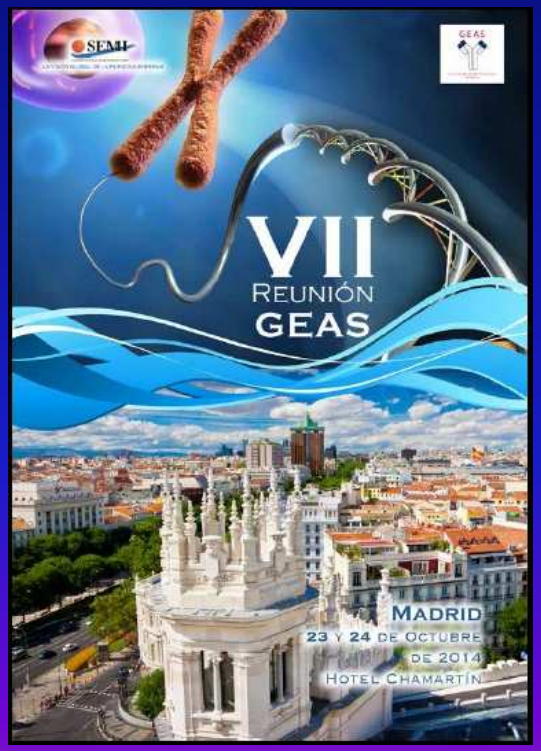
Novedades en el diagnóstico y tratamiento en las EAS: TOP 5 del 2014

ESCLERODERMIA

V. Fonollosa Pla - CP. Simeón Aznar
Unidad de Enfermedades Autoinmunes Sistémicas
Servicio de Medicina Interna



ESCLERODERMIA. Tratamiento

Factor XIII
Colquicina
Fotoféresis
Áferesis
Radiación
Clorambucil
5-fluoruracil
Dimetil sulf
N-acetilciste
Ciclofenil
Potaba
IECAs
ARA 2
Aspirina
Globulina anti-T

Metotrexato
Dexametasona
D-penicilamina
Ketanserina
Ketotifeno

Vitamina D
Nifedipino
Omeprazol
Octreotido
Cisapride
Prednisona

Ciclofosfamida
Azatioprina
Iloprost
Simpatectomía
Biofeedback
m
na
nte MO
a
Colágeno tipo I
Halofuginona
Minociclina
Bosentan
Probucol
Fluoxetina

No drug has been proven totally ineffective until it's been tried in scleroderma" ***Eric Bywathers***

Targeted therapies for systemic sclerosis

(1)

Christopher P. Denton & Voon H. Ong

NATURE REVIEWS | RHEUMATOLOGY 2013

Table 2 | Current clinical trials in SSc*

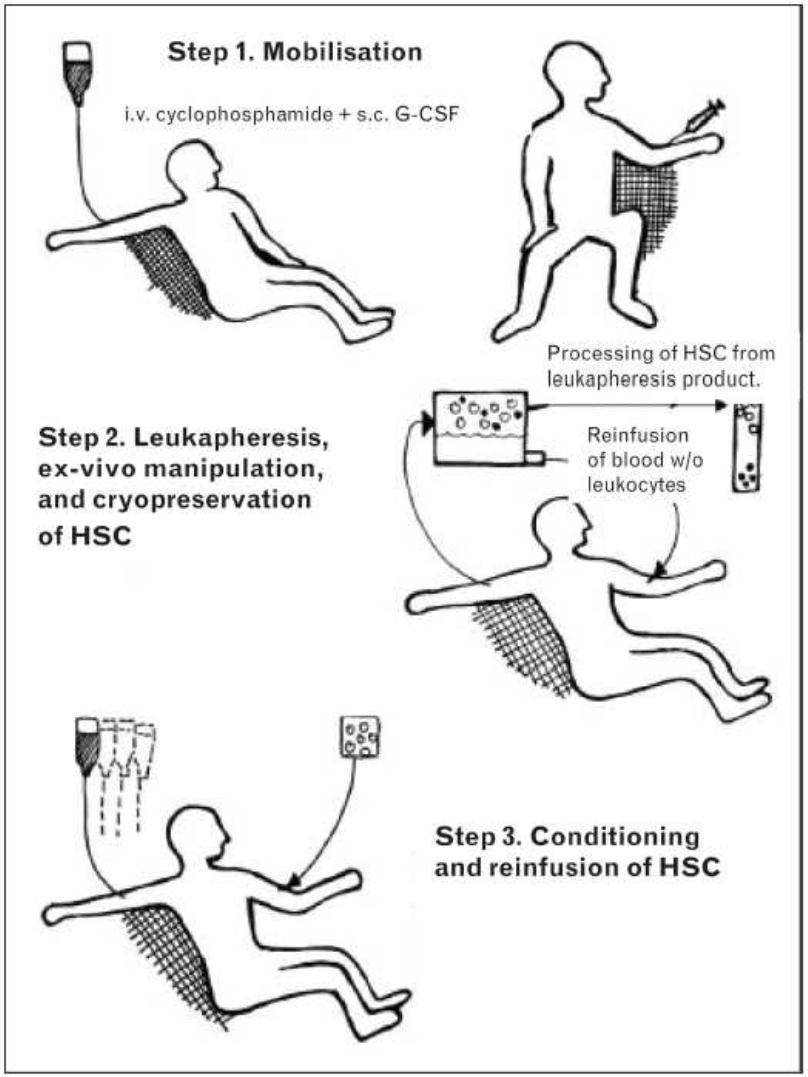
Study; identifier (date record updated)	Agent (type)	Condition	Primary endpoint	Intervention in active arm	Design	Phase and status
SEDUCE; NCT01295736 (Oct 2012)[137]	Sildenafil (type 5 phosphodiesterase inhibitor)	SSc with ischaemic DUs	Time to healing of ischaemic DUs at 90 days	20 mg three times per day	Double-blind RCT	Phase III, recruiting
SCOT; NCT00114530 (July 2011)[138]	Autologous SCT	dcSSc	Event-free survival at 48 and 54 months post randomization, FVC, SSc–HAQ, mRSS	Autologous SCT and high-dose immunosuppressive therapy	RCT	Phase II, ongoing
Allogeneic hematopoietic-cell transplantation after nonmyeloablative conditioning for patients with severe SSc; NCT00622895 (Oct 2012)[21]	Allogeneic SCT	dcSSc	Event-free survival at 2 years	Allogeneic SCT and high-dose immunosuppressive therapy	Open label	Phase I/II, ongoing
Study of ambrisentan with antifibrotic agent combination therapy in diffuse SSc; NCT01093885 (March 2010)[30]	Ambrisentan (ERA)	dcSSc	mRSS at 12 months	5–10 mg daily	Open label	Phase I
High-dose intravenous NAC versus iloprost for early, rapidly progressive diffuse SSc; NCT00428883 (Jan 2007)[139]	NAC	dcSSc	mRSS	NAC versus iloprost	RCT	Phase II/III, recruiting
Study of pomalidomide (CC-4047) to evaluate safety, tolerability, pharmacokinetics, pharmacodynamics and effectiveness for subjects with SSc with ILD; NCT01559129 (Oct 2012)[22]	Pomalidomide (derivative of thalidomide)	SSc and progressive lung fibrosis	Change in mRSS and FVC at week 52	1 mg daily over 52 weeks	Double-blind RCT	Phase II, recruiting
IL1-TRAP, rilonacept, in SSc; NCT01538719 (July 2012)[26]	Rilanocept (fusion protein, IL-1 inhibitor)	dcSSc	4-gene biomarker of skin disease and mRSS	320 mg day 0 and 160 mg weekly for 5 weeks, subcutaneously	Double-blind RCT	Phase I/II, recruiting

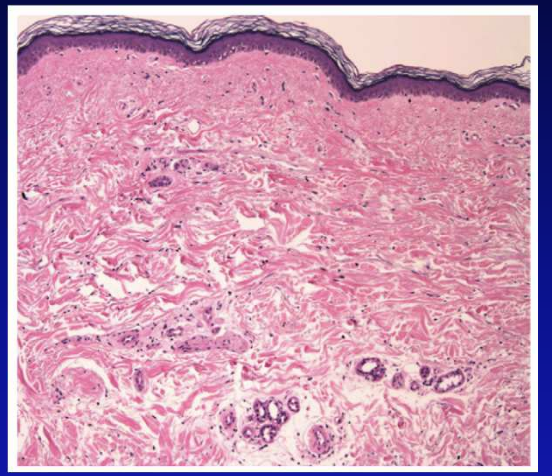
Targeted therapies for systemic sclerosis (2)

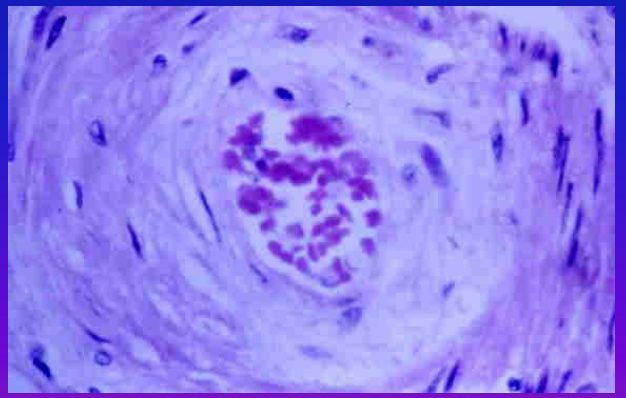
Christopher P. Denton & Voon H. Ong NATURE REVIEWS | RHEUMATOLOGY 2013

A trial of tadalafil in ILD of scleroderma; NCT01553981 (Dec 2012)[31]	Tadalafil (PDE5 inhibitor)	SSc and lung fibrosis	Change in FVC over 6 months	20 mg alternate days over 5 months	Double-blind RCT	Phase III, recruiting
Fresolimumab in SSc; NCT01284322 (July 2012)[115]	Fresolimumab (GC1008)	dcSSc	Change in TGFβ-regulated gene expression in skin over 7 weeks	One-off intravenous dose of 1 mg/kg or 5 mg/kg	Open label	Phase I, recruiting
Rituximab for treatment of SSc–PAH; NCT01086540 (Nov 2012)[140]	Rituximab (anti-CD20 antibody)	SSc–PAH	Change in PVR over 24 weeks	2 infusions, 1,000 mg each, 14 days apart	Double-blind RCT	Phase II, recruiting
Macitentan for the treatment of DUs in SSc patients; NCT01474109 (Sep 2012)[141]	Macitentan (selective ERA)	SSc with DUs	Reduction of new DUs at 16 weeks	3 mg or 10 mg daily for 16 weeks	Double-blind RCT	Phase III, recruiting
SLSII; NCT00883129 (Sep 2010)[25]	MMF; cyclophosphamide	SSc and lung fibrosis	FVC over 24 months	MMF max 1.5 g twice daily for 2 years or oral cyclophosphamide max 2 mg/kg for 12 months	RCT	Phase II, recruiting
A study of RoActemra/Actemra (tocilizumab) versus placebo in patients with SSc; NCT01532869 (Feb 2013)[29]	Tocilizumab (anti-IL-6 receptor antibody)	dcSSc	mRSS at 6 months	162 mg once per week, subcutaneously	Double-blind RCT	Phase II, recruiting
A protocol-based treatment for early and severe SSc with (anti-CD20), rituximab; NCT00379431 (Feb 2013)[142]	Rituximab	dcSSc	Death or major organ involvement at 28 weeks	1,000 mg on days 1 and 15 and at week 26–28, intravenously with 100 mg methylprednisolone prior to each infusion	RCT	Phase II, ongoing
AIMSPRO in established dcSSc; NCT00769028 (Aug 2011)[143]	AIMSPRO® (hyper immune goat serum)	dcSSc	mRSS at week 26	Subcutaneous injection of serum, 1 ml twice weekly for 6 months	Double-blind RCT	Phase II, ongoing

