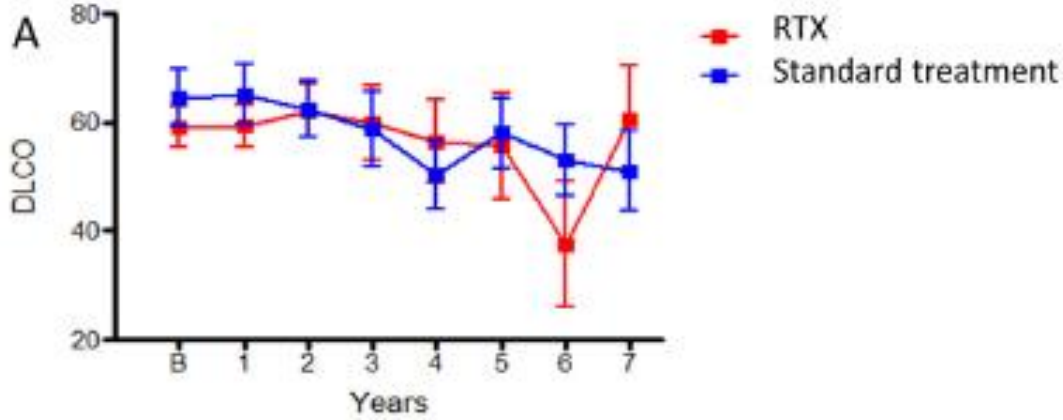


Daoussis et al. *Semin Arthr Rheum* 2016

PHRCN 2015 : acronyme "EvER-ILD" coordonné par le Pr Sylvain-Marchand Adam (Equipe 2 du CEPR/Inserm U1100).

Evaluation de l'Efficacité et de la tolérance du Rituximab en association avec le mycophénolate mofetil comparé au mycophénolate mofetil seul chez les patients ayant une pneumopathie interstitielle et non répondeurs à une première ligne de traitement immunosuppresseur : essai randomisé en double-insu contre placebo.

The Journal of Rheumatology

The Journal of Rheumatology Volume 43, no. 9

A New Era in the Treatment of Scleroderma-associated Interstitial Lung Disease?

DAVID LAUNAY

J Rheumatol 2016;43;1619-1621
http://www.jrheum.org/content/43/9/1619

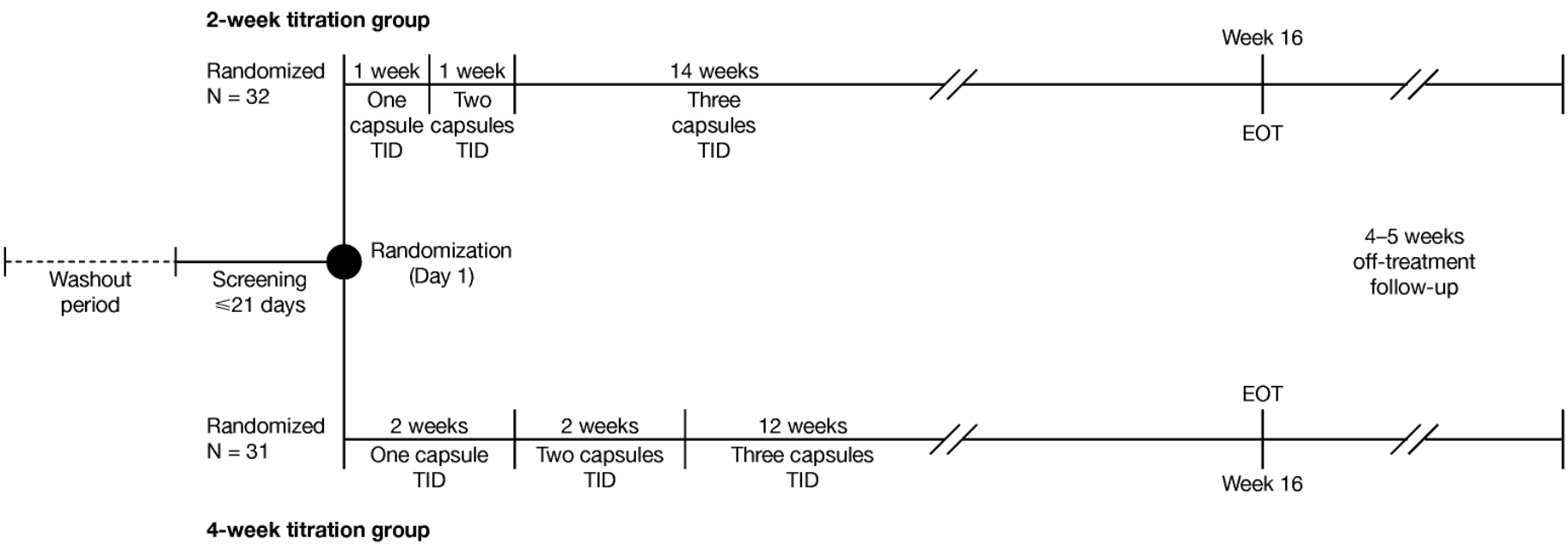
The Journal of Rheumatology

The Journal of Rheumatology Volume 43, no. 9

An Open-label, Phase II Study of the Safety and Tolerability of Pirfenidone in Patients with Scleroderma-associated Interstitial Lung Disease: the LOTUSS Trial

