## II Curs de Malalties Autoimmunes de la SCR

# Algoritmo terapéutico de la Enfermedad Pulmonar Intersticial difusa asociada a la Esclerosis Sistémica

**Dr. Javier Narváez**
**Servicio de Reumatología**
**Hospital Universitari de Bellvitge**

# Esclerodermia y EPID.

- **Prevalencia:** 55-65% (TCAR).

- **Tipo:** Neumonía intersticial no específica (NINE): 78%
  Neumonía intersticial usual (NIU).

- **Pronóstico:** actualmente la EPID es la principal causa de muerte en la SSc (35% en la cohorte EUSTAR).

- No se han observado diferencias significativas en función del patrón histopatológico: supervivencia similar a los 5 años (NINE 91% / NIU 82%).

# Tratamiento: consideraciones generales

- El objetivo del tto es reducir la inflamación alveolar e intersticial **antes de que se desarrolle la fibrosis (lesión irreversible)**, lo que implica la necesidad de un diagnóstico y tratamiento precoz.

- El tto de la EPID & SSc es una cuestión aún por resolver: con los fármacos disponibles en la actualidad el beneficio terapéutico conseguido es modesto.

- Hoy en día se considera que el objetivo terapéutico más realista **es evitar la progresión de la enfermedad (o al menos, retrasarla).**

## Evaluación de respuesta al tto

Valoración de la respuesta al tratamiento mediante los valores de las Pruebas Funcionales Respiratorias de acuerdo con las recomendaciones de la *American Thoracic Society:*

- ✓ **Mejoría:** si se da un aumento de la CVF ≥ 10% o en la DLCO ≥ 15%.
- ✓ **Estabilización: si los cambios en la CVF son menores al 10% o al 15% en la DLCO.**
- ✓ **Empeoramiento:** si la CVF disminuye ≥ 10% o la DLCO ≥ 15%.

# ¿Cuándo tratar?

- Como la yatrogenia potencial de alguno de estos tratamiento (CF, MMF) no es despreciable, se debe individualizar la decisión por edad, antecedentes y pronóstico (PFR y TACAR), haciendo un balance beneficio-riesgo y en decisión conjunta con la paciente.

**No tratar a los pacientes con enfermedad subclínica estable** (*"clinically insignificant disease")*

- *EPID limitada en TACAR (< 20% del parénquima pulmonar).*
- *PFR con alteración leve y **estable** (CVF y DLCO ≥ 80%).*
- *Paciente asintomático.*

# Protocolo de tto en nuestro Servicio

## MEDIDAS GENERALES RECOMENDADAS.

- Prednisona a dosis iniciales de 20 mg/día durante un mes con pauta descendente posterior hasta una dosis de mantenimiento ≤ 10 mg/día, manteniendo esta dosis un año.

**Recordar que el tto con GLC (dosis > 15 mg/día de prednisolona) es un factor de riesgo para el desarrollo de crisis renal esclerodérmica (OR:4.98)**

- Prevención/tratamiento del reflujo gastro-esofágico.
- N-acetilcisteína 600 mg/8 horas v.o en los casos de NIU (eficaz en FPI en 2 ECA).
- Fisioterapia respiratoria.
- Oxigenoterapia si precisa.
- Vacunación (neumococo y gripe) y profilaxis para la infección por Pneumocystis jirovecii en los pacientes tratados con ciclofosfamida.

# Tto inmunosupresor: Ciclofosfamida

- **Evidencia.**

  **Estudios observacionales:** 15 (11 prospectivos / 4 retrospectivos).

  **Ensayos controlados aleatorizados (ECA):** 4.

  **2 Jadad score 5** ***Tashkin DP et al. N Engl J Med 2006 (Scleroderma Lung Study I)***
  ***Hoyles RK et. Arthritis Rheum 2006***

  **Metaanálisis**: 2.

- **Conclusiones.**

- La CF ha demostrado ser eficaz en la estabilización de los parámetros funcionales respiratorios, fundamentalmente de la CVF *(NE Oxford 1A/1B, grado de recomendación A según EULAR/EUSTAR).*

**Estabilización = si los cambios en la CVF son menores al 10% o al 15% en la DLCO.**

- No hay clara evidencia de que sea capaz de mejorarlos (como mínimo la DLCO).

