Afección pulmonar intersticial en la Esclerodermia

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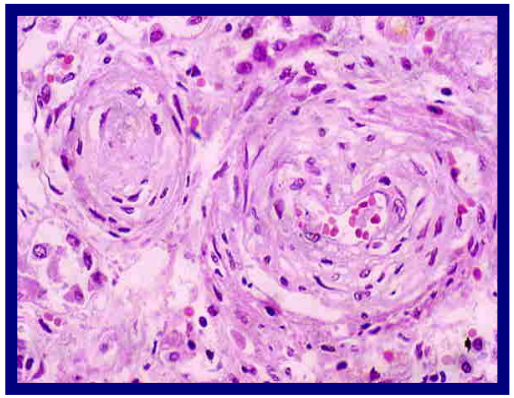
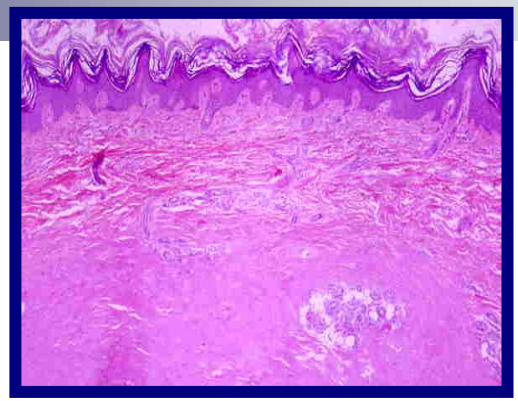
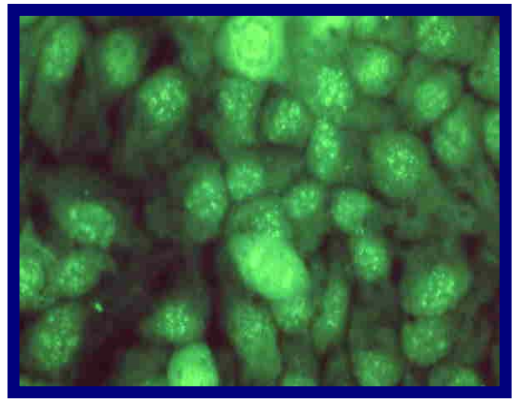
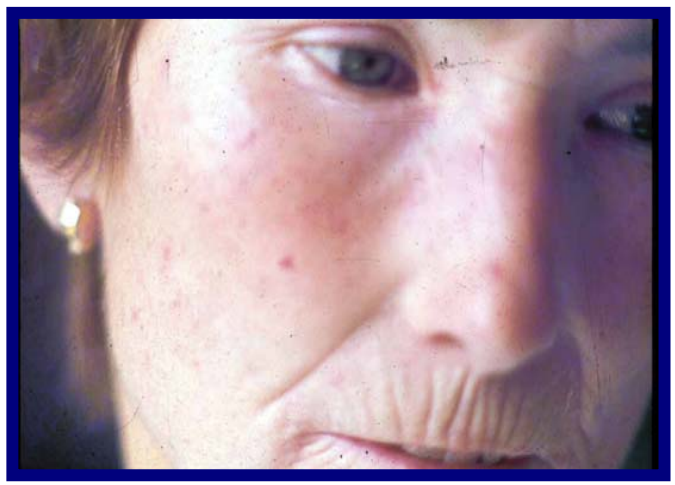
II REUNÓN EN ENFERMEDADES AUTOINMUNES SISTÉMICAS

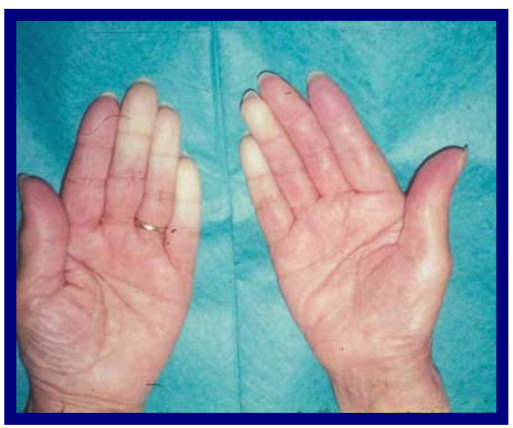
Bilbao 25-26 junio 2009

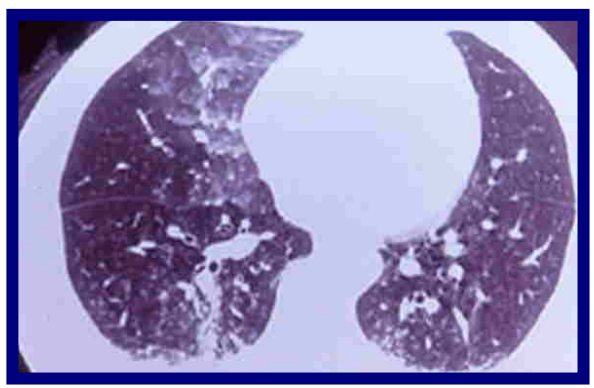


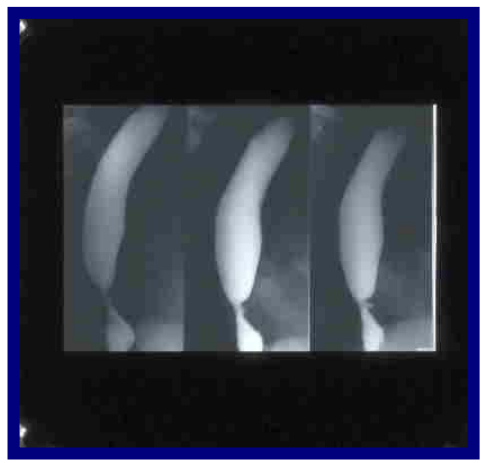






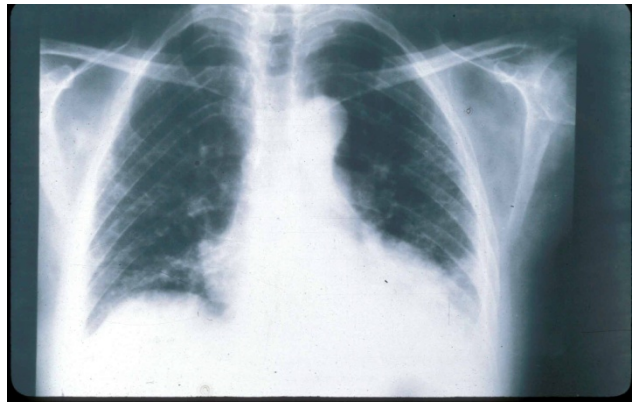






EPID asociada a Esclerodermia.

Prevalencia



N: 348

Fenómeno de Raynaud: 346 (99%)

Úlceras digitales: 171 (49%)

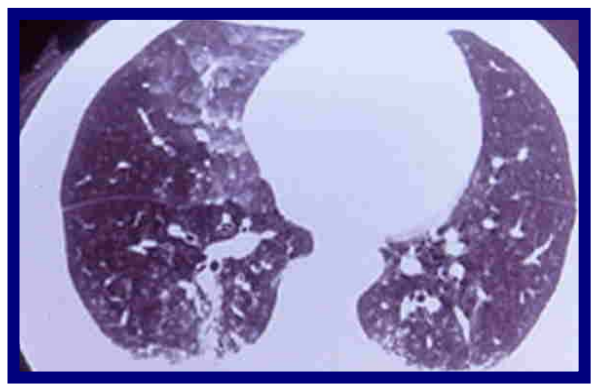
Afección osteomuscular: 245 (70%)

Afección digestiva: 249 (71%)

Afección respiratoria: 261 (75%)