Dinesh Khanna, Carlo Albera, Aryeh Fischer, Nader Khalidi, Ganesh Raghu, Lorinda Chung, Dan Chen, Elena Schiopu, Margit Tagliaferri, James R. Seibold and Eduard Gorina

J Rheumatol 2016;43;1672-1679
http://www.jrheum.org/content/43/9/1672



Inclusion Criteria:

1.Diagnosis of systemic sclerosis−related (SSc) confirmed by the American College of Rheumatology classification criteria of systemic sclerosis (Masi 1980); duration of diagnosis less than (<) 7 years

2.Diagnosis of SSc-ILD based on an high-resolution computed tomography (HRCT) scan

3.Screening forced vital capacity (FVC) greater than equal to (>=) 50 percent (%) of the predicted value, and screening carbon monoxide diffusing capacity (DLCO) >=40% of the predicted value

4.At study entry, the participant either was not taking SSc-ILD medication or was taking cyclophosphamide or mycophenolate

Exclusion Criteria:

1.Clinically significant pulmonary hypertension

2.Known underlying liver disease

3.Clinical evidence of significant aspiration or uncontrolled gastroesophageal reflux

4.History of clinically significant asthma or chronic obstructive pulmonary disease

5.Active infection

6.Diagnosis of another connective tissue disorder

7.Evidence of a malignancy that is likely to result in significant disability or require significant medical or surgical intervention

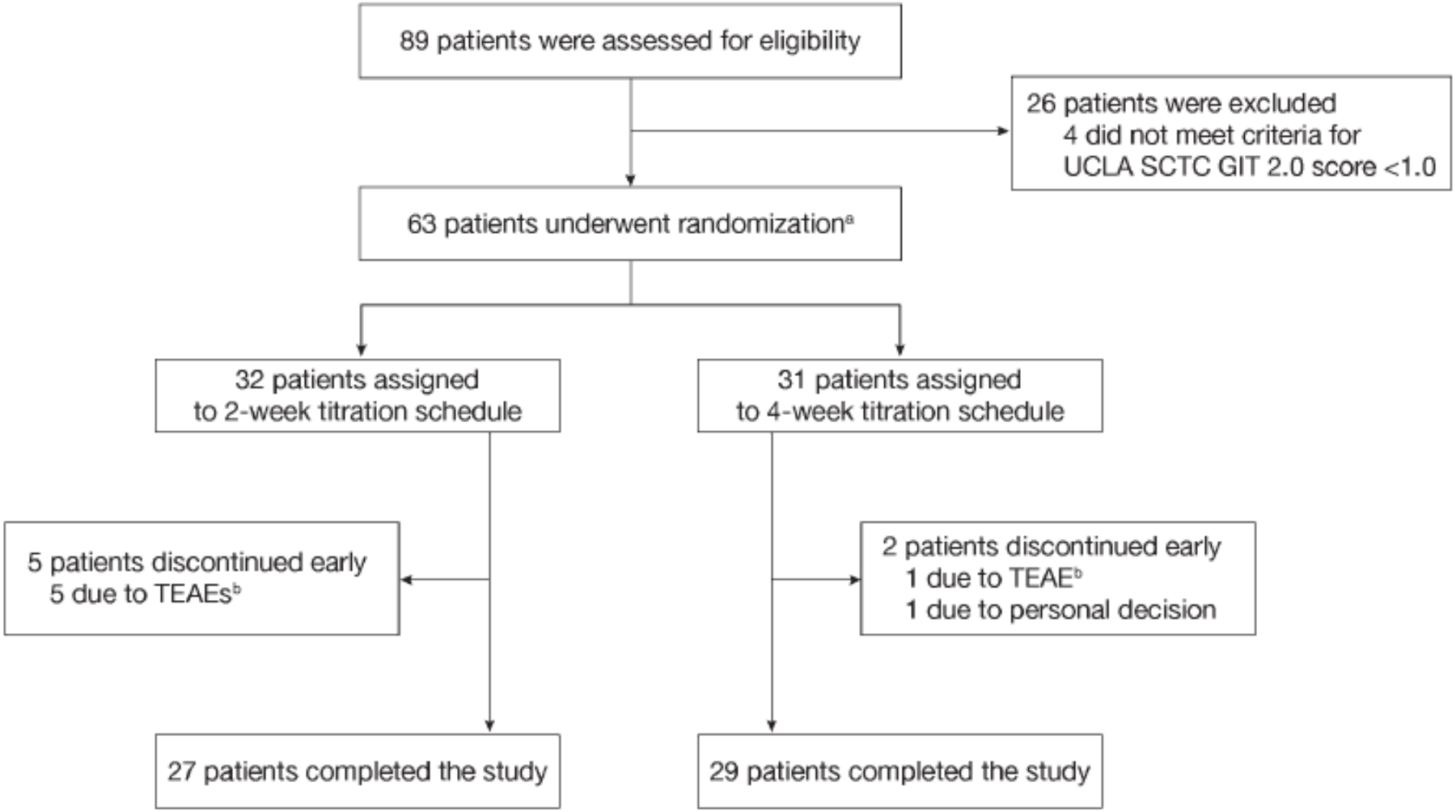
8.History of unstable or deteriorating cardiac or pulmonary disease (other than SSc-ILD)