Stem cell transplantation in systemic sclerosis







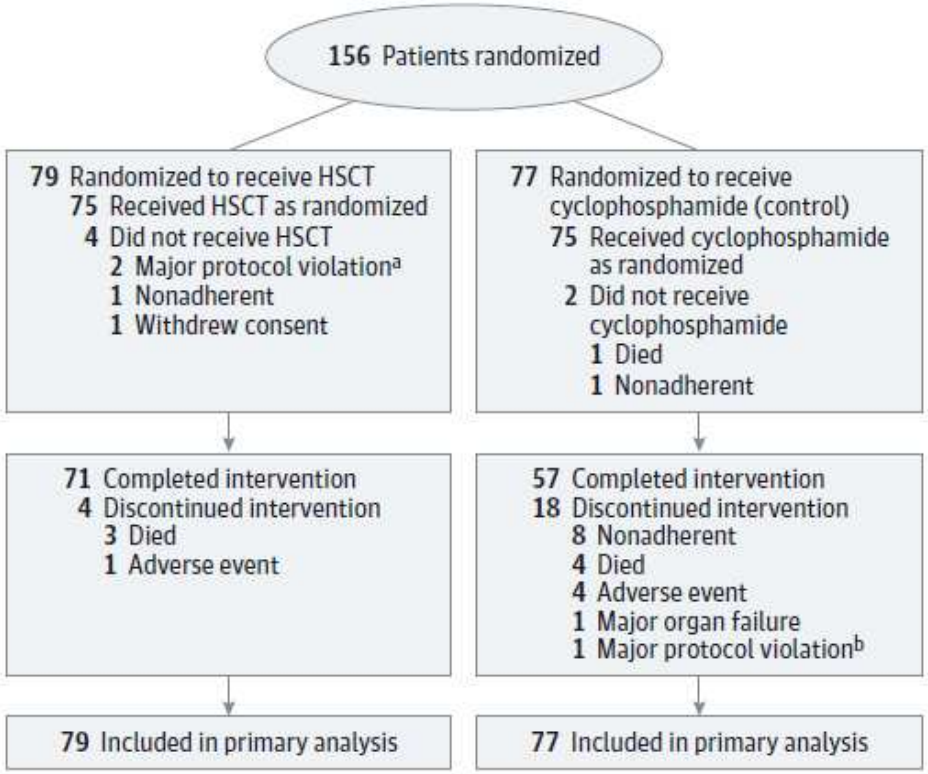
Autologous Hematopoietic Stem Cell Transplantation vs Intravenous Pulse Cyclophosphamide in Diffuse Cutaneous Systemic Sclerosis

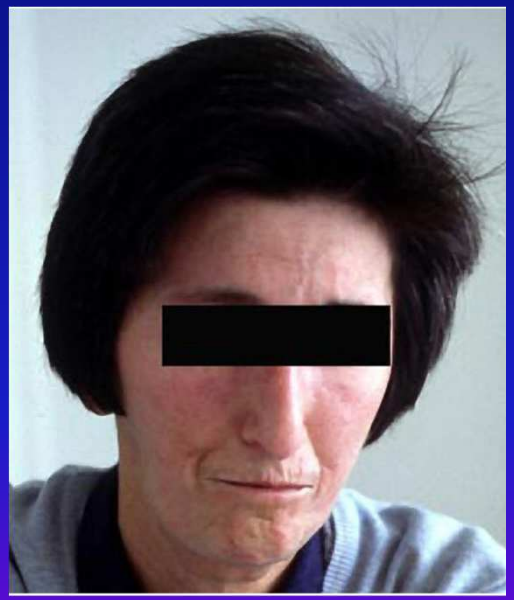
A Randomized Clinical Trial

***Jacob M. van Laar et al*.**

JAMA. 2014;311(24):2490-2498.

Figure 1. Flow of ASTIS (Autologous Stem Cell Transplantation International Scleroderma) Trial





Autologous Hematopoietic Stem Cell Transplantation vs Intravenous Pulse Cyclophosphamide in Diffuse Cutaneous Systemic Sclerosis

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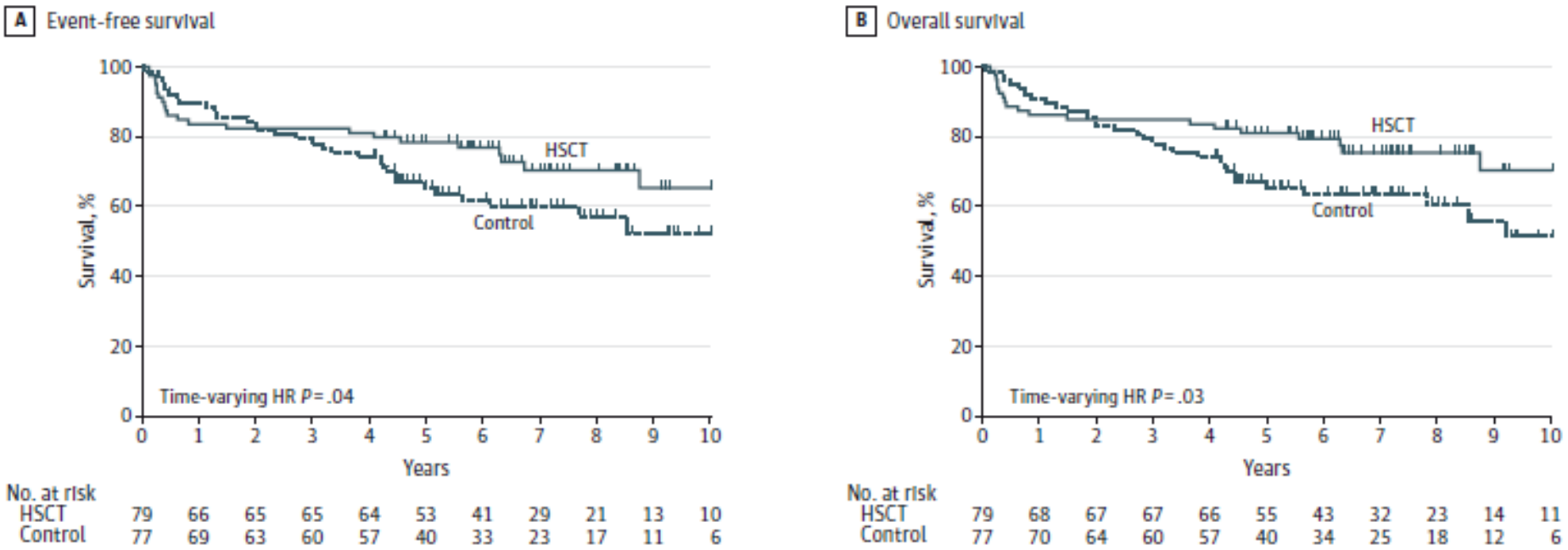
JAMA. 2014;311(24):2490-2498.

Figure 2. Event-Free and Overall Survival During 10-Year Follow-up



Autologous Hematopoietic Stem Cell Therapy in Severe Systemic Sclerosis
Ready for Clinical Practice?

Dinesh Khanna, MD, MS; George E. Georges, MD; Daniel R. Couriel, MD, MS

JAMA. 2014;

Mortalidad relacionada con el tratamiento: 10,1%

Recaídas postrasplante: 22,4% (12 – 24 meses)

Efectos adversos graves: 62,9 %

Selección de los pacientes

Autologous Hematopoietic Stem Cell Therapy in Severe Systemic Sclerosis
Ready for Clinical Practice?

Dinesh Khanna, MD, MS; George E. Georges, MD; Daniel R. Couriel, MD, MS

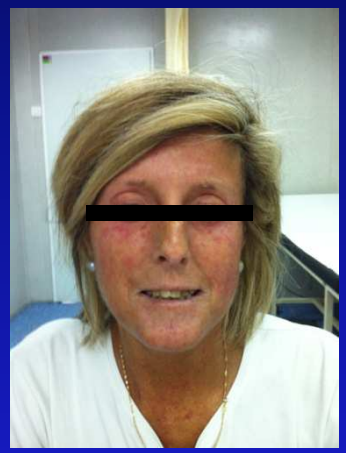
JAMA. 2014;

Patients who are candidates for HSCT should be enrolled in protocols that aim to:

1. find disease biomarkers that identify patients likely respond to HSCT and that predict relapse,

2. improve the treatment regimen,

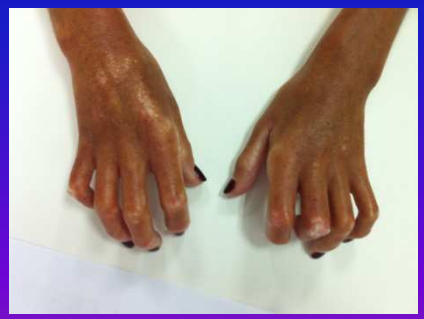
3. provide careful follow-up to evaluate long-term outcome.



Currently, consideration should be limited to patients with:

1. diffuse cutaneous systemic sclerosis within the first 4 to 5 years of onset with mild-to-moderate internal organ involvement (severe internal organ involvement will make patients ineligible because of risks associated with HSCT)

2. limited cutaneous systemic sclerosis with progressive internal organ involvement.




Autologous HSCT for systemic sclerosis
Richard Burt and colleagues (March 30, p 1116)[1] propose from a retrospective analysis of autologous haemo stem-cell transplantati 90 patients wi that comprehen including fluid patient selection. higher treatment- in the ASTIS trial[2] their study) to less screening, which ma heart catheterisation onl pulmonary arterial hype echo. However
Autologous Hematopoietic Stem Cell Transplantation vs Intravenous Pulse Cyclophosphamide in Diffuse Cutaneous Systemic Sclerosis
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Autologous Hematopoietic Stem Cell Therapy in Severe Systemic Sclerosis
Ready for Clinical Practice?
???
Dinesh Khanna, MD, MS; George E. Georges, MD; Daniel R. Couriel, MD, MS
received a similar
Lastly, the a
that HSCT s
as first-line trea
patients with syste
they do not explain
nor corroborate this wi
The prognosis of systemic sc
improved due to better care an
effective use of immunosuppre
medication.[4] Given the risks and cos
associated with HSCT, more controlled
studies are necessary to establish the
place of HSCT in systemic sclerosis
treatment.
thiotep
systemic
Improving safety in autologous HSCT for systemic sclerosis

Targeting pathogenic processes in SSc.

Attenuate autoantigen-driven inflammation and antibody-mediated pathology

Stimulate controlled vascular regeneration and repair endothelial damage

Systemic sclerosis complications		Immunosuppressive agents
Active skin involvement		Mycophenolate mofetil Methotrexate Cyclophosphamide Rituximab Intravenous immunoglobulin
Organ complications	Pulmonary fibrosis	Mycophenolate mofetil Cyclophosphamide Rituximab
	Cardiac scleroderma	Mycophenolate mofetil Cyclophosphamide
	Renal crisis	low dose MMF

Reduce inappropriate or excessive ECM deposition

Targeted immunotherapies in systemic sclerosis

J. Avouac and Y. Allanore

Clin Exp Rheumatol 2014; 32 (Suppl. 81): S165-S172.