EPID: 195 (56%) **(CVF<70%: 84 (24%)**

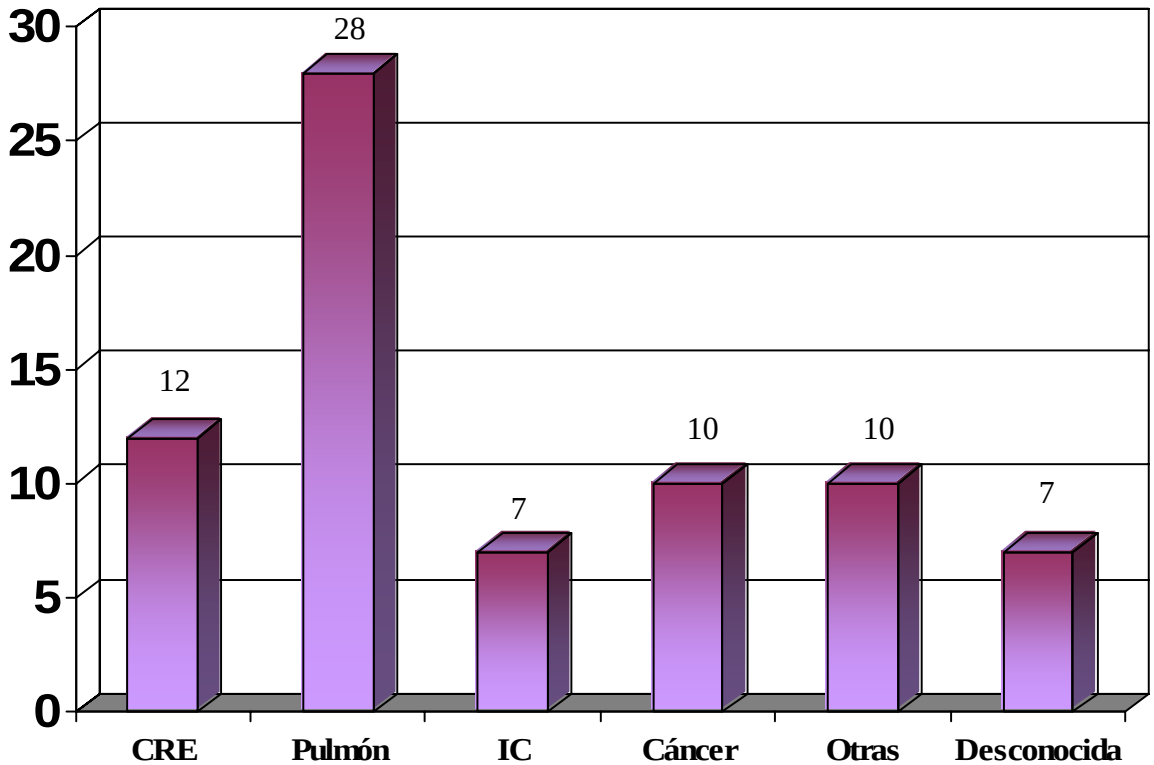
HTAP: 66 (19%) (HTAP (s> 55mmHg): 32 (9.7%)



Afección cardíaca: 164 (47%)

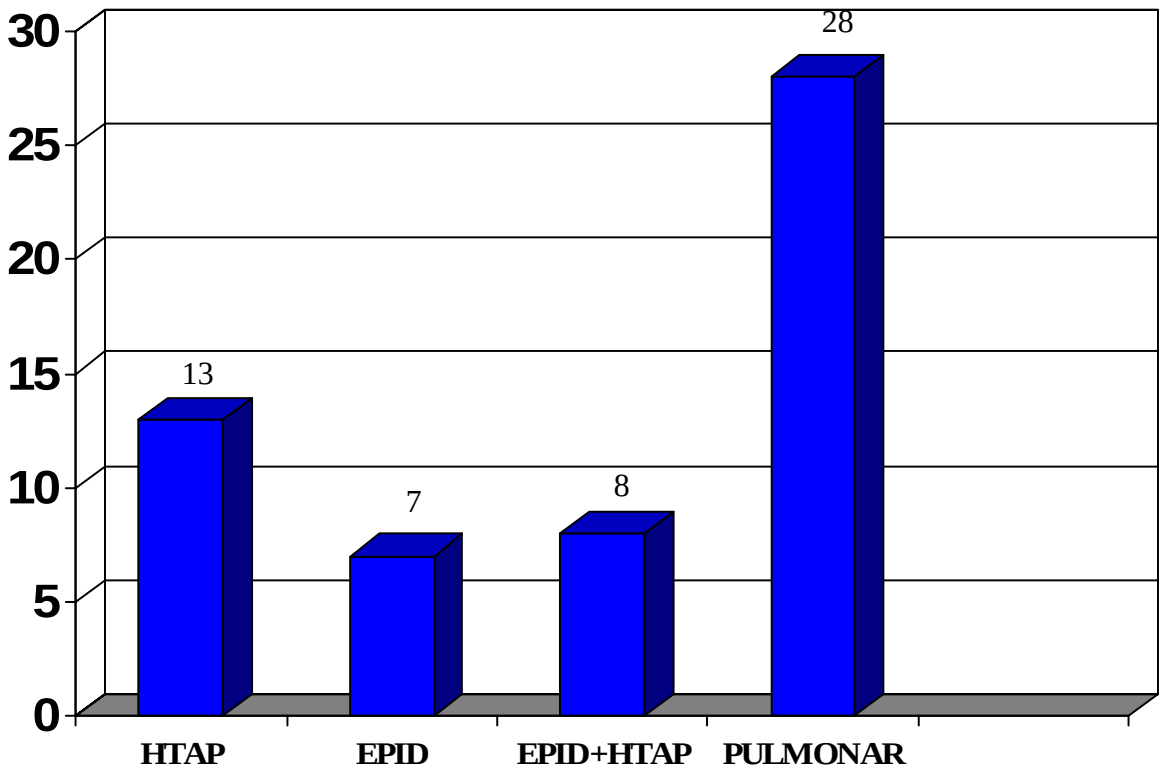
Afección renal (CRE): 14 (4%)

EPID asociada a Esclerodermia. Factor pronóstico



HVH pacientes 317 N° de muertes: 74

EPID asociada a Esclerodermia. Factor pronóstico

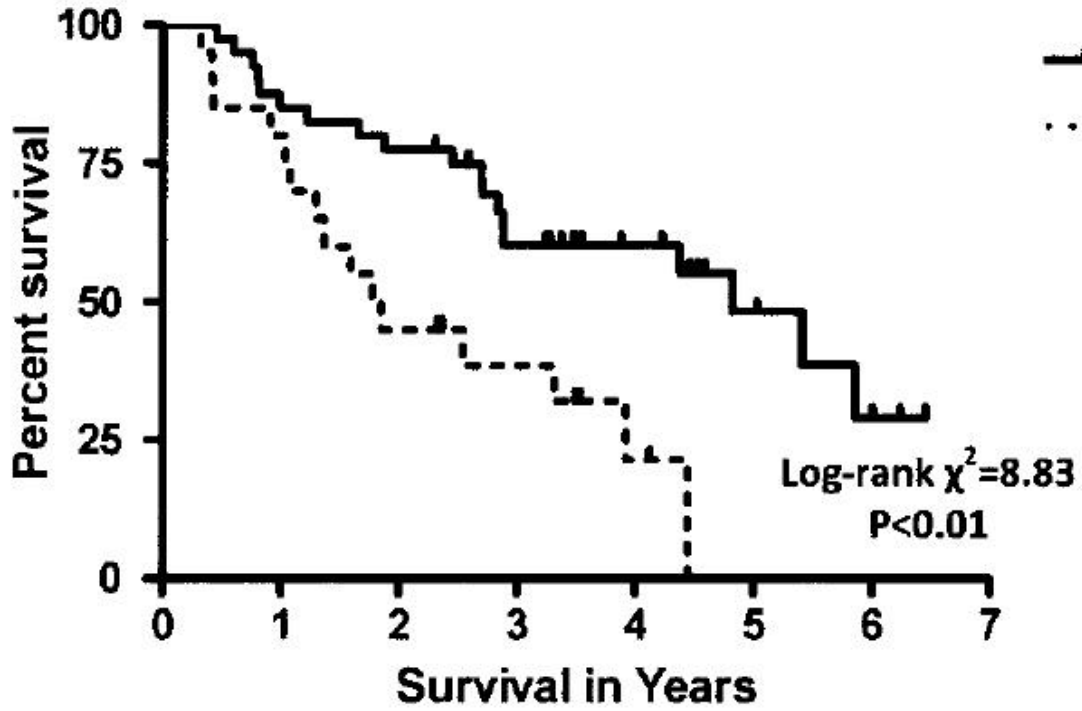


HVH pacientes 317 N° de muertes: 74

Survival in Pulmonary Hypertension Associated With the Scleroderma Spectrum of Diseases