9.Pregnancy or lactation

10.Creatinine clearance <40 milliliters per minute (mL/min)

11.Prior use of pirfenidone

12.Unsuitable for enrollment or unlikely to comply with study requirements



Khanna et al. *Rheumatol.* 2016

TEAE*	Pirfenidone, 2403 mg/day		
	2-week Titration Group, n = 32	4-week Titration Group, n = 31	Total, n = 63
At least 1 TEAE	31 (96.9)	30 (96.8)	61 (96.8)
Maximal intensity of TEAE**			
Mild***	7 (21.9)	12 (38.7)	19 (30.2)
Moderate	15 (46.9)	15 (48.4)	30 (47.6)
Severe***	9 (28.1)	3 (9.7)	12 (19.0)
Life-threatening	0	0	0
Relationship of TEAE to study treatment†‡			
Not related	3 (9.4)	2 (6.5)	5 (7.9)
Possibly related	7 (21.9)	6 (19.4)	13 (20.6)
Related	21 (65.6)	22 (71.0)	43 (68.3)
At least 1 TE SAE	3 (9.4)	0	3 (4.8)
At least 1 treatment-related TE SAE††	1 (3.1)	0	1 (1.6)
Discontinuation of study treatment due to TEAE***	5 (15.6)	1 (3.2)	6 (9.5)
Death as an outcome of a TEAE	0	0	0

Khanna et al. *Rheumatol.* 2016

Variables	Pirfenidone, 2403 mg/day				
	2-week Titration Group, n = 32	4-week Titration Group, n = 31	No MMF, n = 23	MMF, n = 40	Total, n = 63
Predicted FVC, %, mean (SD)					
Baseline	72.8 (14.39)	79.4 (13.32)	78.7 (13.99)	74.5 (14.19)	76.0 (14.15)
Week 16	71.4 (15.14)	78.7 (13.60)	75.5 (14.26)	75.0 (15.13)	75.2 (14.71)
Change from baseline to Week 16*	–0.6 (8.91)*	–0.6 (5.90)	–0.3 (9.50)**	0.6 (5.82)***	–0.6 (7.44)*
Predicted DLCO, %, mean (SD)†					
Baseline	59.3 (14.36)	60.1 (18.64)	56.8 (14.92)	61.4 (17.26)	59.7 (16.47)
Week 16	60.6 (19.12)*	63.4 (18.12)	57.0 (14.96)**	64.7 (19.80)***	62.0 (18.51)
Change from baseline to Week 16*	0.7 (9.57)*	3.2 (10.00)	–0.2 (7.12)**	3.2 (10.85)***	2.0 (9.79)*

Khanna et al. *Rheumatol.* 2016

SENSCIS™ - Trial Objectives

Boehringer Ingelheim

Nintedanib 150 mg bid

COMPARED TO

Placebo 150 mg bid

- Demonstrate a reduction in the annual rate of decline in FVC
- Demonstrate efficacy in regard to skin fibrosis (mRSS)
- Demonstrate an improvement of patient's symptoms (SGRQ)
- Assess safety and tolerability, mortality, the effects on different systemic organ manifestations of SSc, pharmacokinetics and the effects of nintedanib on patient's perception of his/her disease

✓ One adequately sized Phase III study accepted by FDA and EMA

Randomized, double blind, placebo controlled

TREATMENT
Soft gelatine capsules
150 mg twice daily

Nintedanib 260 patients

Placebo 260 patients

52 weeks to 100 weeks treatment

520 patients - 20 countries - 200 sites –18 months recruitment
First patient in Nov 2015 - Last patient out May 2018

SENSCIS™ - Efficacy Endpoints

Boehringer Ingelheim

Primary Endpoint	Annual rate of decline in FVC in mL over 52 weeks
Key Secondary Endpoints	Absolute change from baseline at week 52: ▪ in the modified Rodnan Skin Score (mRSS) ▪ in SGRQ total score
Secondary Endpoints	Annual rate of decline in FVC in percent predicted over 52 weeks Absolute change from baseline in FVC in mL at week 52 Relative change from baseline (%) of mRSS at week 52 Time to all-cause mortality Absolute changes from baseline at week 52: • in DLCO (percent predicted) • in digital ulcer net burden • in HAQ-DI score • in FACIT dyspnoea score