RITUXIMAB

Table I. Results of available trials regarding the efficacy and safety of rituximab in systemic sclerosis.

Smith *et al.* (40)	n=8 9-30 months of disease duration mostly diffuse cutaneous SSc	1000 mg RTX at days 1 and 15 + 100 mg methylprednisolone 5/8 + MTX	At week 24, reduction of skin score from 24.8 (3.4) to 14.3 (3.5) (40% improvement)	SSc-DAS score at 6 months: 4.5 (1.5-7.5) to 1.0 (0.0-2.0) HAQ-DI at 6 months: 1.3 (0.8-2.1) to 1.1 (0.3-2.1)	2 serious side effects not related to RTX (one myocardial infarction and one unexplained fever)
(41)		New treatment at week 26 and 28	Stability of Rodnan skin score at 2 years: 13.8 (5.6)	Stability of SSc-DAS score at 2 years: 2.1 (0.0-5.5) Stability of HAQ-DI at 2 years: 1.3 (0.4-2.0)	At 2 years, 3 additional serious side effects (one infection of digital ulcer, one sepsis and one episode of hyperventilation)
Lafyatis *et al.* (42)	n=15 dcSSc 1st symptoms <18 months	1000 mg RTX at days 1 and 15	No change of the skin score at 6 months: -0.37 (-14.5; +14) (20.6 to 20.2)	No change of DLCO (79.7±8.3 to 77.8±7.5), FVC (89.2±10.8 to 92.7±10.3) and HAQ : 0.67±0.32 to 0.64±0.36	Infusion reaction: 47% 1 urinary tract infection 1 dental abscess 1 prostatic cancer
Bosello *et al.* (43)	n=9 diffuse cutaneous SSc Cutaneous progression despite CYC Disease duration: 49±73 months	1000 mg RTX at days 1 and 15 + 100 mg methylprednisolone 2/9 + MTX	Skin score: 21.1±9 to 12.0 ±6.1 (6 months) and 7.0±4.0 (12 months) (global improvement 57%)	SSc-DAS 10.5±3.2 to 7.2±2.8 (6 months) and 6.2±2.8 (12 months) SSc-HAQ: 0.9±0.7 to 0.4±0.5 (6 months) and 0.3±0.7 (12 months) No change of DLCO and FVC	1 breast cancer
Daoussis *et al.* (44)	n=14 dcSSc Disease duration >5 years Topoisomerase-I antibodies + and presence of ILD	Randomisation 8 *vs.* 6 No placebo 4 X 375 mg/m2/s at inclusion and at 6 months	Improvement of 1/ FVC: + 10.2% *vs.* decrease of 5.0% in the control group 2/ DLCO: + 19.5% vs. decrease of 7.5% in the control group 3/ skin score: 39.2% decrease vs. 20.1% decrease in the control group	HAQ: 0.69 (0.3-1.25) to 0.31 (0.12-0.69) at 12 months in the RTX group vs. non significant change in the control group 0.31 (0.1-0.9) to 0.125 (0.1-0.4)	1 infection requesting IV antibiotics

Two-year Results of an Open Pilot Study of a 2-treatment Course with Rituximab in Patients with Early Systemic Sclerosis with Diffuse Skin Involvement

VANESSA SMITH, YVES PIETTE, JENS T. VAN PRAET, SASKIA DECUMAN, ELLEN DESCHEPPER, DIRK ELEWAUT, and FILIP DE KEYSER

Objective. To study safety and potential efficacy of a 2-treatment course (month 0/6) with rituximab (RTX) in early diffuse systemic sclerosis (dcSSc).

Methods. Two years' followup (open-label study) was done of 8 patients with early dcSSc. Patients received an infusion of 1000 mg RTX 2 times at months 0 and 6, with 100 mg methylprednisolone. Clinical measurements, Disease Activity Score, functional status, and CD19+ peripheral blood count were performed at months 0, 3, 6, 12, 15, 18, and 24 and histopathological evaluation of the skin at months 0, 3, 12, and 24.

Results. There was a clinically significant change in skin score, with a mean Modified Rodnan skin score of 24.8 at baseline (SD 3.4) and 13.6 at Month 24 [SD 5.6; mixed models analyses (MMA) $p < 0.0001$] and a significant decrease in Disease Activity Score (DAS), with a median of 4.5 at baseline (range 1.5–7.5) and 0.5 at Month 24 (range 0.0–5.5; MMA $p < 0.0001$). Indices of internal organ involvement remained stable throughout the study. RTX induced effective B cell depletion at baseline and Month 6 (< 5 CD19+ cells/μl blood). The blindly assessed hyalinized collagen score changed significantly over time (MMA $p = 0.009$), with a mean of 69.3 at baseline (SD 22.8) and 33.1 at 24 months (SD 27.0). Five serious adverse events were considered unrelated to the RTX treatment.

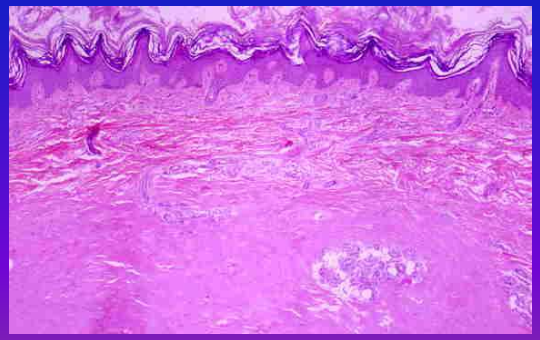
Conclusion. A 2-treatment course (months 0/6) with RTX appears to be well tolerated and may have potential efficacy for skin disease and stabilization of internal organ status in early dcSSc. Clinical Trials Registration NCT00379431. (First Release Nov 1 2012; J Rheumatol 2013;40:52–7; doi:10.3899/jrheum.120778)

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

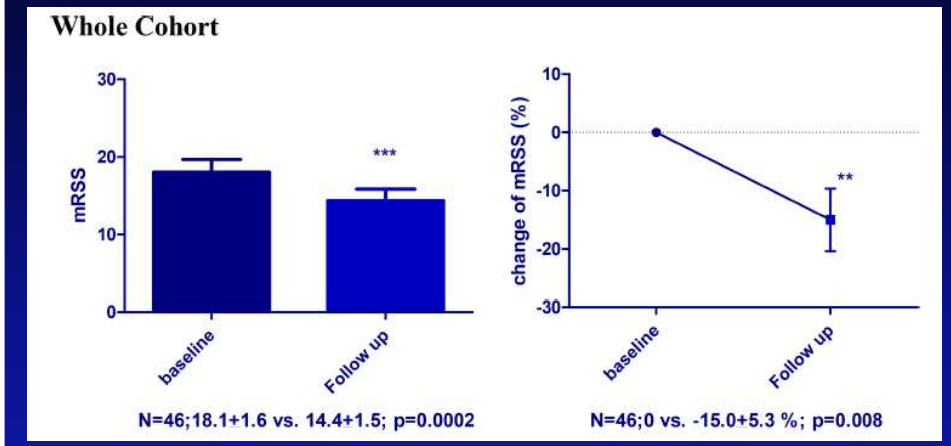
Jordan S, et al. *Ann Rheum Dis* 2014;

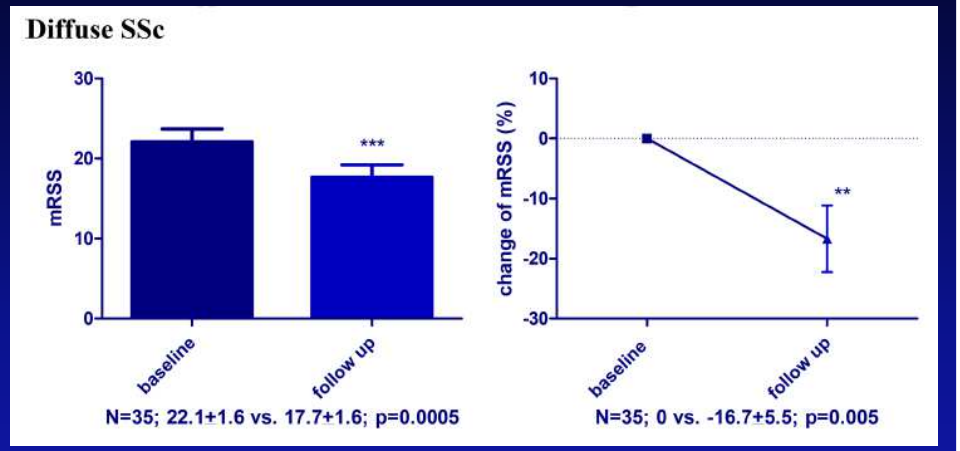
Table 1 Baseline demographics and clinical characteristics of all analysed SSc patients (N=63)

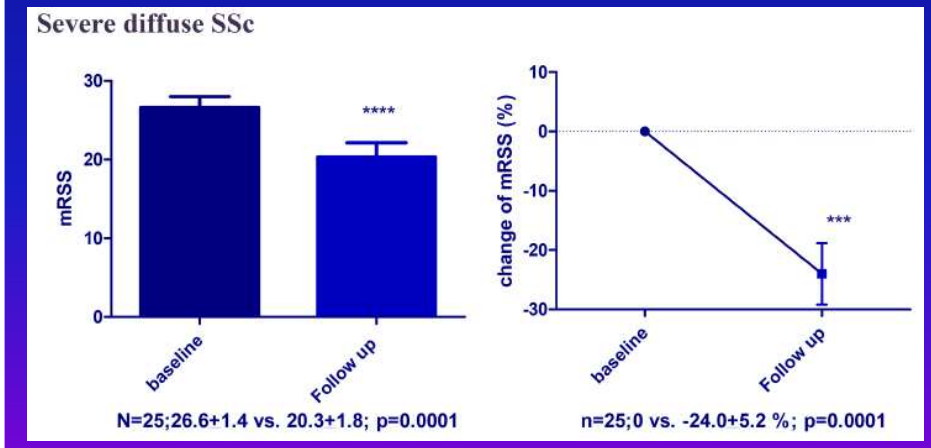
Baseline characteristics (N=63)		
Age (years) mean±SEM	N=63; 50.9±1.6	
Sex	n	(%)
Female	45	71.4
Scleroderma subtype		
Diffuse	46	73.0
Limited	17	27.0
Disease duration in years median (IQR)	N=60; 6 (3–11)	
Follow-up in months (IQR)	7 (4–9)	
Autoantibodies positive	n/N	(%)
ACA	3/62	4.8
Anti-RNA polymerase III	3/52	5.8
Anti-Scl-70	42/61	68.9
Anti-U1-snRNP	2/50	4.0

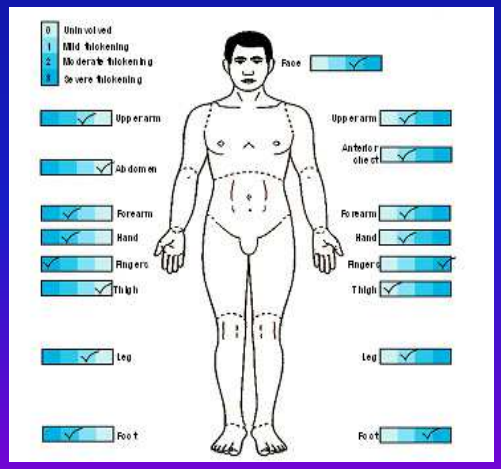


Change of modified Rodnan Skin Score (mRSS)