Impact of Interstitial Lung Disease

ARTHRITIS & RHEUMATISM
Vol. 60, No. 2, February 2009, pp 569–577



39
20

	ES. Limitada n= 185	ES.Difusa n= 64
Tiempo inic-diag*	8.3a	1.4a
Fenómeno de Raynaud *	175/94%	46/71%
Telangiectasias	140/75%	48/75%
Calcinosis	48/ 23%	17/26%
Afección esofágica	110/59%	41/ 64%
HTAP	35/18%	13/20%
HTAP aislada*	13/7%	0/ 0%
Dilatación capilar*	134/ 83%	25/52%
Anticentrómero*	93/ 52%	1/ 1.7%
Roces tendinosos*	2/ 0.9%	8/12.5%
Afección visceral temprana:		
CRE*	3/ 1.7%	10/15.6%
EPID*	87/44.6%	47/ 73.4%
CVF<70*	35/23%	27/53%
Pérdida capilar*	18/11%	22/45.8%
Anti-Scl 70 *	17/10%	32/ 56%

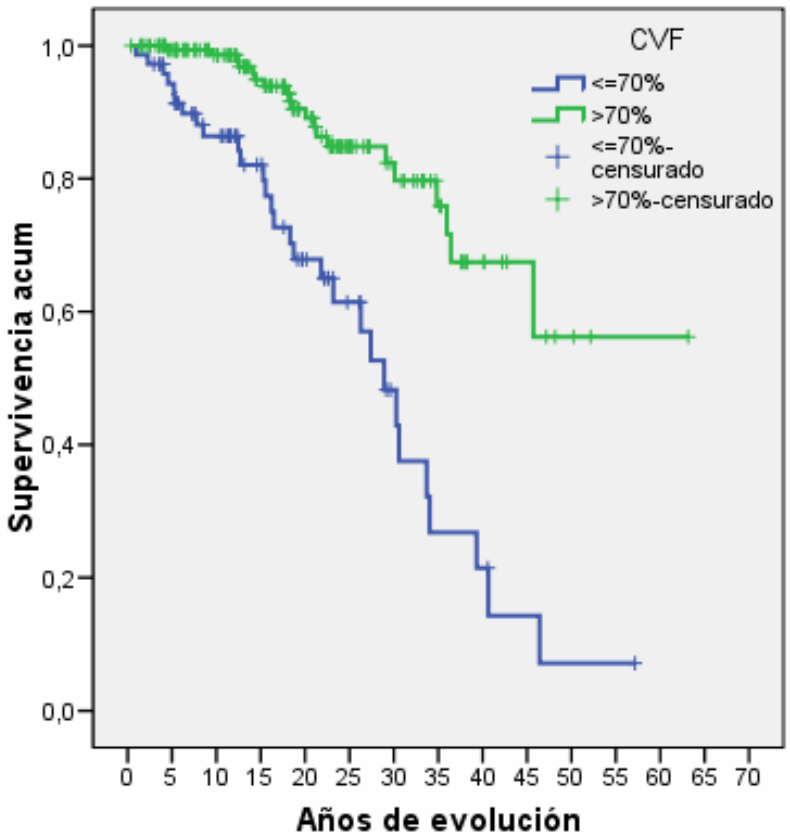
Hospital Vall d´Hebron, n=317

ES sin esclerodermia ES Limitada

N	44	(13%)	185	(58.5%)
ARA*	6	(13)	144	(77)
Úlceras *	7	(15)	94	(50.5)
Telangiec*	28	(62)	140	(75)
Calcinosis*	5	(7)	48	(26)
Osmusc	26	(57)	132	(71)
Digestiva	32	(71)	145	(78)
EPID	**16**	**(36)**	**87**	**(44.6)**
HTAP	13	(29)	35	(18)
Cardiaca	26	(58)	106	(57)
Renal	2	(4.4)	7	(4)
AAN	41	(91)	180	(97)
ACA	20	(46.5)	93	(53)
Lento	33	(80.5)	134	(82.7)

Hospital Vall d´Hebron, n=317

EPID asociada a Esclerodermia. Pronóstico.



Factores pronósticos	RR	*p*
Esclerodermia difusa	2,730	0,001
Edad de comienzo	1,079	0,0001
Fibrosis pulmonar	2,463	0,003
HTAP	2,802	0,0001
Crisis renal	30,062	0,0001

Hospital Vall d´Hebron n=317

EPID asociada a Esclerodermia. Diagnóstico.

Diagnóstico
Gravedad y pronóstico
Seguimiento
Decisión tto
Respuesta al tto.

⇒

PFR: espirometría
DLCO/VA

TACAR

Rheumatology 2008;47:v65–v67

Pulmonary function tests

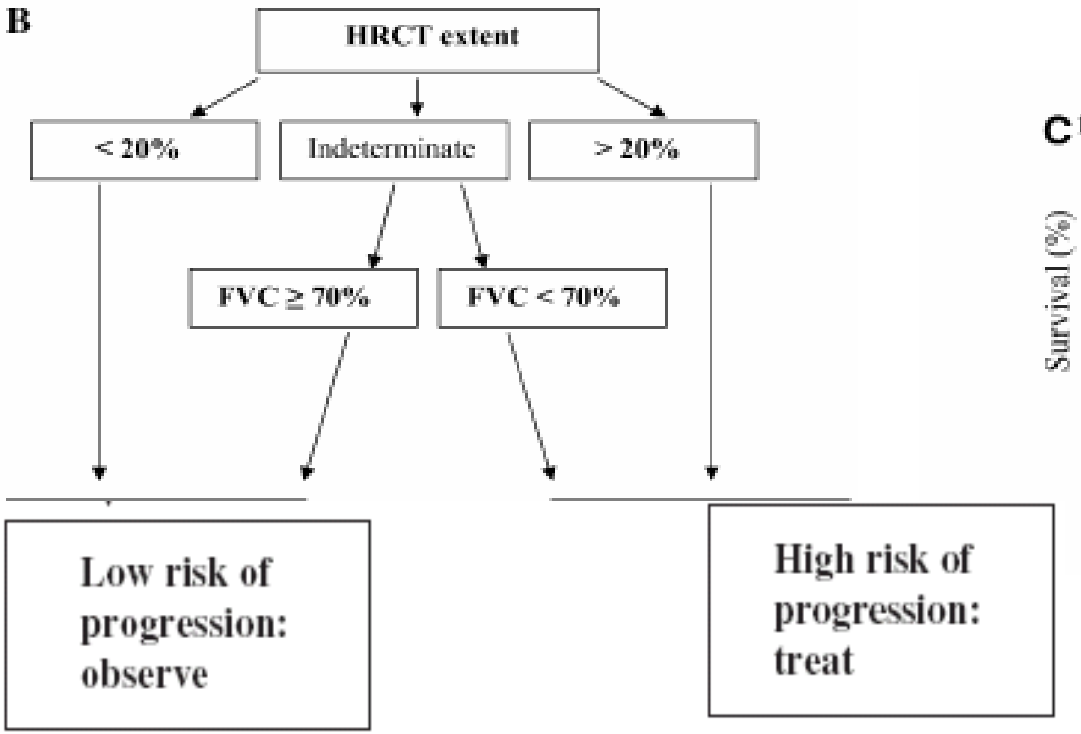
J. Behr[1] and D. E. Furst[2]

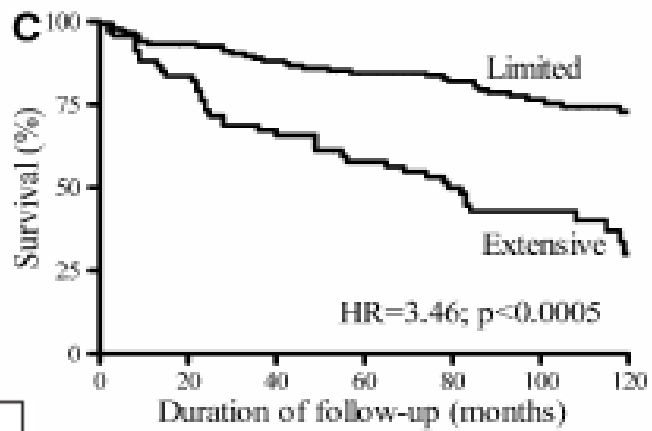
Rheumatology key messages

- Lung involvement in SSc is frequent and leads to significant morbidity and mortality.
- Lung function assessment should be performed in every newly diagnosed patient with SSc and once yearly during follow-up in the absence of abnormal findings.
- Lung function assessment should include spirometry and single-breath diffusing capacity as a minimum; additionally, BPG and CPET significantly add to comprehensive functional characterization of the SSc patients.
- Serial PFTs, especially FVC and DLco, are helpful to follow up the course of the disease and to monitor treatment effects.