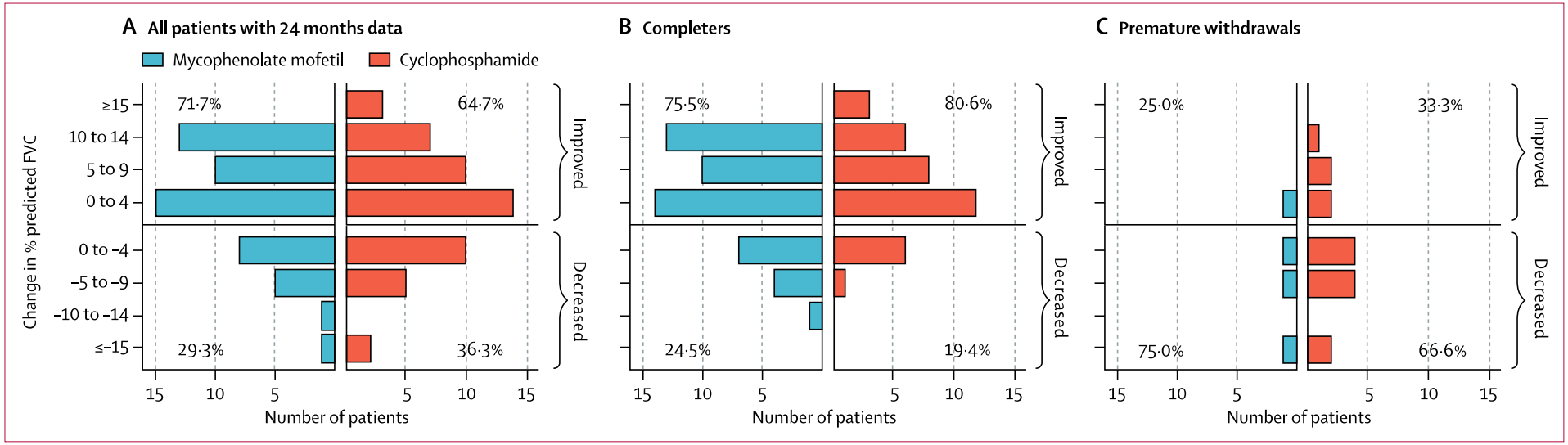
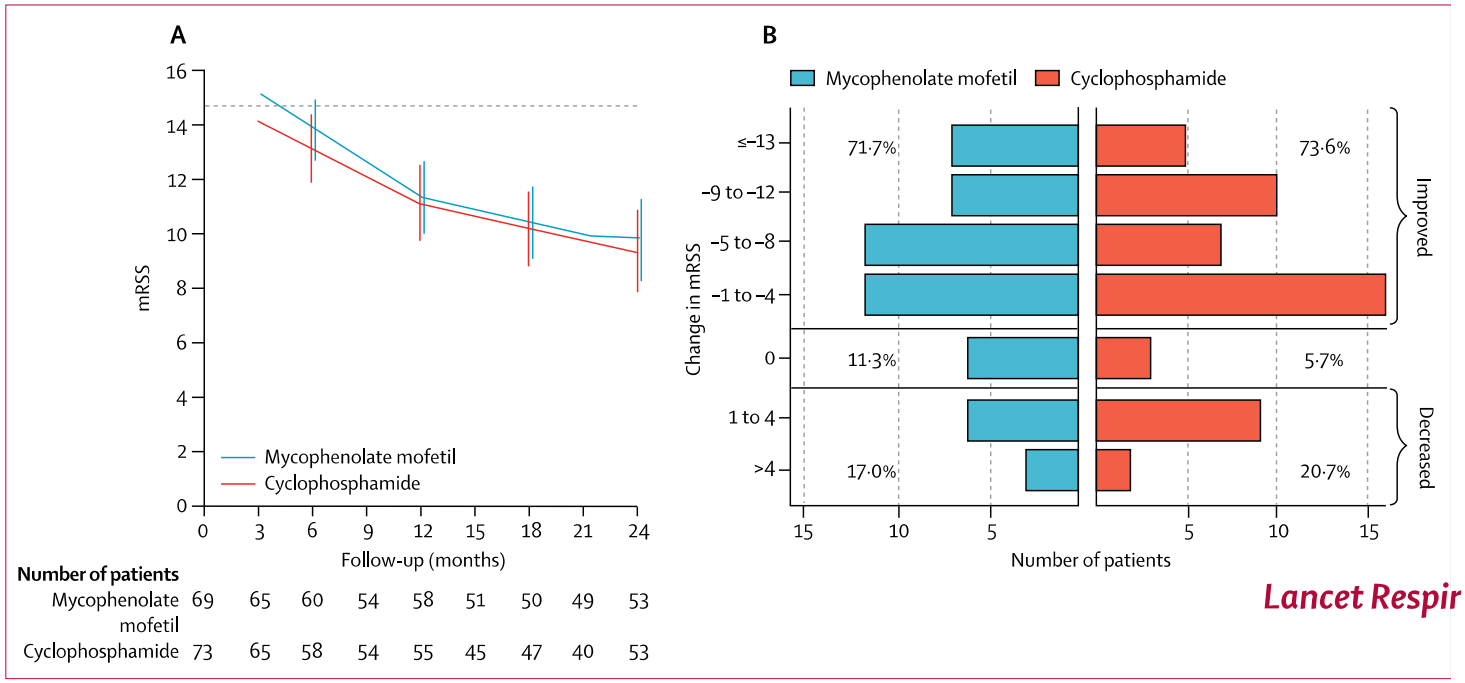


Figure 3: **Frequency distribution of changes from baseline to 24 months in % predicted FVC**
(A) The observed data of all patients with data at 24 months includes mycophenolate mofetil (n=58) and cyclophosphamide (n=51). (B) The completers population includes mycophenolate mofetil (n=49) and cyclophosphamide (n=36). (C) The premature withdrawals population includes mycophenolate mofetil (n=4) and cyclophosphamide (n=15). % predicted FVC=change in forced vital capacity as a percentage of the predicted normal value.