***Kowal-Bielecka O et al. Ann Rheum Dis 2009;68:620–628***

# EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR)

O Kowal-Bielecka,[1] R Landewé,[2] J Avouac,[3] S Chwiesko,[1] I Miniati,[4] L Czirjak,[5] P Clements,[6] C Denton,[7] D Farge,[8] K Fligelstone,[9] I Földvari,[10] D E Furst,[6] U Müller-Ladner,[11] J Seibold,[12] R M Silver,[13] K Takehara,[14] B Garay Toth,[15] A Tyndall,[16] G Valentini,[17] F van den Hoogen,[18] F Wigley,[19] F Zulian,[20] Marco Matucci-Cerinic,[4] and the EUSTAR co-authors

**Table 1** The final set of 14 recommendations based on both evidence from the literature and expert opinion

| No | Recommendation | Strength of recommendation | References |
|---|---|---|---|
| IV | SSc-ILD | | |
| 9 | In view of the results from two high-quality RCT and despite its known toxicity, cyclophosphamide should be considered for treatment of SSc-ILD | A | 62,63 |

*Ann Rheum Dis 2009;68:620-8*

# Ciclofosfamida

- **Factores predictivos de respuesta:** CVF < 70%, extensión de la afección pulmonar en el TACAR > 50% y MRSS ≥ 23.

- No diferencias en cuanto a la eficacia entre CF oral o IV.

- Permanece por aclarar cuánto tiempo debe durar el tratamiento (6, **12** o 24 meses).

- **Una vez suspendida, su efecto beneficioso sobre la función pulmonar se mantiene sólo los 6 primeros meses desapareciendo al año**, por que es necesario añadir un tto de mantenimiento.

- Otra duda por resolver: ¿qué terapia de mantenimiento debemos utilizar después de su retirada? *(Micofenolato?, AZA?).*

# Micofenolato

- **Evidencia.**

  Estudios observacionales no controlados: 10 (5 prospectivos / 5 retrospectivos)

  Ningún ensayo controlado aleatorizado.

  Un metaanálisis.

- **Conclusiones.**

  - Tratamiento de primera línea: eficaz en la estabilización de los parámetros funcionales respiratorios (CVF y DLCO).

  - ¿Alternativa de no inferioridad a la CF?: en marcha ECA CF oral *vs* MMF 2 años *(Scleroderma Lung Study II).*

  - De los estudios observaciones se infiere su utilidad como terapia de mantenimiento tras CF.

# Azatioprina

TABLE 3 AZA in the treatment of SSc

| Author | No. of patients | Type of study | AZA treatment | Duration, months | Outcome measures |
|---|---|---|---|---|---|
| Nadashkevich *et al.* [13] | 60 | RCT | AZA 2.5 mg/kg/day for 12 months then 2 mg/kg/day for 6 months *vs* CYC 2 mg/kg/day for 12 months then 1 mg/kg/day for 6 months | 18 | FVC (difference T0 – T18, AZA group): −11.1% ($P < 0.001$)<br>$DL_{CO}$ (difference T0 – T18, AZA group): −11.6% ($P < 0.001$)<br>mRSS (difference T0 – T18, AZA group): +0.2 ($P > 0.05$) |
| Dheda *et al.* [29] | 11 | Retrospective | | 12 | FVC (difference T0 – T12): +9.1% ($P = 0.101$) |
| Mass *et al.* [30] | 19 | Retrospective | AZA 2-2.5 mg/kg/day | Mean 47 months (range 6–114 months) | No patient had worsening of lung function |
| Hoyles *et al.* [12] | 45 | RCT | AZA 2.5 mg/kg/day as maintenance treatment after 6 months of i.v. CYC | 12 | FVC (difference CYC + AZA *vs* placebo): +4.19% favouring CYC + AZA ($P = 0.08$)<br>$DL_{CO}$ (difference CYC + AZA *vs* placebo): $P = 0.64$ |
| Paone *et al.* [31] | 13 | Prospective | AZA 100 mg/day | 12 | No outcome measures deteriorated during maintenance treatment with AZA |

- **Conclusiones.**

**- Primera opción de tto:**

Eficacia inferior a la de la CF oral en 1 ECA.