In general, the reproducibility of FVC is better than that of DLco. In serial lung function measurements, therefore, changes of 10% in FVC and of 15% in DLco are generally regarded as significant [4].

EPID asociada a Esclerodermia. Diagnóstico.

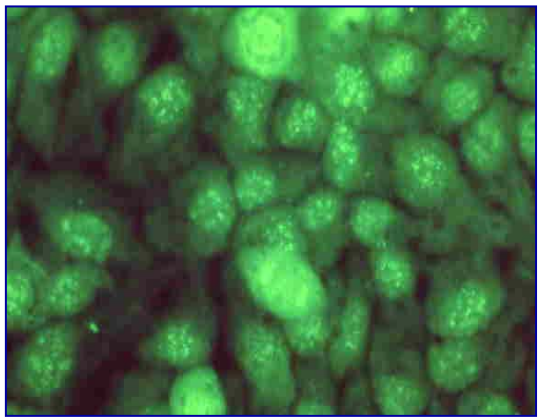




Goh,Wells et al. ILD in SSc. A simple staging system. AJRCCM 2008

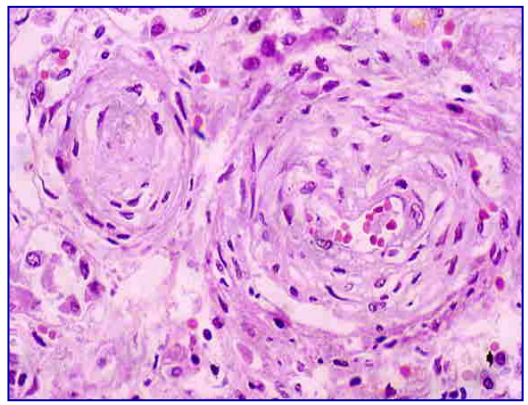
Wells et al. Rheumatology 2008;47. Curr Opin Rheumatol 2008 20.

EPID asociada a Esclerodermia. Patogenia.

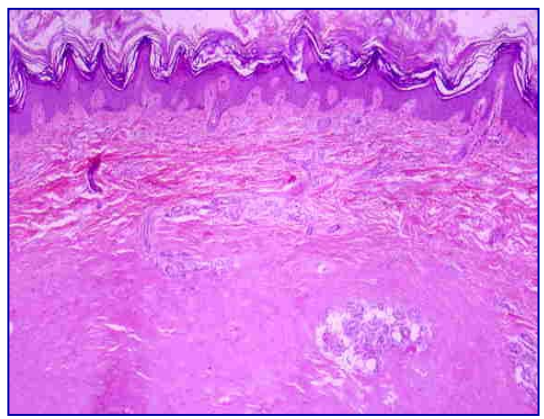


Inflamación/
Autoinmunidad

¿?



Vasculopatía



Fibrosis

EPID asociada a Esclerodermia. Patogenia.

LBA: "alveolitis"
TACAR: vidrio esmerilado
HP: NINE

LBA: "alveolitis" no se modifica con IS
TACAR: patrón reticular 93%
vidrio esmerilado 50%
HP: NINE subtipo fibrótico±NIU

EPID asociada a Esclerodermia. Tratamiento.

Terapia antifibrótica

Interferon *(N Engl J Med 2004)*
Pirfenidona *(Am J Resp Crit Care Med 2005)*
Bosentan *(BUILD)(Am J Resp Crit Care Med 2008)*
Anti-TNF *(Clin Exp Rheumatol 2007)*
Anti-TGF *(Arthritis Rheum 2007)*

ARTHRITIS & RHEUMATISM
Vol. 56, No. 1, January 2007, pp 323–333
DOI 10.1002/art.22289

Recombinant Human Anti–Transforming Growth Factor β1 Antibody Therapy in Systemic Sclerosis

A Multicenter, Randomized, Placebo-Controlled Phase I/II Trial of CAT-192

Table 3. Summary of deaths and serious adverse events occurring during the study, by treatment group

Parameter	Placebo treatment (n = 11)	CAT-192 treatment 0.5 mg/kg (n = 11)	CAT-192 treatment 5 mg/kg (n = 11)	CAT-192 treatment 10 mg/kg (n = 10)	No. (%) of all CAT-192 (n = 32)	No. (%) of all patients (n = 43)
No. of patients experiencing an event*						
Serious adverse event†	2	5	4	2	11 (34)	13 (30)
Death‡	0	1	3	0	4 (12.5)	4 (9)
No. of individual serious adverse events						
Progression of skin involvement	1	2	3	0	5	6
Gastrointestinal manifestations	0	3	1	2	6	6
Weight loss	0	1	0	0	1	1
Gastrointestinal hemorrhage/anemia	1	2	1	1	4	5
Infusion reaction	0	0	1	0	1	1
Autoantibody response	0	0	0	1	1	1
Constitutional symptoms	0	1	1	2	4	4
Musculoskeletal pain	0	3	0	1	4	4
Cardiac manifestations	0	1	3	0	4	4
Infection	1	0	2	0	2	3
Pulmonary manifestations	0	4	3	0	7	7
Impaired mobility	0	2	0	0	2	2
Total no. of serious adverse events	3	19	15	7	41	44

* Patients often experienced multiple serious adverse events: 41 occurred in 11 patients receiving CAT-192 (34%), and 3 occurred in 2 patients receiving placebo (18%).

Conclusion. We report the first evaluation of a systemically administered and repeatedly dosed anti-TGFβ1 drug. In this pilot study, CAT-192, in doses up to 10 mg/kg, showed no evidence of efficacy. The utility of

EPID asociada a Esclerodermia. Tratamiento.

Terapia antifibrótica

Interferon *(N Engl J Med 2004)*
Pirfenidona *(Am J Resp Crit Care Med 2005)*
Bosentan *(BUILD)(Am J Resp Crit Care Med 2008)*
Anti-TNF *(Clin Exp Rheumatol 2007)*
Anti-TGF *(Arthritis Rheum 2007)*
Imatinib *(Rheumatology 2009)*

Rheumatology 2009;48:2–4
Advance Access publication 23 November 2008
doi:10.1093/rheumatology/ken431

Editorial

Imatinib as a novel therapeutic approach for fibrotic disorders

Casos aislados:

- 1 EMTC con fibrosis pulmonar: mejoría CF no en CVF
- 1 ES con estabilización de CVF y TACAR a los 7 meses
- 1 ES mejoría de m-Rodnan
- 2 con Fibrosis sistémica nefrogénica

Alerta: casos de neumonitis intersticial

Rheumatology 2009;48:49–52
Advance Access publication 24 September 2008
doi:10.1093/rheumatology/ken369

Concise Report

A novel therapeutic approach to the treatment of scleroderma-associated pulmonary complications: safety and efficacy of combination therapy with imatinib and cyclophosphamide

I. Sabnani[1], M. J. Zucker[1], E. D. Rosenstein[2], D. A. Baran[1], L. H. Arroyo[1], P. Tsang[1], M. Zubair[1] and V. Rivera[1]

TABLE 1. Summarizing the clinical features, response and outcome in a series of five patients with SSc-related ILD

Pt #	Age yrs/Sex	Duration of SSc/ILD, yrs	Previous therapy	Duration of imatinib therapy, months	Percentage of DLCO at 0/6/12 months	Percentage of TLC at 0/6/12 months	Percentage of FVC at 0/6/12 months	Outcome
1	50/F	9/3	Oral CYC	18	23/24/49	49/99/37	49/38/40	Alive
2	62/M	7/4	Oral CYC	12	43/57/50	82/101/88	80/81/89	SCT
3	35/F	2/1.5	Penicillamine	12	20/20	18/18	20/22	Died after 12 months
4	51/M	4/6	IFN-γ	6	21/20	57/50	57/40	Lung transplant
5	54/M	10/6	Oral CYC	3	20	40	41	Died after 3 months

EPID asociada a Esclerodermia. Tratamiento.