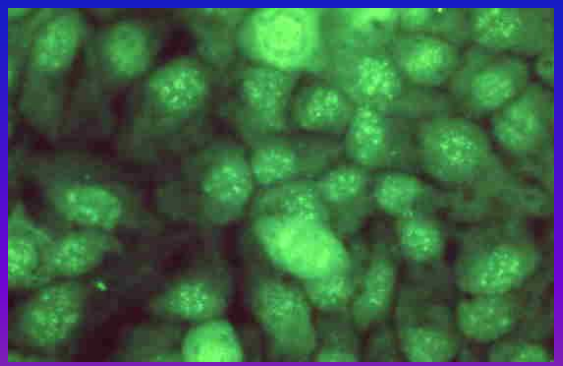
Effects and safety of rituximab in systemic sclerosis: an analysis from the European Scleroderma Trial and Research (EUSTAR) group

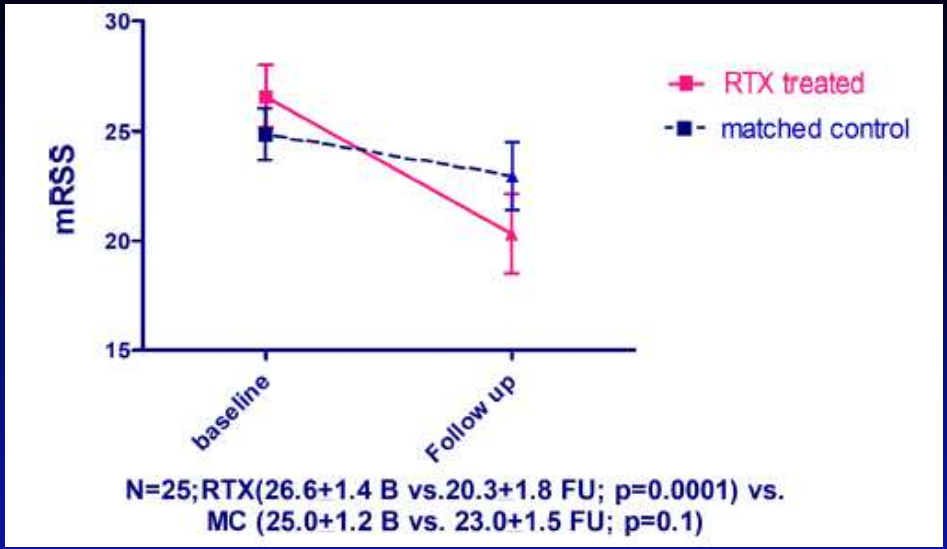
Jordan S, et al. *Ann Rheum Dis* 2014;

Table 3 Baseline demographics and clinical characteristics of diffuse, severe SSc patients treated with RTX matched with diffuse, severe control SSc patients (N=25 pairs)

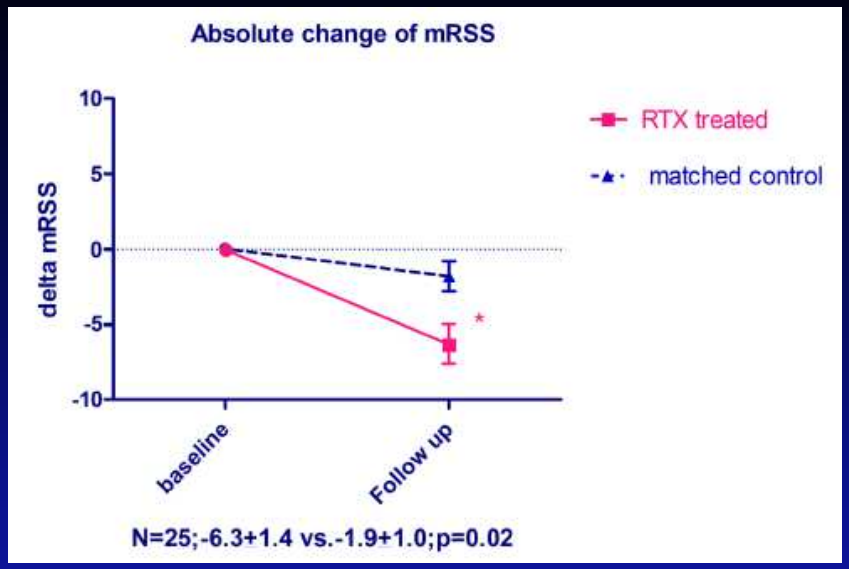
Baseline characteristics of SSc patients with diffuse severe skin fibrosis (N=25 each group)

	RTX treated		Matched control		p Value
Age (years) mean±SEM	N=25; 45.0±2.4		N=25; 50.0±3.0		0.2
Sex	n/N	%	n/N	%	
female	16	64.0	19	76.0	0.5
mRSS	N=25; 26.6±1.4		N=25; 25.0±1.2		0.03*
Disease duration in years median (range)	5 (3–7)		5 (3–7)		0.9
Follow-up in months (range)	6 (5–9)		7 (4–9)		0.4
Autoantibodies positive	19/25	76.0	15/20	75.0	1.0
ACA	1/25	4.0	1/18	5.5	1.0
Anti-RNA polymerase III	3/21	14.3	1/11	9.1	1.0
Anti-Scl-70	16/23	69.6	14/20	70.0	1.0
Anti-U1-snRNP	0/22	0	1/15	6.7	0.4
DMARDs treatment	20/24	83.3	16/22	72.7	0.5

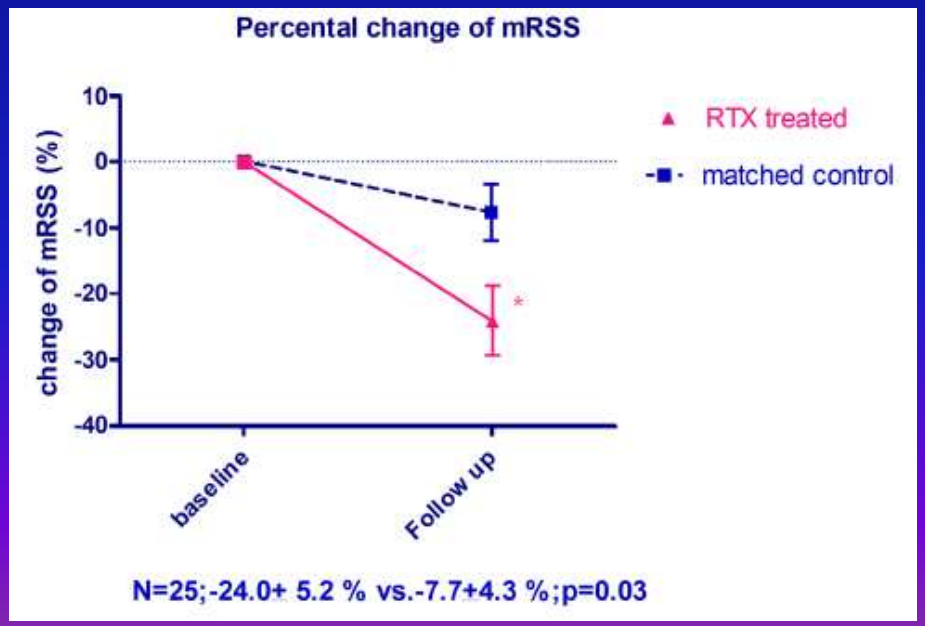




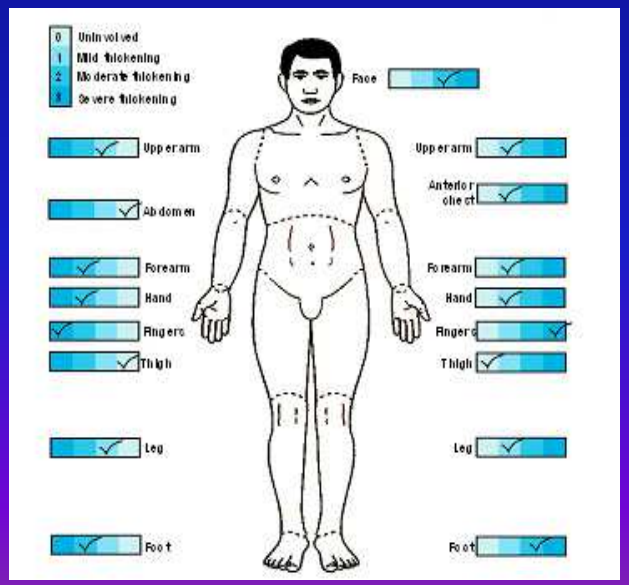
N=25;RTX(26.6+1.4 B vs.20.3+1.8 FU; p=0.0001) vs.
MC (25.0+1.2 B vs. 23.0+1.5 FU; p=0.1)