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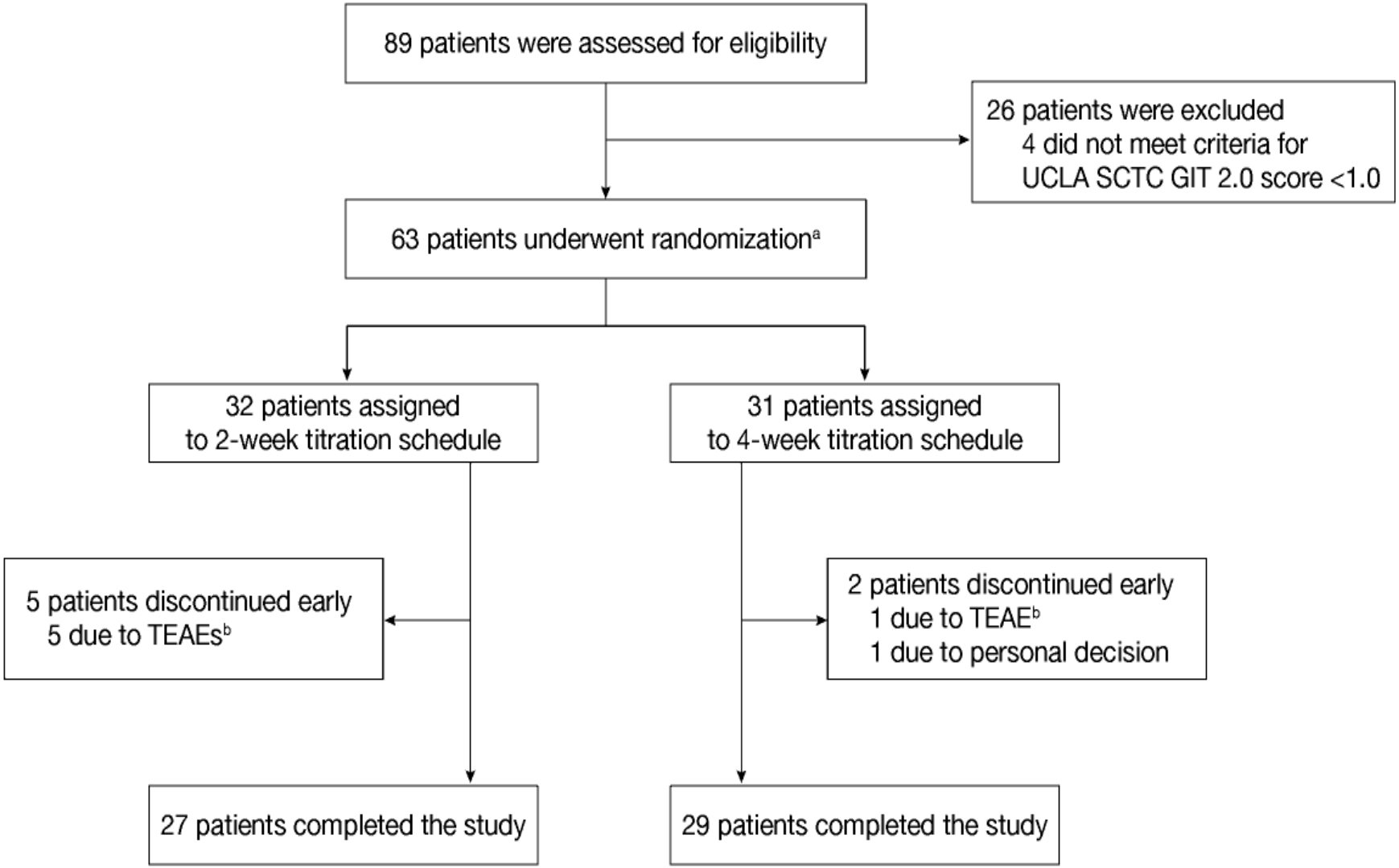

89 patients were assessed for eligibility
26 patients were excluded
4 did not meet criteria for
UCLA SCTC GIT 2.0 score <1.0
63 patients underwent randomization[a]
32 patients assigned
to 2-week titration schedule
31 patients assigned
to 4-week titration schedule
5 patients discontinued early
5 due to TEAEs[b]
2 patients discontinued early
1 due to TEAE[b]
1 due to personal decision
27 patients completed the study
29 patients completed the study

Table 1. Baseline demographic and clinical features in rp-dcSSc treated with AHSCT and with immunosuppressive conventional agents