Terapia antifibrótica

Interferon *(N Engl J Med 2004)*
Pirfenidona *(Am J Resp Crit Care Med 2005)*
Bosentan *(BUILD 2)*
Anti-TNF *(Clin Exp Rheumatol 2007)*
Anti-TGF *(Arthritis Rheum 2007)*
Imatinib *(Rheumatology 2009)*

Terapia vascular

N-acetil-cisteína
N Engl J Med 2005; 353:2229-42

Terapia inmunológica

Glucocorticoides
Azatioprina *Clin Rheumatol 2006; 25:205*
Ciclofosfamida

EPID asociada a ES. Tratamiento con *bolus* ciclofosfamida.

- **Black and Korn**. *Treatment of scleroderma lung disease.*
UpToDate 2001, 2002, 2003, 2004, 2005, 2006.

- **White.** *Interstitial lung disease in scleroderma.*
Rheum Dis Clin N Am 2003.

- **Latsi and Wells.** *Evaluation and management of alveolitis and interstitial lung disease in scleroderma.*
Current Opinion Rheum 2003.

- **Highland and Silver.** *New developments in scleroderma interstitial lung disease.*
Current Opinion Rheum 2005.

EPID asociada a ES. Tratamiento con *bolus ciclofosfamida*.

- Schnable *et al.* *Arthritis Rheum 1998.* **(n=2).**
- Varai *et al.* *J Rheumatol 1998.* **(n=5)** (ns)
- Davas *et al.* *Clin Rheumatol 1999.* **(n=16)**
  (vidrio esmerilado y parámetros de PFR)
- Pakas *et al.* *J Rheumatol 2002.* **(n=28)**
  (sólo mejoría e.s. en el grupo con dosis altas de GC)
- Giacomelli *et al.* *J Rheumatol 2002.* **(n=23)** (ns)
- Griffiths *et al.* *J Rheumatol 2002*. **(n=14)**
  (mejoría en el *"score"* del TAC)
- Mittal *et al.* *J Rheumatol 2003.* **(n=11)** (ns)
- Airò *et al.* *Clin Exp Rheumatol 2004* **(n=16)** (FVC y DCO)

EPID asociada a ES. Tratamiento con *bolus* ciclofosfamida.

White. *Ann Intern Med 2000; 132: 947-54*

Estudio retrospectivo, no randomizado.

* n=103. Alveolitis en 69 (LBA o Biopsia)
* Grupo 1(n=39) con CF y afección pulmonar grave
  Grupo 2(n=30) no tto con CF
* A los 16 meses de seguimiento:

  DLCO y CVF mejoraron o se estabilizaron en el Grupo 1 y empeoraron en el Grupo 2.

  Supervivencia a los 5 años: 89% Grupo 1 vs 71% Grupo 2.

EPID asociada a ES.
Tratamiento con *bolus* ciclofosfamida.

Estudio: Marzo 2000 –Diciembre 2006 : 16 enfermos.

Tratamiento:

Ciclofosfamida: 600 mg/m^2. Dos años de tratamiento:

- ✓ Mensual: 6 meses
- ✓ Bimensual: 6 meses.
- ✓ Trimestral: 12 meses.

Prednisona: 50mg/d durante 2 semanas y descenso rápido.
MESNA y antieméticos

Valoración basal, a los 6, a los 12 y a los 24 meses de tratamiento de:

Clínica: grado de disnea y Clase Funcional.
PFR con DCO.
TAC Torácico de alta resolución:
Dos patrones: vidrio esmerilado/reticular
Porcentaje de cada patrón en 5 secciones pulmonares

Características clínico - epidemiológicas

Pts	Sexo	Edad	Duración en	Subtipo	Evolución Af. pulm	C.F	ANA	Scl – 70	ACA
1	M	49	15	Difusa	6	III	640	+	-
2	M	60	4	Limitada	0	II	2.560	+	-
3	M	40	12	Difusa	2	II	320	-	-
4	M	45	22	Limitada	9	III	1280	-	-
5	H	36	1	Limitada	1	I	80	-	-
6	M	36	12	Difusa	1	I	1280	+	-
7	M	37	4	Limitada	3	II	1280	+	-
8	M	43	3	Difusa	2	III	640	+	-
9	M	38	13	Difusa	12	III	1280	+	-
10	M	20	5	Difusa	2	II	160	-	-
11	M	56	9	Difusa	8	I	640	-	-
12	M	65	22	Limitada	3	I	640	+	-
13	M	28	1	Difusa	0	I	1280	+	-
14	M	58	0,5	Difusa	0	III	640	+	-
15	M	22	4	Difusa	0,5	I	320	+	-
16	M	52	10	Limitada	1	I	160	-	+

Ciclofosfamida en *bolus*. Evolución de la CVF (%)

Pts.	Inicio	6 m.	1 a.	2 a.	CVF %	Evol.
1	58,5	55,4				Estable
2	55	84,9	61.7	71,2	+29,49	Mejoría
3	50,8	58	60	55	+8,2	Estable
4	41,6	44,6	40	37,8	-9,3	Estable
5	77,7	58,8	65,6	54,9	-29,34	Peor
6	92,7	82	82		-12	Peor
7	54	54,8	54	62,6	+16	Mejoría
8	34	34	34,6	32,7	-3,8	Estable
9	32	31,6			-1,25	Estable
10	56	68,1	61,3	73,7	+31,6	Mejoría
11	64,2	73,4	80,5	71,3	+11	Mejoría
12	56,9	64,5	65,5	59,1	+3,8	Estable
13	53,3	62,2	53	48,6	-8,8	Estable
14	51,3	52,5	50,6	50,3	-1,9	Estable
15	70,6	63,3				Peor
16	88,7	86,8				Estable
Med	55,5	60,5	60	58,5	+5,4	Estable

Intravenous Cyclophosphamide Pulse Therapy in the Treatment of Systemic Sclerosis-Related Interstitial Lung Disease: A Long Term Study

The Open Respiratory Medicine Journal, 2008, *2*, 39-45

C.P. Simeón-Aznar[1], V. Fonollosa-Plá[1], C. Tolosa-Vilella[2], A. Selva-O´Callaghan[1], R. Solans-Laqué[1], E. Palliza[3], X. Muñoz[4] and M. Vilardell-Tarrés[1]

FVC (%)			
Time 0	6 Months	12 Months	24 Months
58.5	55.4	-	-
55	84.9	61.7	71.2
50.8	58	60	58.5
41.6	44.6	-	-
77.7	58.8	65.6	54.9
92.7	82	-	-
85.2	54.8	58	62.6
34	34	34.6	32.7
32	32.8	31.6	31.6
56	68.1	61.3	73.7
55.5	56.7	60	58.5

Table 3. Percentages of Ground Glass Pattern in Serial Pulmonary HRCT

Patients	Baseline (%)	at 6 Months (%)	at 12 Months (%)	at 24 Months (%)
1	32	30	-	-
2	4	6	8	5
3	14	12	14	14
4	32	28	-	-
5	18	28	24	24
6	8	8	-	-
7	26	34	34	30
8	14	14	14	12
9	18	10	10	10
10	32	14	24	10
Median	18	14	14	12

EPID asociada a ES. Tratamiento
Ensayos multicéntricos con ciclofosfamida.

Hoyles RK et al. Arthrtis Rheum 2006; 54:3962-3970.

n: 45

ciclofosfamida iv mensual/6 meses seguido de azatioprina vs placebo

duración y seguimiento: 1 año

efectos beneficiosos: CVF **(grupo cyc 2.4%, placebo:-3%)** ns

toxicidad: baja

Mejoría de CVF no significativa ¿pocos enfermos?