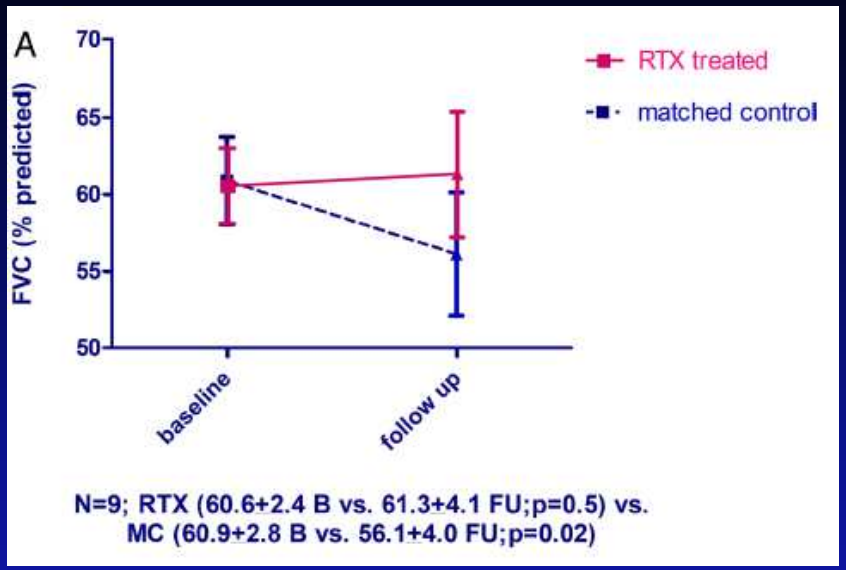


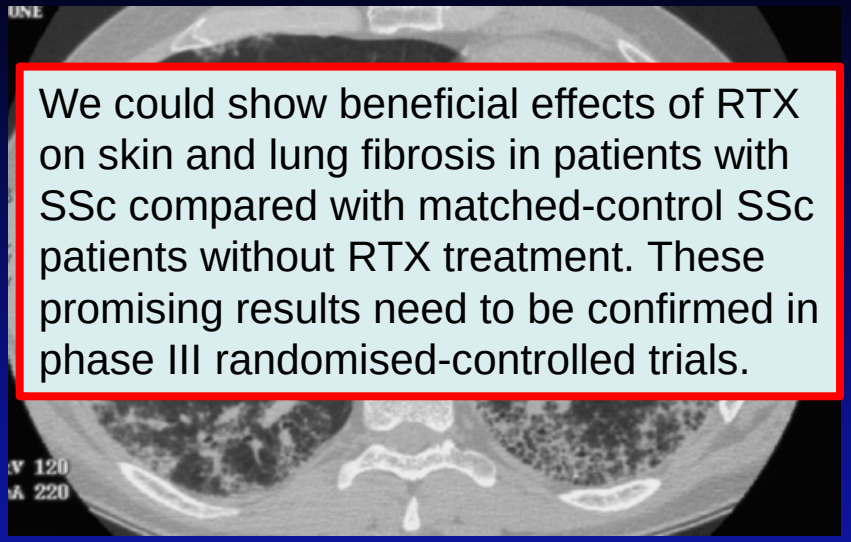
N=25;-6.3+1.4 vs.-1.9+1.0;p=0.02



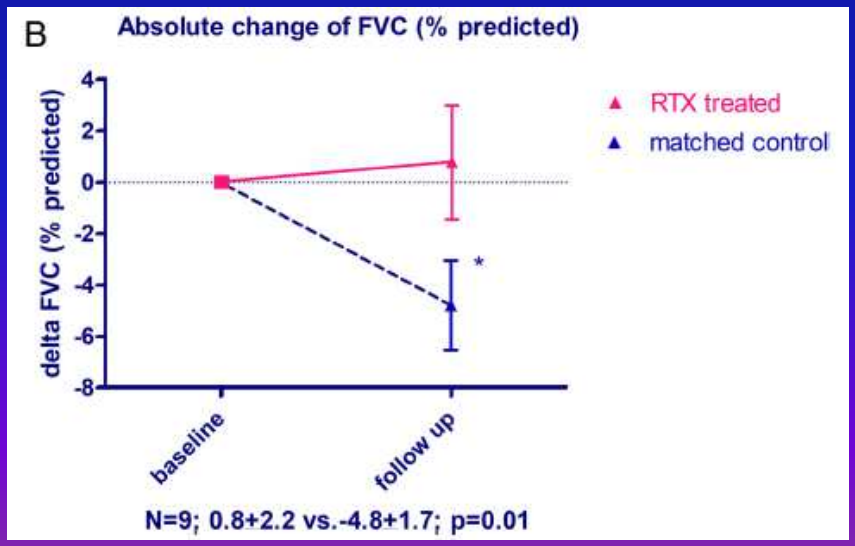
N=25;-24.0+ 5.2 % vs.-7.7+4.3 %;p=0.03

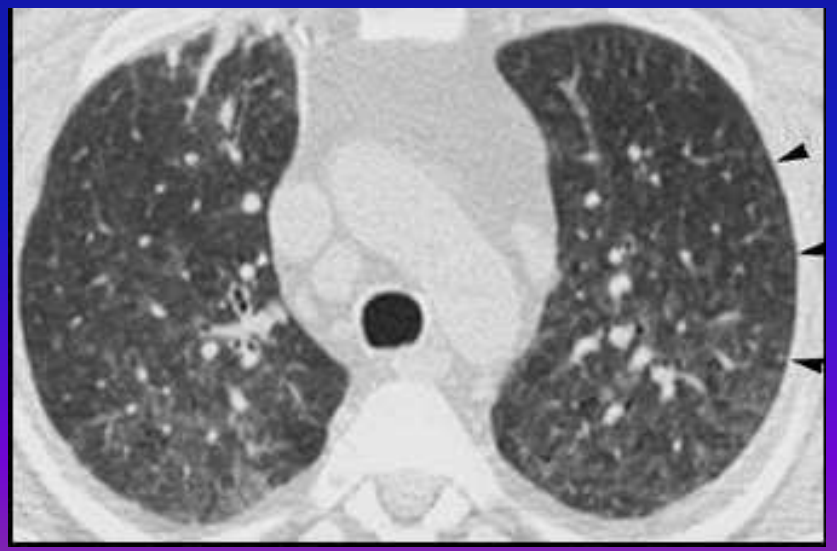






We could show beneficial effects of RTX on skin and lung fibrosis in patients with SSc compared with matched-control SSc patients without RTX treatment. These promising results need to be confirmed in phase III randomised-controlled trials.





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Rheum Dis Clin N Am
34 (2008) 1–15

RHEUMATIC
DISEASE CLINICS
OF NORTH AMERICA

The Many Faces of Scleroderma

Virginia D. Steen, MD

Department of Medicine, Georgetown University, 3800 Reservoir Road, LL Gorman, Washington, DC 20007, USA

In summary, scleroderma-specific autoantibodies are strongly associated with meaningful clinical manifestations. These antibodies can be helpful in determining prognosis, and monitoring and treating patients. They should be used in performing clinical trials and in doing genetic and basic research. Hopefully, these scleroderma antibodies will lead to a better understanding of the pathogenesis of scleroderma.

Table 1
Features of patients with limited scleroderma-specific autoantibodies

Antibody	ACA	Th/To	Pm/Scl	U1-RNP
No. of patients	291	72	36	71
Male sex, %*	**8**	19	19	21
African African, %*	3	4	3	**13**
Age of onset*	42	40	38	**33**
Diffuse SSc, %*	5	7	22	20
Disease duration				
At diagnosis*	**8.7**	**7.9**	3.2	3.2
Joints, %*	60	60	75	**94**
Digital ulcers, %*	**61**	29	47	49
Gangrene, %*	**18**	5	5	11
Digital tuft	**27**	7	**32**	17
Resorption* (x-ray numbers actually performed)	(41/151)	(2/28)	(7/22)	(5/29)
Calcinosis, %*	**46**	**22**	**39**	14
Muscle inflammation, %*	1	6	**58**	**27**
Any GI, %	57	33	39	39
Severe GI, %*	8	**13**	0	14
Any lung, %	45	62	58	53
Number with PFTs	(184)	(49)	(22)	(49)
Severe fibrosis, %*	6	**16**	**27**	**22**
Lowest FVC,* % predicted	87	**70**	74	75
Isolated PAH*	**19**	**32**	3	14
Severe heart, %*	4	7	6	11
Renal crisis, %*	1	4	4	7
Survival, % cumulative survival from diagnosis				
5 y, 10 y	85,75	**78,65**	95,72	**78,65**

Major differences in bold.

Abbreviations: ACA, anticentromere antibody; FVC, forced vital capacity; GI, gastrointestinal; PFT, pulmonary function test; PAH, pulmonary arterial hypertension; SSc, systemic sclerosis.

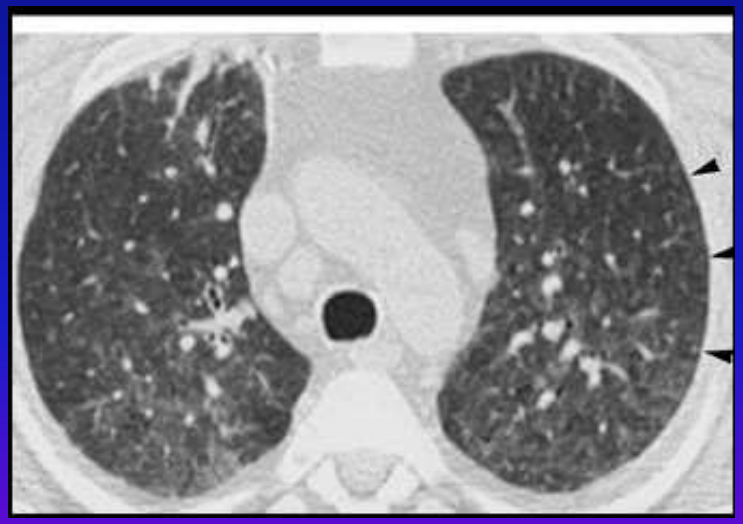
* $P < .001$ by analysis of variance.

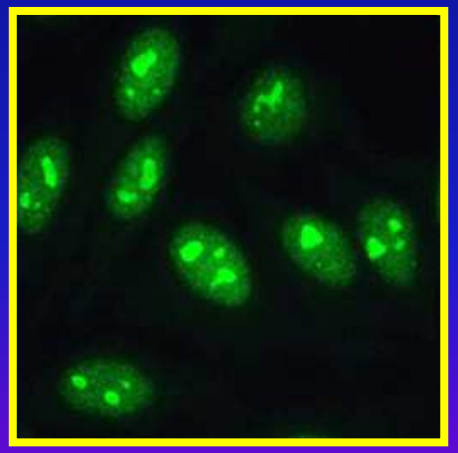
Steen, 2008

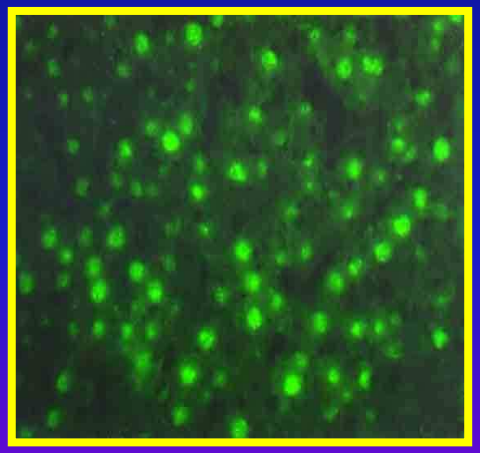
Good outcome of interstitial lung disease in patients with scleroderma associated to anti-PM/Scl antibody

Alfredo Guillen-Del Castillo, MD[a,*], Carmen Pilar Simeón-Aznar, MD, PhD[a], Vicent Fonollosa-Pla, MD, PhD[a], Serafín Alonso-Vila, MD[a], María M. Reverte-Vinaixa, MD[b], Xavier Muñoz, MD, PhD[c], Esther Pallisa, MD[d], Albert Selva-O'Callaghan, MD, PhD[a], Andreu Fernández-Codina, MD[a], Miquel Vilardell-Tarrés, MD, PhD[a]

Seminars in Arthritis and Rheumatism ∎ (2014)