Features	*AHSCT* (n = *18)*	*Conventional therapies* (n = *36)*
Age, median (range), years	41 (20–64)	44 (19–62)
Women, number (%)	13 (72)	26 (72)
Disease duration, median (range), months[a]	24.0 (10–48)	24.2 (6–48)
mRss, median (range)	20.0 (15–32)	19.5 (14–32)
ESSG score, median (range)	5.0 (4.0–8.0)	5.0 (4.0–8.5)
DLCO, median (range), % of predicted value[b]	68 (51–100)	67 (53–98)
LVEF %, median (range)	65.0 (53–71)	62.0 (45–76)
PAPs, mm Hg, median (range)	26.5 (25.0–28.0)	30.3 (28.0–32.5)
HRTC		
Normal, no. (%)	6 (35)	14 (39)
Abnormal, no. (%)[c]	12 (67)	22 (61)
Serum autoantibodies		
Anti-nuclear antibody positive, no. (%)	18 (100)	36 (100)
Anti-topoisomerase positive, no. (%)	14 (78)	26 (72)

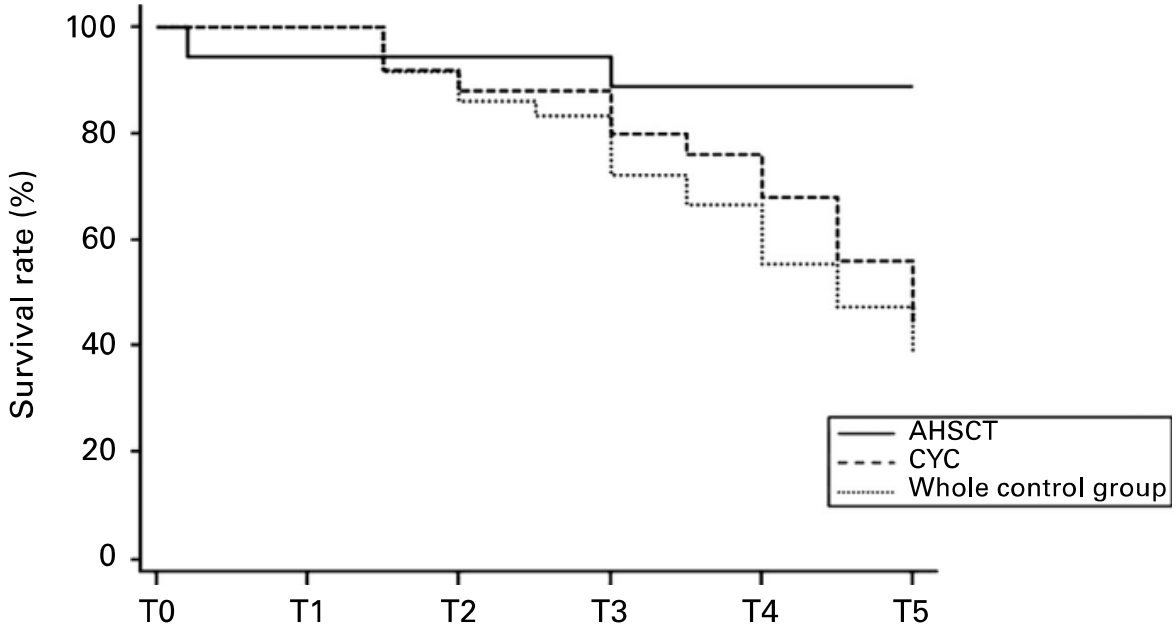
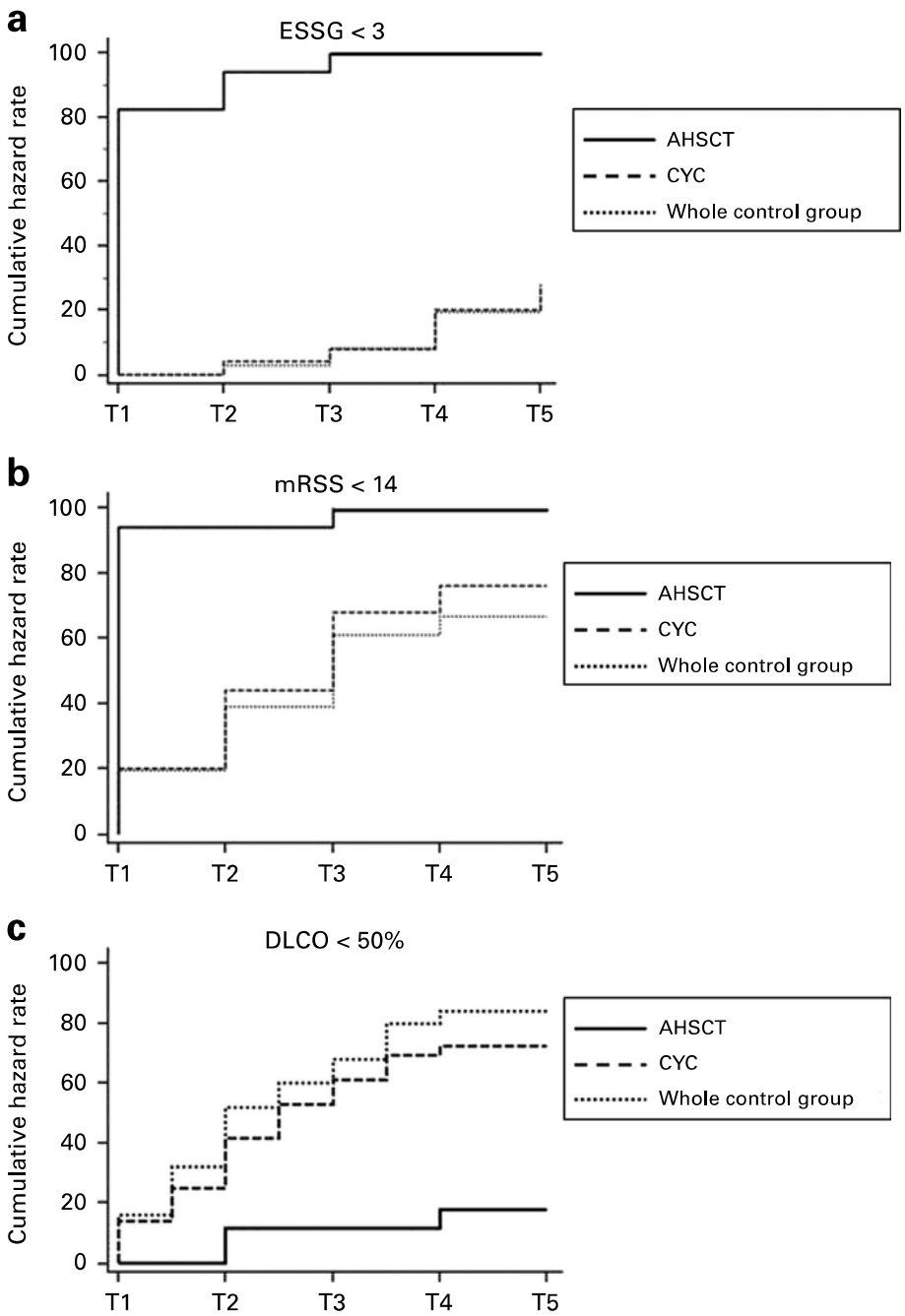
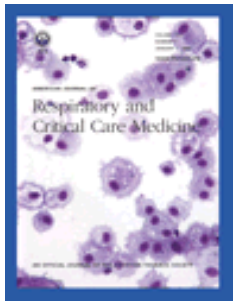