Thaskin D et al. N Engl J Med 2006; 354: 2655-2666.

n: 158 (79/79)

ciclofosfamida oral (1mg/K/d) vs palcebo

duración y seguimiento: 1 año

efectos beneficiosos: **(grupo cyc:-1% placebo: -2.6%)** $p<0.05$ grado de disnea, calidad de vida y grado de esclerosis cutánea

toxicidad: hematurias, leucopenias, neumonias

Efecto modesto. Efectos adversos importantes

ORIGINAL ARTICLE

Cyclophosphamide versus Placebo in Scleroderma Lung Disease

Donald P. Tashkin, M.D., Robert Elashoff, Ph.D., Philip J. Clements, M.D., M.P.H.,

CONCLUSIONS

One year of oral cyclophosphamide in patients with symptomatic scleroderma-related interstitial lung disease had a significant but modest beneficial effect on lung function, dyspnea, thickening of the skin, and the health-related quality of life. The effects on lung function were maintained through the 24 months of the study.

EDITORIALS

Cyclophosphamide for Scleroderma Lung Disease

Fernando J. Martinez, M.D., and W. Joseph McCune, M.D.

In conclusion, this well-designed trial will be regarded as a sentinel study confirming a beneficial response to cyclophosphamide in highly selected patients with scleroderma-related interstitial lung disease. In the absence of long-term follow-up data on mortality and the development of malignant diseases, however, the modest therapeutic response and the potential for significant toxic effects do not, in our opinion, support the conclusion that one year of daily cyclophosphamide should be considered routine therapy for all such patients. Additional analyses based on the

Tratamiento de la EPID asoc a ES. Ciclofosfamida Reflexiones.

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*

AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 176 2007

What This Study Adds to the Field

The present report provides the first evidence that, during an additional year of follow-up in the same patients off of study drug, the benefits of cyclophosphamide persist for several additional months, but are generally no longer apparent at 2 years.

Tratamiento de la EPID asoc a ES. Ciclofosfamida Reflexiones.

Furst DE, Clements PJ, Tashkin DP, Eckman MH. Med Decis Making. 2008 Apr 28.

Oral Cyclophosphamide for Active Scleroderma Lung Disease: A Decision Analysis.

RESULTS. In the base-case analysis, CYC-treated patients fared worse, with a small loss of 0.21 QALYs (16.84 v. 17.15). CYC remained inferior across sensitivity analyses for most variables. In analyses assuming a survival benefit with CYC, CYC resulted in a clinically significant gain (18.17 v. 17.15 QALYs).
CONCLUSIONS: **CYC therapy for 1 y results in a small loss in QALYs compared with no CYC for SSc-ILD. The lack of a beneficial impact on survival and the transience of CYC's impact on decline in pulmonary function drive this conclusion.**

Tratamiento de la EPID asoc a ES. Ciclofosfamida Reflexiones.

Daily Cyclophosphamide for Scleroderma
Are Patients with the Most to Gain Underrepresented in this Trial?

AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 176 2007

Three strategies used to minimize cyclophosphamide exposure in rheumatic disease are potentially applicable to lung disease in SSc:

1. Long-term monthly intravenous cyclophosphamide was, for many years, the standard of care in lupus nephritis, with cumulative doses of approximately 16 g over 3 years, compared with a cumulative dose of 30–50 g after 1 year in the study by Tashkin and colleagues (10). Hemorrhagic cystitis,

2. In lupus nephritis, sequential therapy, changing from initial intravenous cyclophosphamide, used to induce remission, to a less toxic long-term agent (azathioprine or mycophenolate mofetil [MMF]) has been reported to be associated with improved outcomes and significantly fewer episodes of infection,

3. MMF may prove to be an adequate substitute for cyclophosphamide, as it is in severe lupus. In a meta-analysis of ran-

EPID asociada a Esclerodermia. Tratamiento.

Terapia antifibrótica

Interferon *(N Engl J Med 2004)*
Pirfenidona *(Am J Resp Crit Care Med 2005)*
Bosentan *(BUILD 2)*
Anti-TNF *(casos aislados: malos resultados)*
Anti-TGF *(Arthritis Rheum 2007)*
Imatinib *(Rheumatology 2009)*

Terapia vascular

N-acetil-cisteína
N Engl J Med 2005; 353:2229-42

Terapia inmunológica

Glucocorticoides
Azatioprina *Clin Rheumatol 2006; 25:205*
Ciclofosfamida
Micofenolato

Rheumatology 2006;45:1005–1008
Advance Access publication 20 February 2006

Mycophenolate mofetil as first-line treatment improves clinically evident early scleroderma lung disease

S. N. C

Rheumatology 2006; 1 of 4 doi:10.1093/rheumatology/kel244

Concise Report

Mycophenolate mofetil in diffuse cutaneous systemic sclerosis—a retrospective analysis

Svetlana I. Nihtya
Christopher P. De

Mycophenolate Mofetil Is Safe, Well Tolerated, and Preserves Lung Function in Patients With Connective Tissue

A pilot study of mycophenolate mofetil combined to intravenous methylprednisolone pulses and oral low-dose glucocorticoids in severe early systemic sclerosis

M. Vanthuyne
E. Coche

Effect of Mycophenolate Mofetil on Pulmonary Function in Scleroderma-Associated Interstitial Lung Disease

Anthony J. Gerbino, Christopher H. Goss and Jerry A. Molitor

Chest published online December 10, 2007;
DOI 10.1378/chest.06-2861

Rheumatology 2006; 1 of 4 doi:10.1093/rheumatology/kel244

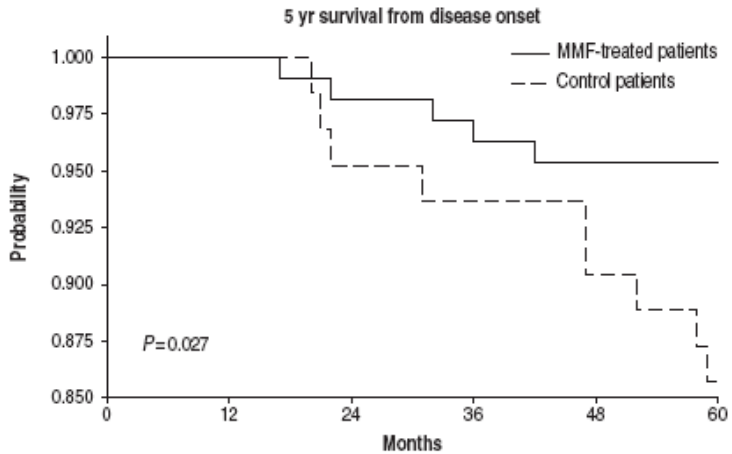
Concise Report

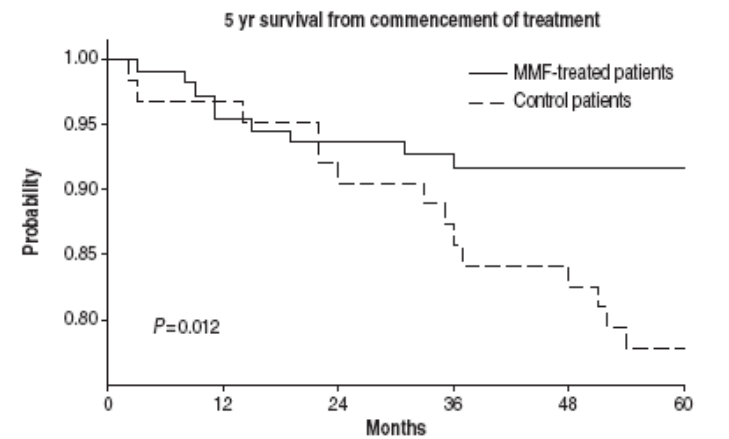
Mycophenolate mofetil in diffuse cutaneous systemic sclerosis—a retrospective analysis

Svetlana I. Nihtyanova, Geraldine M. Brough, Carol M. Black and Christopher P. Denton

	MMF patients % (No)	Controls % (No)
Patients	100 (109)	100 (63)
Female sex	82.6 (90)	81 (51)
Race		
Asian	9.2 (10)	9.5 (6)
Black	7.3 (8)	6.3 (4)
Caucasian	79.8 (87)	79.4 (50)
Other	3.7 (4)	4.8 (3)
Diffuse disease	92.7 (101)	98.4 (62)
Age at onset (yrs) mean ± s.d.	47 ± 13	45 ± 12
Overlap		
Total	23.9 (26)	22.2 (14)
>1 overlap	3.7 (4)	1.6 (1)
Polymyositis/dermatomyositis	11.9 (13)	14.3 (9)
Arthritis	8.3 (9)	7.9 (5)
Sjogren's	1.8 (2)	0 (0)
SLE	3.7 (4)	1.6 (1)
Vasculitis	3.7 (4)	1.6 (1)
Antibodies		
Scl 70	32.1 (35)	27 (17)
RNA polymerase	23.9 (26)	22.2 (14)
nRNP	4.6 (5)	3.2 (2)
U3RNP	4.6 (5)	6.3 (4)
ACA	1.8 (2)	1.6 (1)
PM/Scl	1.8 (2)	4.8 (3)
dsDNA	4.6 (5)	0 (0)
Ro	5.5 (6)	7.9 (5)
Sm	1.8 (2)	0 (0)
Non-defined Abs	30.3 (33)	30.2 (19)
Organ involvement		
Skin	100 (109)	100 (63)
Raynaud's	100 (109)	100 (63)
GIT[a]	78 (85)	87.3 (55)
Lung	56 (61)	63.5 (40)
Joint	19.3 (21)	14.3 (9)
Muscle	13.8 (15)	15.9 (10)
Heart	6.4 (7)	6.3 (4)
Kidney	22.9 (25)	4.8 (3)

[a]GIT, gastrointestinal tract.