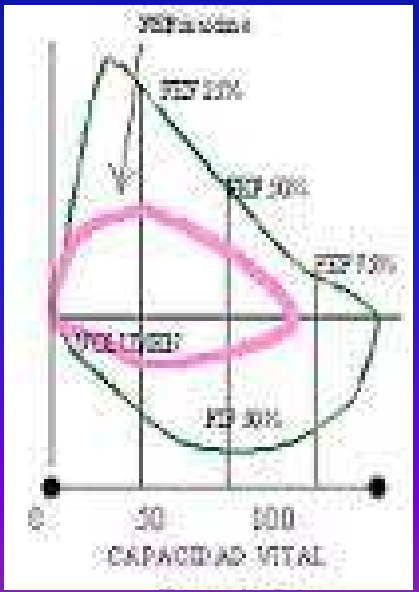


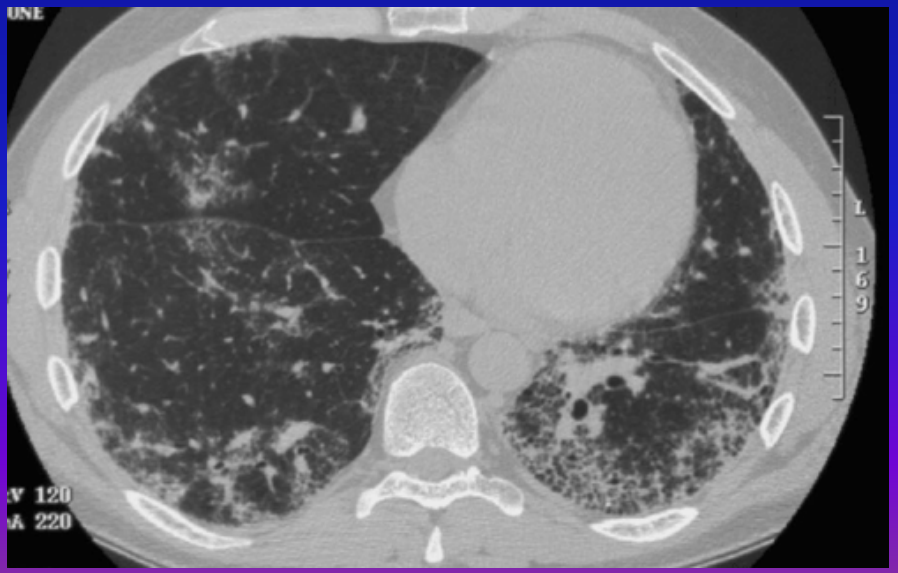


63 Pacientes ESC – EPID : 14 anti-PM/Scl >< 49 anti-Scl 70

Lung outcome

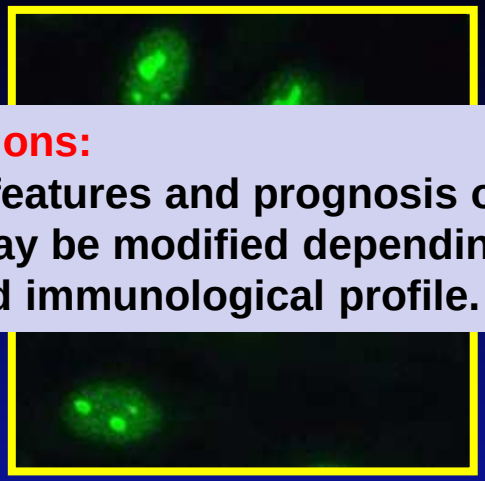
	Global (n = 63)	Anti-Scl-70 (n = 49)	Anti-PM/Scl (n = 14)	P value
Dyspnea, n (%)	43 (68.2)	36 (73.4)	7 (50)	0.03
Pulmonary hypertension, n (%)	19 (30.1)	16 (32.7)	3 (21.4)	0.52
Follow-up[a], median (IQR), years	7.0 (3.5–10.0)	7.1 (3.7–9.1)	5.8 (2.8–11.1)	0.86
Differences in PFTs, median (IQR)				
ΔFVC, % predicted	−7.2 (−16.0 to −0.1) (n = 55)	−10.9 (−24.5 to −2.3) (n = 42)	1.1 (−9.1 to 13.4) (n = 13)	0.004
ΔKCO, % predicted	−12.8 (−24.7 to −0.3) (n = 32)	−7.5 (−25.0 to −0.2) (n = 23)	−14.6 (−31.3 to −4.6) (n = 9)	0.36
Differences in PFTs/year median (IQR)				
ΔFVC, % predicted/year	−1.2 (−4.0 to −0.0) (n = 55)	−1.8 (−5.0 to −0.4) (n = 42)	0.1 (−1.6 to 1.9) (n = 13)	0.01
ΔKCO, % predicted/year	−1.6 (−3.7 to −0.3) (n = 32)	−1.2 (−3.7 to −0.3) (n = 23)	−1.8 (−3.8 to −0.1) (n = 9)	0.57
Worsening FVC ATS/ERS, n (%)	24/55 (43.6)	22/42 (52.4)	2/13 (15.4)	0.01
Improvement FVC ATS/ERS, n (%)	7/55 (12.7)	3/42 (7.1)	4/13 (30.8)	0.04
FVC < 50%, n (%)	19/55 (34.5)	18/42 (42.9)	1/13 (7.7)	0.02





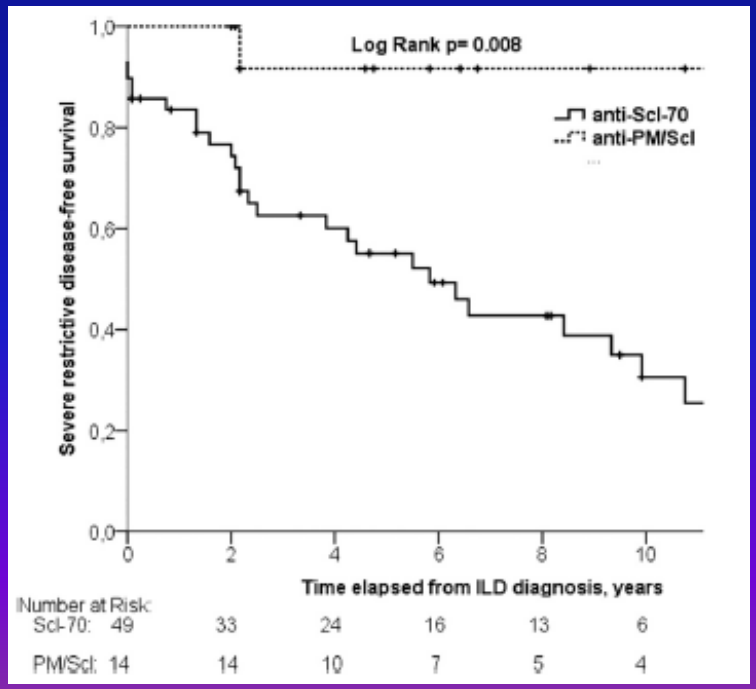
Regimens of treatment

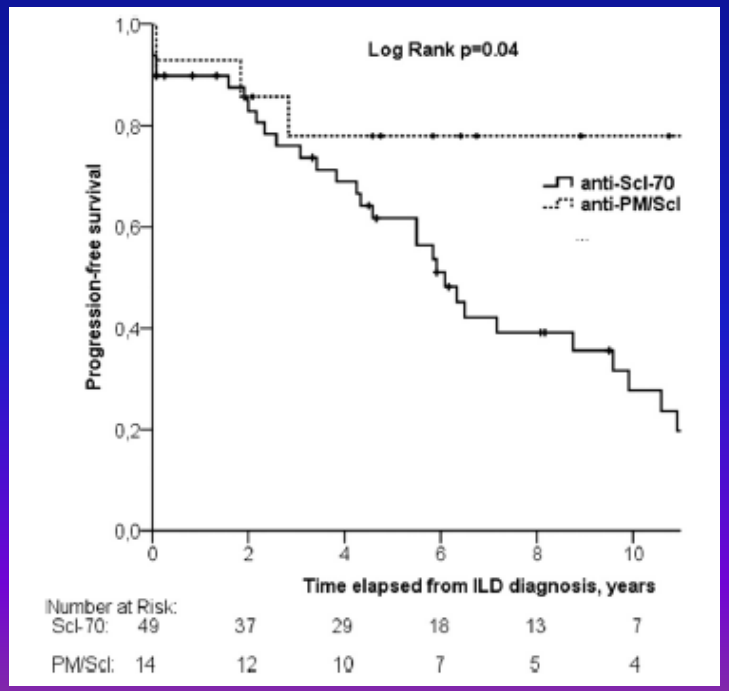
	Global ($n = 63$)	Anti-Scl-70 ($n = 49$)	Anti-PM/Scl ($n = 14$)	*P* value
Prednisone < 10 mg/day (> 3 months)	37 (58.7)	28 (57.1)	9 (64.3)	0.63
Prednisone > 10 mg/day (> 3 months)	38 (60.3)	31 (63.3)	7 (50.0)	0.37
Cyclophosphamide	21 (33.3)	20 (40.8)	1 (7.1)	0.02
Mycophenolate	21 (33.3)	20 (40.8)	1 (7.1)	0.02
Azathioprine	18 (28.6)	14 (28.6)	4 (28.6)	1.0
Ciclosporin A or tacrolimus	8 (12.7)	1 (2.0)	7 (50.0)	< 0.001
Intravenous immunoglobulin	8 (12.7)	4 (8.2)	4 (28.6)	0.06
Rituximab	4 (6.3)	4 (8.2)	0 (0.0)	0.27
Oxigenotherapy	4 (6.3)	4 (8.2)	0 (0.0)	0.27



Conclusions:

Several features and prognosis of ILD inSSc may be modified depending on the identified immunological profile.






ESCLERODERMIA
ESCLERODERMIA
ESCLEROSIS
ANTI-CENTRÓMERO
C.R.E.S.T.
ESCLERODERMIA
RAYNAUD PRIMARIO
ESCLEROSIS
Anti-nucleolares
ESCLERODACTILIA
C.R.S.I.
SISTÉMICA
Antitopoisomerasa I
MORFEA
PROGRESIVA
HTAP
Síndrome de Raynaud
Sistémica
LOCALIZADA
Calcinosis

*Report of a Meeting of Physicians and Scientists, Royal Free Hospital School of Medicine, London**

Panel: **Classification of the systemic sclerosis subsets**

1. **"Pre-scleroderma"** Raynaud's phenomenon plus nailfold capillary changes; disease specific circulating anti-nuclear autoantibodies (anti-topoisomerase-I, anti-centromere [ACA], or nucleolar); and digital ischaemic changes.
2. **Diffuse cutaneous SSc (dcSSc)** Onset of skin changes (puffy or hidebound) within 1 year of onset of Raynaud's; truncal and acral skin involvement; presence of tendon

4. Scleroderma sine scleroderma Raynaud's; no skin involvement; presentation with pulmonary fibrosis, scleroderma renal crisis, cardiac or gastrointestinal disease; antinuclear antibodies may be present (Scl70, ACA, nucleolar)

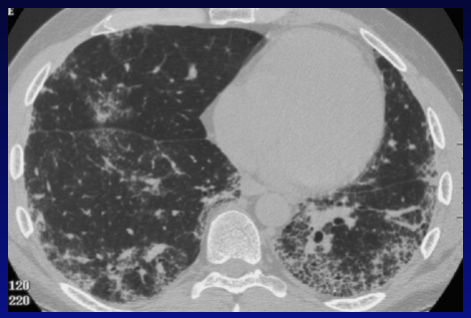
late incidence of pulmonary hypertension, with or without interstitial lung disease, skin calcification, telangiectasiae and gastrointestinal involvement; high prevalence of ACA (70–80%); dilated nailfold capillary loops, usually without capillary dropout.