Figure 2. Kaplan–Meier curves were built and HR computed to analyze the overall survival rate of AHSCT-treated population with respect to that of the whole disease control group and, separately, of the control patients treated with CYC. The overall survival rate is significantly lower in both the whole control group (HR 6.94 (3.05–15.79 CI), $P < 0.002$) and the CYC-treated group (HR 5.98 (2.24–15.99 CI), $P < 0.006$) in comparison with the AHSCT group.


a
ESSG < 3
Cumulative hazard rate
100
80
60
40
20
0
T1
T2
T3
T4
T5
AHSCT
CYC
Whole control group
b
mRSS < 14
Cumulative hazard rate
100
80
60
40
20
0
T1
T2
T3
T4
T5
AHSCT
CYC
Whole control group
c
DLCO < 50%
Cumulative hazard rate
100
80
60
40
20
0
T1
T2
T3
T4
T5
AHSCT
CYC
Whole control group

Bronchoalveolar Lavage and Response to Cyclophosphamide in Scleroderma Interstitial Lung Disease

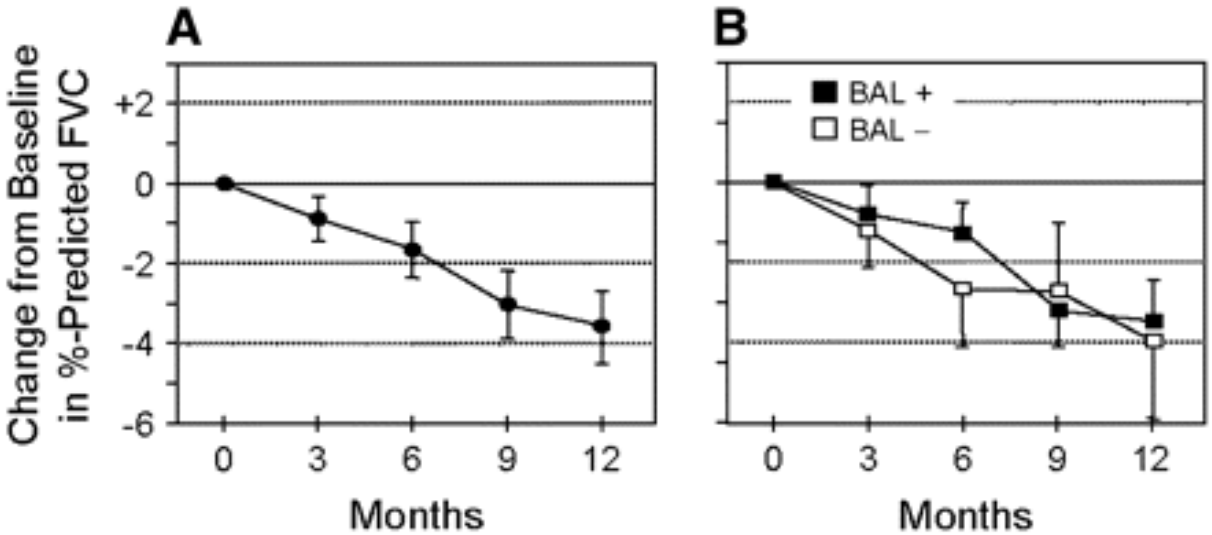
Charlie Strange[1], Marcy B. Bolster[2], Michael D. Roth[3], Richard M. Silver[2], Arthur Theodore[4], Jonathan Goldin[5], Philip Clements[6], Joanie Chung[7], Robert M. Elashoff[7], Robert Suh[5], Edwin A. Smith[2], Daniel E. Furst[6], Donald P. Tashkin[3], and the Scleroderma Lung Study Research Group*