Effect of Mycophenolate Mofetil on Pulmonary Function in Scleroderma-Associated Interstitial Lung Disease

Anthony J. Gerbino, Christopher H. Goss and Jerry A. Molitor

Chest published online December 10, 2007;
DOI 10.1378/chest.06-2861

N= 13

Table 2—*Mean Change in VC Prior to and During Treatment With MMF

Variables	Change in VC vs Treatment Onset			
	Compared With 12-Month Imputed Values		Compared With Measured Values†	
	Prior to MMF	During MMF	Prior to MMF	During MMF
Mean change, % predicted	− 5.4% (CI, − 10.5 to − 0.3%); p = 0.02	+ 4.2% (CI, 1.9 to 6.5%); p = 0.002	− 5.3% (CI, − 9.3 to − 1.3%); p = 0.02	+ 4.3% (CI, 2.0 to 6.6%); p = 0.002
Mean change, mL	− 239 (CI, − 477 to − 0.5); p = 0.01	+ 159 (CI, 30 to 289); p = 0.01	− 228 (CI, − 384 to − 72); p = 0.02	+ 129 (CI, 52 to 205); p = 0.005

*Twelve-month imputed values are predicted from slopes of regression lines computed using all data points in a 24-month period either prior to or after treatment onset, and are compared to VC at treatment onset.

†Measured values reflect VC measurements made either prior to treatment onset (median, 14 months; range, 7 to 20 months) or at last follow-up on MMF (median, 20 months; range, 9 to 43 months) and are compared to VC at treatment onset.

Tto. de la EPID asoc a ES con micofenolato sódico durante 1 año.

Tabla 1 Características de los pacientes.

Edad	54.50(23-71)
Mujer/Hombre	13/14
Subtipo Difusa	8/14
Ac Topoisomerasa I	8/14
Duración de la enfermedad	6.5(2-57)
Diagnóstico de EPID (años)	2.8(1-15)
Alteraciones en el TACAR	
Panal	2/14
Vidrio esmerilado/reticular	12/14
IS previos (2 años)	
Ciclofosfamida	10/14
Azatioprina	6/14
CVF, L(% esperado)	
12 meses antes de tratamiento(n=11)	2.17±0.60**(59.80±17.38)**
Basal	2.17±0.47**(55.50±19.72)**
12 meses de MS	1.97±0.52**(59.00±22.32)**
DLCO/VA, Mmol/min/kPa/L(%esperado)	
12 meses antes de tratamiento (n=8)	1.19±0.24(67.05±6.83)
Basal (n=10)	1.11±0.13(62.45±7.19)
12 meses de MS (n=10)	1.02±0.19(55.0±11.37)

Tto. de la EPID asoc a ES con micofenolato sódico durante 1 año. Resultados

Tabla 2: Diferencias en medianas de CVF (%) valores esperados 12 meses antes, al inicio y después de 12 meses de tto. Con MS

Variables	Antes de MS	Inicio MS	12 meses de MS
CVF(%)	59.80	55.5	59.00
cambio (%)	-7.2		+ 6.3
p value	0.3115		0.951

EPID asociada a Esclerodermia. Reflexiones sobre el tratamiento.

"In this scenario, prevention of disease progression is a more realistic goal and it is incorrect to regard stability as a therapeutic failure."

".....prevention of disease progression appears to be the most realistic therapeutic goal with immunological modulation in SSc most cases"

"Thus , is not necessary for clinicians to demonstrate the presence of reversible pulmonary disease in order to justify prolonged therapeutic intervention. In SSc, stability of extensive disease with treatment should be viewed as a therapeutic sucess."

K.M. Antoniou and A.U. Wells
Curr Opin Rheumatol Nov 2008

EPID asociada a Esclerodermia. Nuevos Tratamientos.

ARD Online First, published on December 22, 2008 as 10.1136/ard.2008.095463

Rituximab in diffuse cutaneous systemic sclerosis: an open-label clinical and histopathological study

Vanessa Smith†; Jens T. Van Praet*†; Bernard Vandooren*†; Bert Vander Cruyssen†; Jean-Marie Naeyaert‡§; Saskia Decuman†, Dirk Elewaut†, and Filip De Keyser†*

N=8
24 semanas

Table 1b Changes in clinical and laboratory parameters in the study upon treatment with rituximab

Parameter	Statistic	Week 0 (n=8)		Week 12 (n=8)		Week 24 (n=7)	
Total Skin Score*	Mean, SD	24.8	3.4	19.4	5.4	14.3	3.5
	Median	24.5		18.0		15.0	
	Minimum, maximun	21.0	30.0	12.0	26.0	9.0	18.0
DLCO (% of normal)†	Mean, SD	73.3	22.7	68.5	22.1	73.0	18.1
	Median	60.5		60.0		64.0	
	Minimum, maximun	54.0	111.0	46.0	106.0	55.0	98.0
Lung Vital Capacity (% of normal)†	Mean, SD	92.8	8.6	88.5	12.9	88.3	9.3
	Median	92.5		92.5		91.0	
	Minimum, maximun	76.0	106.0	68.0	101.0	71.0	99.0
Forced Expiratory Volume (% of normal)†	Mean, SD	83.9	8.1	81.0	17.7	77.0	9.8
	Median	87.0		82.5		78.0	
	Minimum, maximun	71.0	94.0	49.0	104.0	66.0	93.0

Alerta: casos de neumopatía intersticial

EPID asociada a Esclerodermia. Nuevos Tratamientos.

B Cell Depletion With Rituximab in Patients With Diffuse Cutaneous Systemic Sclerosis

Robert Lafyatis,[1] Eugene Kissin,[1] Michael York,[1] Giuseppina Farina,[1] Kerry Viger,[1] Marvin J. Fritzler,[2] Peter A. Merkel,[1] and Robert W. Simms[1]

ARTHRITIS & RHEUMATISM
Vol. 60, No. 2, February 2009, pp 578–583
DOI 10.1002/art.24249

Table 2. Clinical and laboratory outcomes in the 15 patients*

	Baseline	6 months	12 months
Modified Rodnan skin thickness score	20.6 ± 4.4 (9–31)†	20.2 ± 5.5 (5–45.5)†	21.1 ± 5.2 (8–45.5)†
Pulmonary function testing			
Forced vital capacity, % of predicted	89.2 ± 10.8 (62–119)	92.7 ± 10.3 (53–120)	
DLCO, % of predicted	79.7 ± 8.3 (61–107)	77.8 ± 7.5 (52–95)	
Health Assessment Questionnaire			
Disability index	0.67 ± 0.32 (0–2.0)	0.64 ± 0.36 (0–2.25)	0.55 ± 0.33 (0–2.25)
Visual analog scale	0.73 ± 0.26 (0–1.875)	0.53 ± 0.21 (0–1.5)	0.56 ± 0.21 (0.03–1.5)
Immunoglobulins, units/ml			
IgM	107 ± 25 (15–172)	86 ± 24 (9–172)	86 ± 24 (11–172)
IgG	1,106 ± 197 (756–2,210)	1,066 ± 173 (696–1,970)	1,021 ± 181 (588–1,970)
IgA	270 ± 100 (61–539)	288 ± 105 (58–546)	274 ± 94 (58–532)
Sedimentation rate, mm/hour	27.9 ± 11.7 (2–69)	20.5 ± 7.8 (6–40)	17.0 ± 6.1 (6–38)
Exploratory outcomes			
B cell score	10.4 ± 4.6 (0–23)	3.4 ± 4.8 (0–30)	
Myofibroblast score	49.5 ± 16.6 (6–81.5)	36.6 ± 16.6 (2–78)	