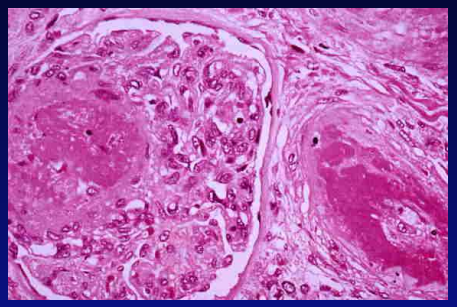
4. **Scleroderma sine scleroderma** Raynaud's; no skin involvement; presentation with pulmonary fibrosis, scleroderma renal crisis, cardiac or gastrointestinal disease; antinuclear antibodies may be present (Scl70, ACA, nucleolar)

Lancet 1996; **347:** 1453–58

Esclerodermia *sine* esclerodermia

Fenómeno de Raynaud
Acs. Antinucleares positivos
Afección visceral típica de ESC
Sin afección cutánea





1954: primer caso
1962: Rodnan y Fennel: “progressive systemic sclerosis *sine* scleroderma
1968: Giordano : Subtipo de esclerodermia *sine* esclerodermia
1988: LeRoy y Medsger: se incluye en esclerodermia cutánea limitada
2000: Poormoghim: 48 casos
2013: Marangoni: 79 casos
2014: Diab: 27 casos

LeRoy[25]	2 subsets: diffuse cutaneous SSc: onset of RP within 1 year; truncal and acral skin involvement; tendon friction rubs; early incidence of ILD, renal failure, diffuse GI disease, myocardial involvement; absence of ACA, abnormal ND; limited cutaneous SSc: RP for years, skin involvement limited to hands, face, feet, forearms or absent; late incidence of PAH, trigeminal neuralgia, calcinosis, telangiectasia; high incidence of ACA, abnormal NC	877

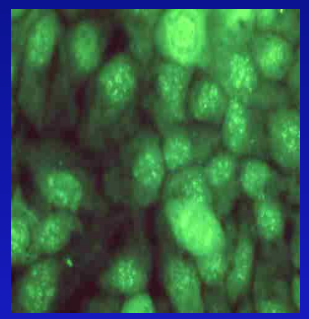
Systemic sclerosis sine scleroderma and limited cutaneous systemic sclerosis: similarities and differences

C.P. Simeón-Aznar[1], C. Tolosa-Vilella[2], L. Gabarró-Juliá[3], M. Campillo-Grau[4], A. Guillén del Castillo[1], V. Fonollosa-Plá[1], M. Vilardell-Tarrés[1]

N: 444

M/V: 398 / 46 (89,6 % / 10,4 %)

Esclerodermia definida:	415	(93,4 %)
Pre-esclerodermia:	29	(6,5%)
Limitada:	267	(60,1 %)
Difusa:	87	(19,5 %)
Sine esclerodermia	61	(13,7 %)



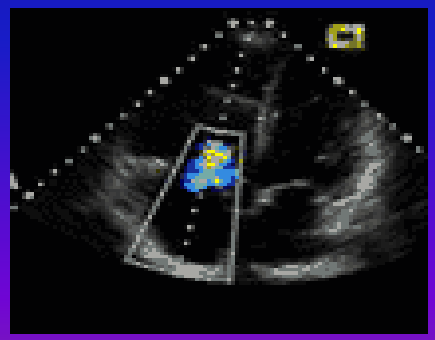


Table I. Organ involvement in 45 patients with ssSSc and 186 patients with lcSSc.

Peripheral vascular	Raynaud's phenomenon	43 (96%)	179 (96%)	0.414
	Digital ulcers	7 (16%)	94 (50%)	**0.000**
	Telangiectasia	28 (62%)	140 (75%)	0.093
	Calcinosis	5 (11%)	48 (26%)	**0.047**
	Raynaud's phenomenon	43 (96%)	179 (96%)	0.414
	Digital ulcers	7 (16%)	94 (50%)	**0.000**
	Telangiectasia	28 (62%)	140 (75%)	0.093
	Calcinosis	5 (11%)	48 (26%)	**0.047**
	Acro-osteolysis	0 (0%)	18 (10%)	**0.028**
	PAH	13 (29%)	35 (19%)	0.15
	Pyrosis	16 (36%)	92 (49%)	0.099
	Barret's oesophagus	1 (2%)	3 (2%)	0.582
	Gastric hypomotility	6 (13%)	24 (13%)	1
	Malabsorption	1 (2%)	6 (3%)	1
	Neoplasia	4 (9%)	13 (7%)	0.750

TABLE 2 Comparison of ssSSc series reported in the medical literature with Brazilian ssSSc patients

Variables	Brazilian	Pittsburgh	*P*	German	*P*	Spain	*P*
Age at disease onset, mean (S.D.) or mean (range)	46.04 (13.1)	51 (17–78)	0.058[a]	NR		44.9 (18.2)	0.671[a]
Female	76/79 (96.2)	41/48 (85)	0.041[b,*]	20/22 (90.9)	0.398[b]	62/69 (89.8)	0.189[b]
Digital ulcers	19/79 (24.1)	16/48 (33)	0.256[c]	7/22 (31.8)	0.461[c]	10/69 (14.5)	0.209[c]
Articular	35/79 (44.3)	21/48 (44)	0.951[c]	7/22 (31.8)	0.293[c]	9/69 (13)	<0.001[c,*]
Muscular	10/79 (12.7)	2/48 (4)	0.132[b]	3/22 (13.6)	>0.999[b]	2/69 (2.9)	0.036[b,*]
Oesophageal dysmotility	64/77 (83.1)	37/48 (77)	0.475[c]	16/22 (72.7)	0.367[b]	31/69 (44.9)	<0.001[c,*]
ILD	37/65 (56.9)	32/47 (68)	0.230[c]	16/22 (72.7)	0.189[c]	44/69 (63.7)	0.418[c]
PH	18/79 (22.8)	11/48 (23)	0.986[c]	3/22 (13.6)	0.349[c]	17/69 (24)	0.791[c]
ACA	33/79 (41.8)	15/45 (33)	0.354[c]	8/22 (36.4)	0.648[c]	27/69 (24.6)	0.977[c]
Mortality rate	6/79 (7.6)	19/48 (40)	<0.001[c,*]	NR		6/69 (8.7)	0.806[c]

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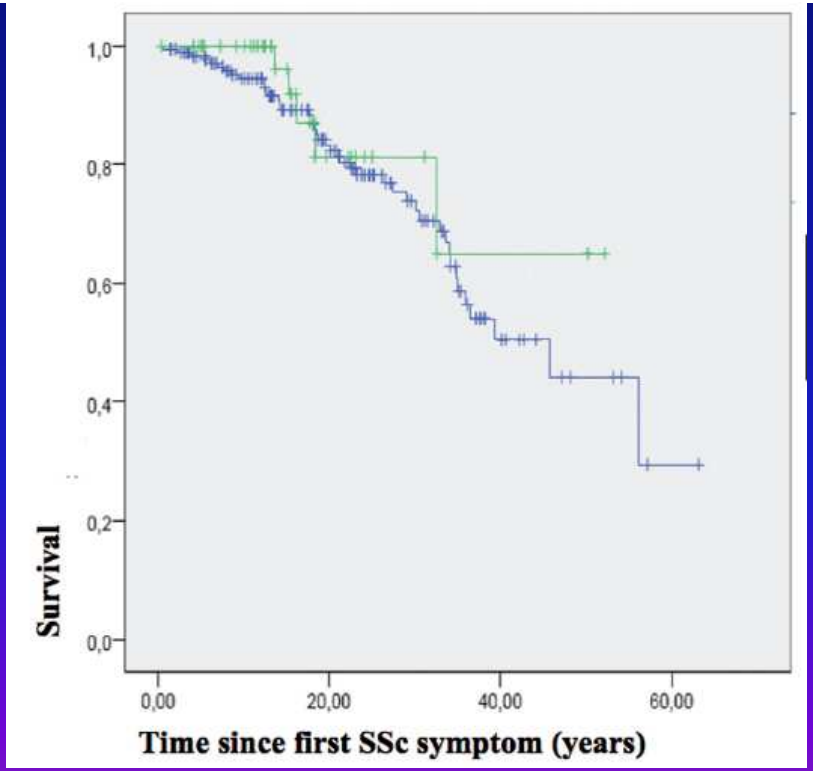
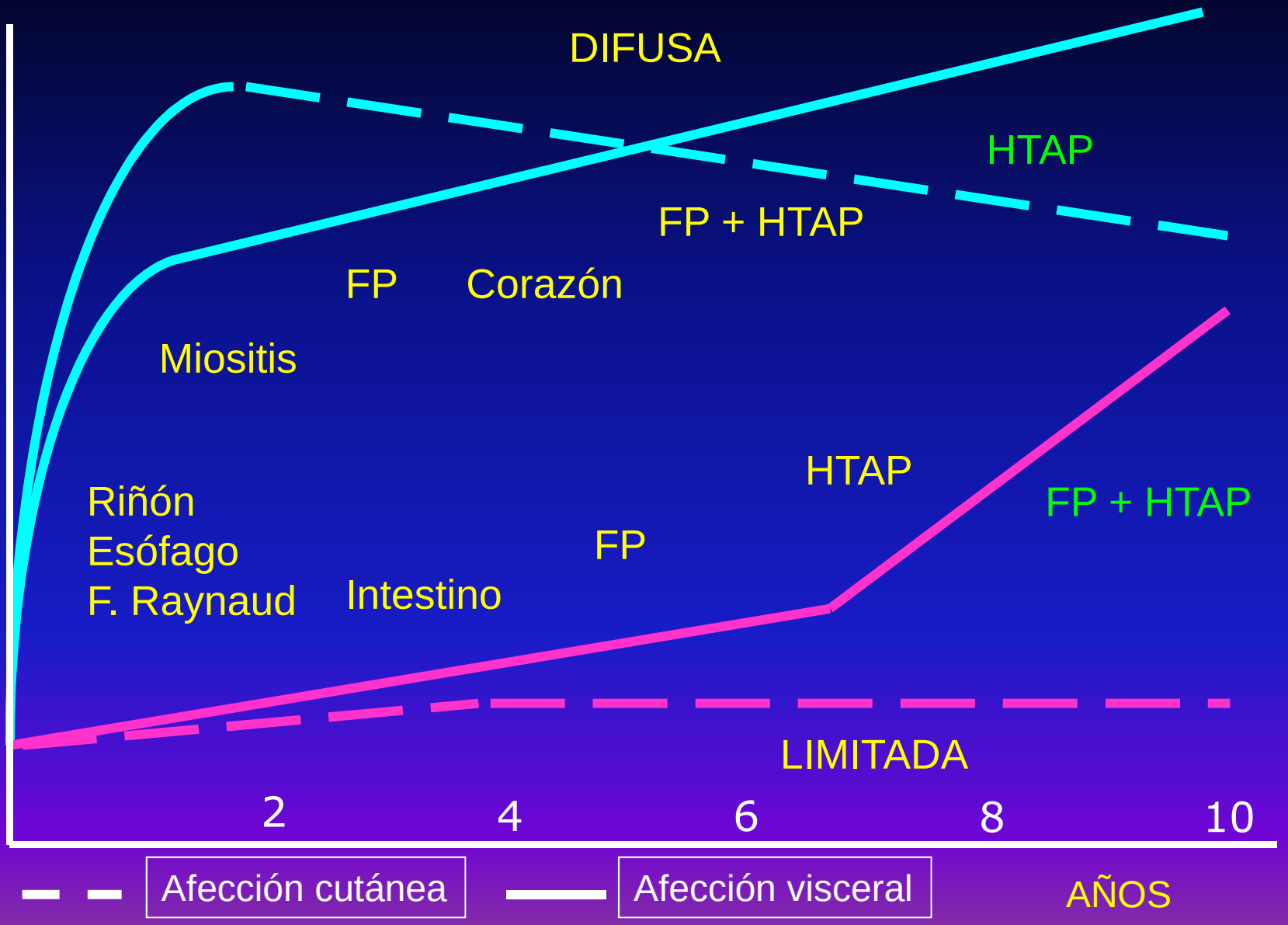
C.P. Simeón-Aznar[1], C. Tolosa-Vilella[2], L. Gabarró-Juliá[3], M. Campillo-Grau[4], A. Guillén del Castillo[1], V. Fonollosa-Plá[1], M. Vilardell-Tarrés[1]