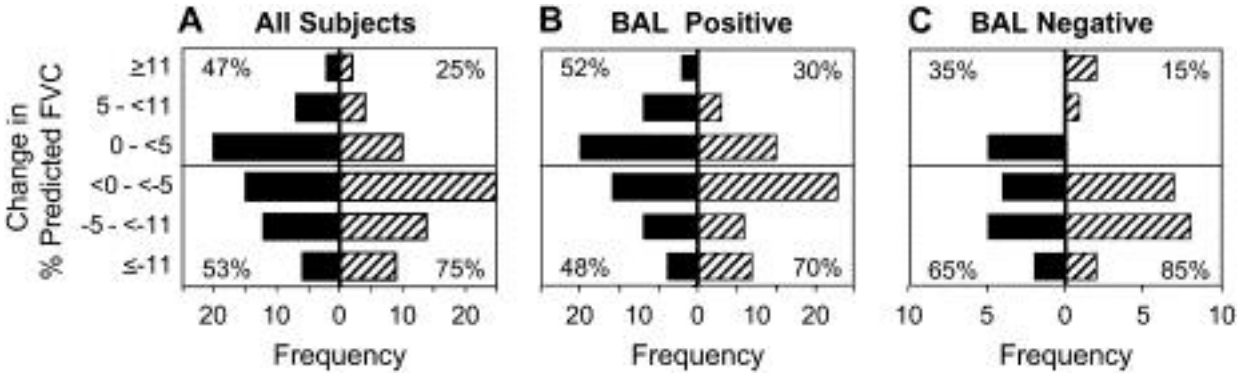


PNN ≥ 3%

et/ou

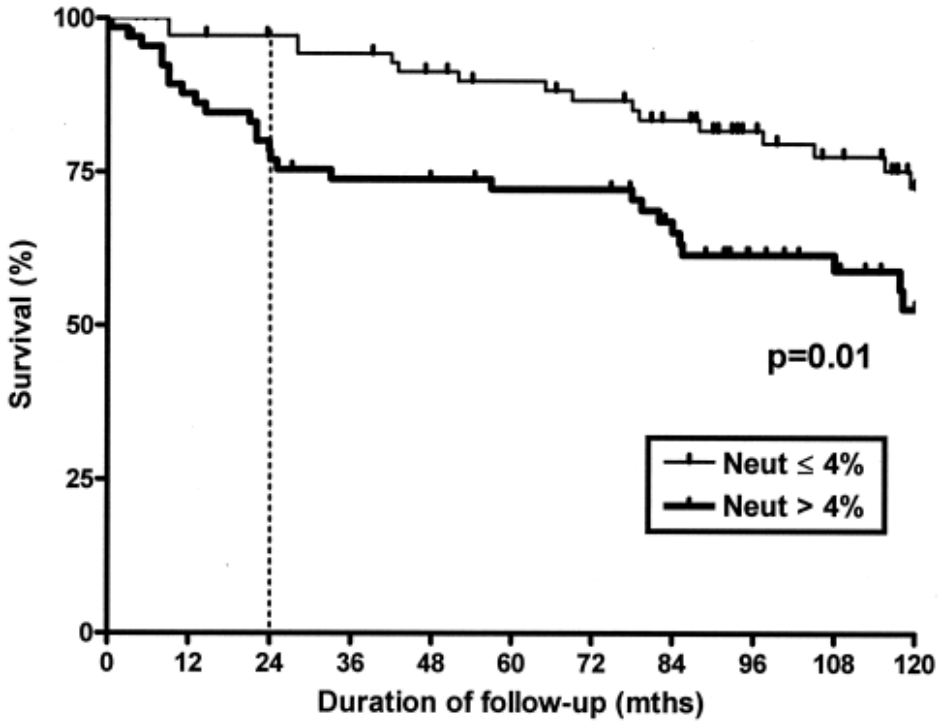
PNE ≥ 2%





Bronchoalveolar Lavage Cellular Profiles in Patients With Systemic Sclerosis–Associated Interstitial Lung Disease Are Not Predictive of Disease Progression

Nicole S. L. Goh,[1] Srihari Veeraraghavan,[2] Sujal R. Desai,[3] Derek Cramer,[1] David M. Hansell,[1] Christopher P. Denton,[4] Carol M. Black,[4] Roland M. du Bois,[1] and Athol U. Wells[1]



Disparition de l'association avec la mortalité globale après ajustement sur la sévérité de la PID

- Lien significatif en analyse multivariée avec la mortalité précoce HR=8.40 (95% IC: 1.91–36.95), p=0.005
- Pas de lien significatif avec la mortalité tardive ou le déclin fonctionnel