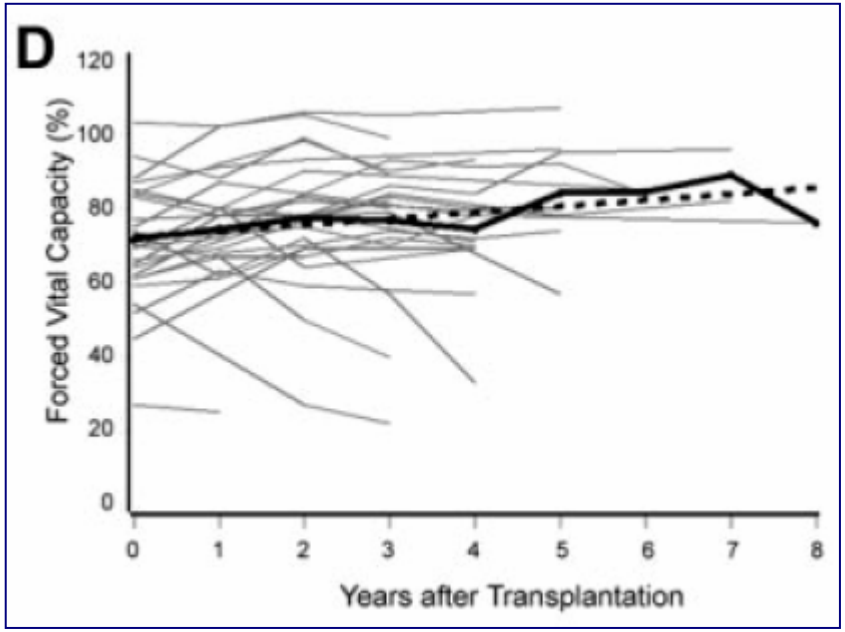
* Values are the mean ± 95% confidence interval (range). DLCO = diffusing capacity for carbon monoxide.
† Total of 19 skin sites assessed at baseline, and 17 at 6 and 12 months.

EPID asociada a Esclerodermia. Nuevos Tratamientos.

High-dose immunosuppressive therapy and autologous hematopoietic cell transplantation for severe systemic sclerosis: long-term follow-up of the US multicenter pilot study

BLOOD, 15 AUGUST 2007 • VOLUME 110, NUMBER 4

N= 34
Cif, ATG,TBI
Éxitus= 12 (7 primer año)
Supervivencia 5a= 64%



P=0.01

N=11

EPID asociada a Esclerodermia. Nuevos Tratamientos.

Long-term follow-up results after autologous haematopoietic stem cell transplantation for severe systemic sclerosis

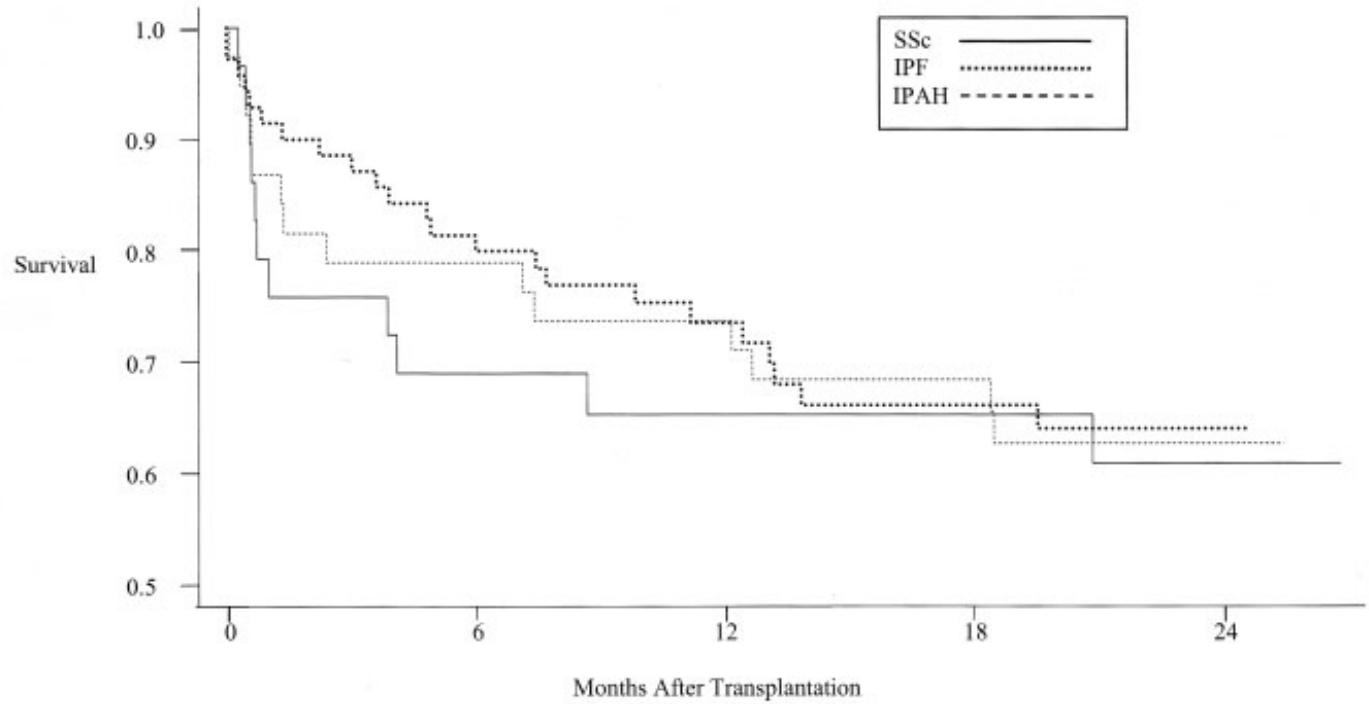
Ann Rheum Dis 2008;**67**:98–104. doi:10.1136/ard.2007.071464

N=26 (seguimiento 5 a)
Éxitus= 2
Supervivencia 7a= 64%

Table 4 Relative changes (median, range) from baseline for the 26 systemic sclerosis (SSc) patients treated by autologous haematopoietic stem cell transplantation with at least 6 months follow-up after the procedure

Relative change from baseline	1 year (n = 26)	3 year (n = 20)	5 year (n = 15)
mRSS	−39% (−86%; 59%)	−72% (−100%; 33%)	−73% (−100%; −25%)
	$p^* < 10^{-3}$	$p^* < 10^{-3}$	$p^* < 10^{-3}$
VC	4% (−13%; 77%)	3% (−32%; 93%)	−7% (−38%; 89%)
	$p^* = 0.019$	$p^* = 0.044$	$p = 0.50$
TLC	0 (−31%; 32%)	1% (−42%; 66%)	−1% (−45%; 62%)
	$p = 0.98$	$p = 0.65$	$p = 0.78$
FEV1	6% (−33%; 91%)	6% (−28%; 100%)	−3% (−56%; 100%)
	$p^* < 0.047$	$p = 0.61$	$p = 0.42$
DLCO	−4% (−43%; 53%)	−7% (−62%; 74%)	−9% (−59%; 64%)
	$p = 0.09$	$p = 0.31$	$p = 0.41$

Lung Transplantation in Scleroderma Compared With Idiopathic Pulmonary Fibrosis and Idiopathic Pulmonary Arterial Hypertension



NO. AT RISK:					
SSc	29	20	17	16	15
IPF	70	56	41	33	26
IPAH	38	30	28	24	22

EPID: 15 HTAP: 11

EPID+HTAP: 3

Schachna L, Arthritis Rheum 2006;54;3956-61

ARTHRITIS & RHEUMATISM
Vol. 56, No. 1, January 2007, pp 9–12
DOI 10.1002/art.22315

EDITORIAL

Treatment of Pulmonary Fibrosis in Systemic Sclerosis: Light at the End of the Tunnel?

Frank A. Wollheim