Conclusions. *ssSSc and lcSSc patients share demographic, clinical and immunologic features. Survival is also similar in both groups. Differences are mainly due to peripheral vascular manifestations. However, despite great similarities, we believe that ssSSc patients should be considered as a different subset in order to avoid misdiagnosis. ssSSc patients should be truly differentiated from early SSc using sensitive and specific studies looking for any asymptomatic organ involvement.*



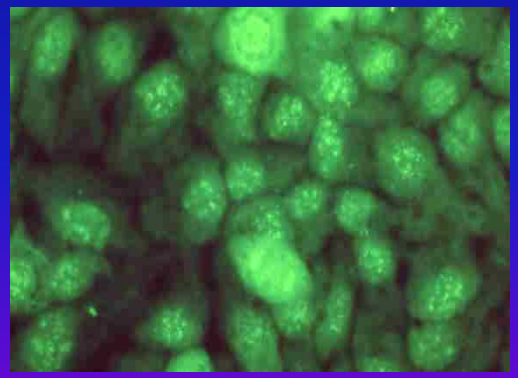
Esclerodermia. Evolución



Early Systemic Sclerosis: Analysis of the Disease Course in Patients With Marker Autoantibody and/or Capillaroscopic Positivity

GABRIELE VALENTINI,[1] ANTONELLA MARCOCCIA,[2] GIOVANNA CUOMO,[1] SERENA VETTORI,[1] MICHELE IUDICI,[1] FRANCESCO BONDANINI,[2] CARLO SANTORIELLO,[3] ALDO CIANI,[2] DOMENICO COZZOLINO,[1] GIOVANNI MARIA DE MATTEIS,[2] SALVATORE CAPPABIANCA,[1] FILIBERTO VITELLI,[2] AND ALBERTO SPANÒ[2]

Arthritis Care & Research
Vol. 66, No. 10, October 2014, pp 1520–1527



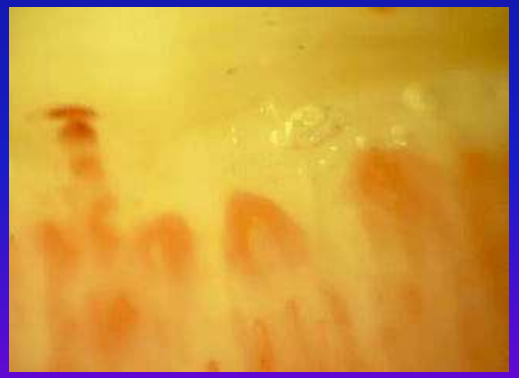
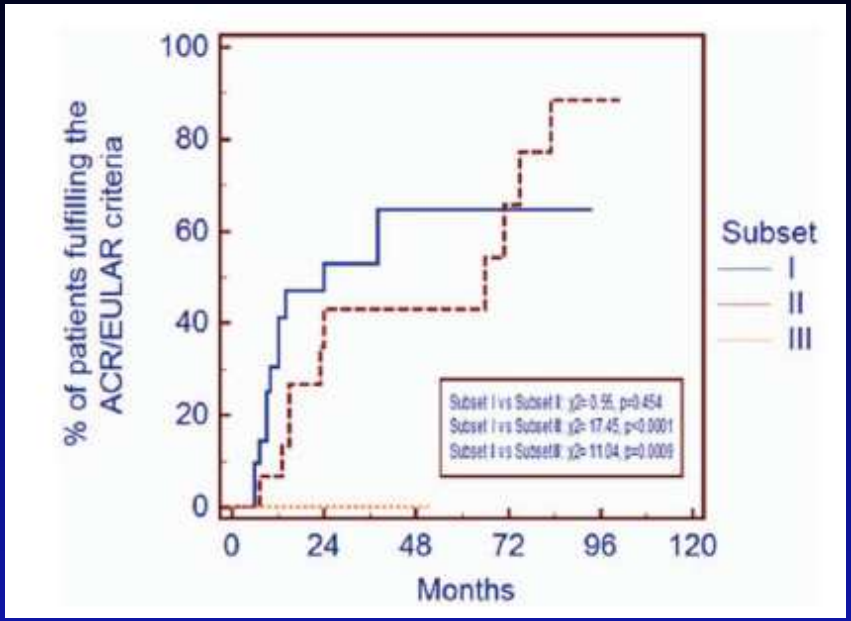
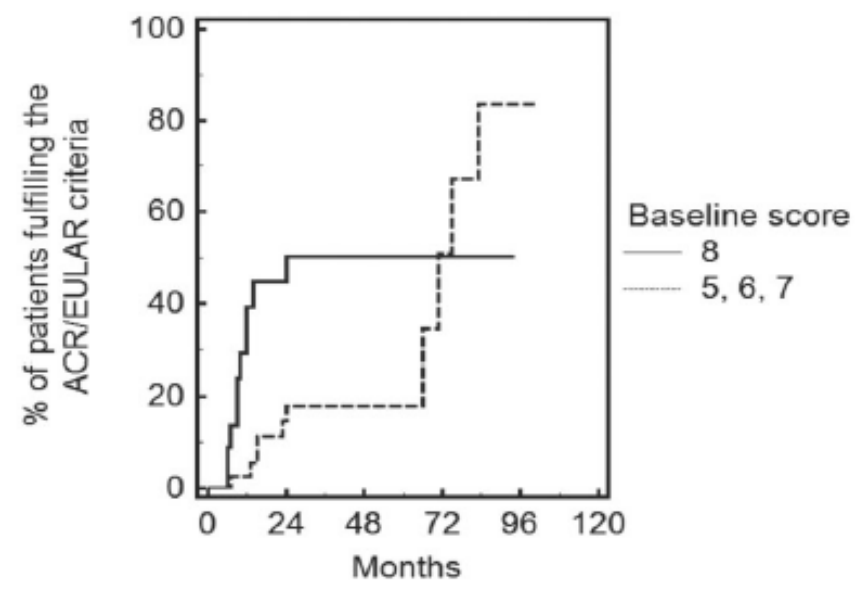
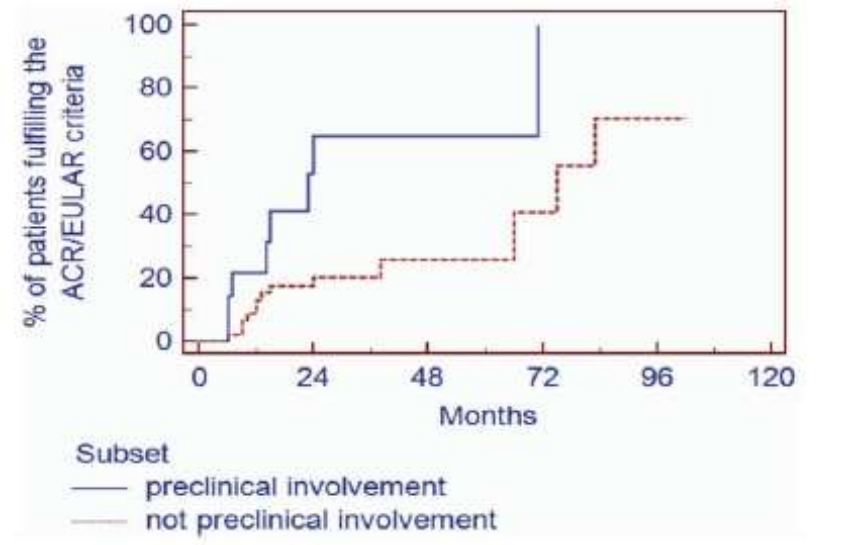


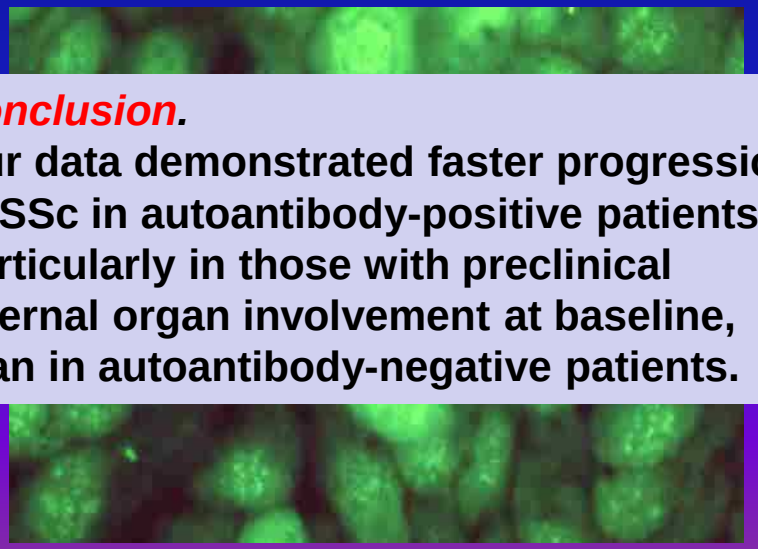
Table 1. Epidemiologic, serologic, and clinical features of the 3 early systemic sclerosis subsets and UCTD patients at baseline*

	UCTD patients (n = 44)	Naples Rheumatology (n = 40)	Rome Angiology (n = 20)	*P*
Sex, F/M	43/1	39/1	17/3	0.060
Age, median (range) years	39 (18–71)	41 (17–73)	34 (16–61)	0.146
Duration from RP onset, median (range) years	4 (0.4–30)	3 (0.5–24)	3 (1–20)	0.185
Subset 1		21	0	0.0001
Anti–Scl-70 positive		6	–	
Anticentromere positive		15	–	
Anti–RNA polymerase positive		0	–	
Megacapillaries only		19	–	
Avascular areas ± megacapillaries		2	–	
Puffy fingers		0	–	
Subset 2		15	0	0.0005
Anti–Scl-70 positive		3	–	
Anticentromere positive		12	–	
Anti–RNA polymerase positive		0	–	
Puffy fingers		1	–	
Subset 3		4	20	0.0001
Megacapillaries only		4	20	0.0001
Avascular areas ± megacapillaries		0	0	–
Puffy fingers		2	20	0.021









Conclusion.

Our data demonstrated faster progression of SSc in autoantibody-positive patients, particularly in those with preclinical internal organ involvement at baseline, than in autoantibody-negative patients.

Pre-esclerodermia >< Esclerodermia inicial

(Very early) *(Early)*

	Pre-SSc	SSc inicial	SSc sine
Fenómeno de Raynaud	Si	Si	Si
Alteraciones capilares	Si	Si	Si
AANs	Si	Si	Si
GI/ILD/HTAP/CRE/COR	No	No	Si
EEI hipotenso	No	Si	----
DLCO <70%	No	Si	----
Disfunción Diastólica	No	Si	----

Stem cell transplantation in systemic sclerosis

Ready for Clinical Practice?

5

Effects and safety of rituximab in systemic sclerosis:

These promising results need to be confirmed in phase III randomised-controlled trials.

Good outcome of interstitial lung disease in patients with scleroderma associated to anti-PM/Scl antibody

Several features and prognosis of ILD inSSc may be modified depending on the identified immunological profile**.**

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we believe that ssSSc patients should be considered as a different subset

Early Systemic Sclerosis: Analysis of the Disease Course in Patients With Marker Autoantibody and/or Capillaroscopic Positivity

Our data demonstrated faster progression of SSc in autoantibody-positive patients, particularly in those with preclinical internal organ involvement at baseline, than in autoantibody-negative patients.