Estabilización de los parámetros funcionales respiratorios en 2 estudios retrospectivos con pocos pacientes.

**-** Eficaz como **terapia de mantenimiento** tras CF.

# Protocolo de tto en nuestro Servicio

## Pacientes candidatos a tto con ciclofosfamida.

- **Pruebas funcionales respiratorias**.
  **Basales:** CVF < 60% y/o DLCO < 40% **(trastorno grave según SEPAR).**
  **Seguimiento:** descenso de FVC ≥ 10% y/o descenso de DLCO ≥ 15%.

- **Afectación en TCAR:**
  **Basal:** extensión de la afección pulmonar ≥ 50% o fibrosis ≥ 20%.
  **Seguimiento:** empeoramiento de la fibrosis.

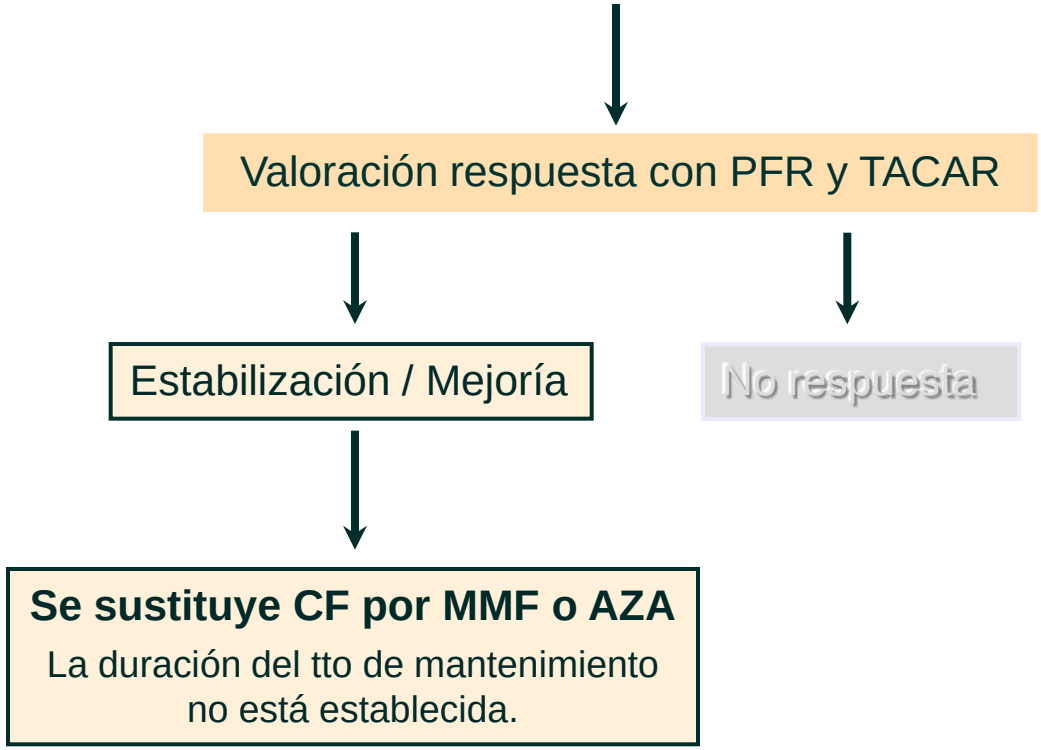
- **Test de la marcha de 6 minutos.**
  **Basal:** saturación < 88%.
  **Seguimiento:** reducción > 50 mts en la distancia recorrida.

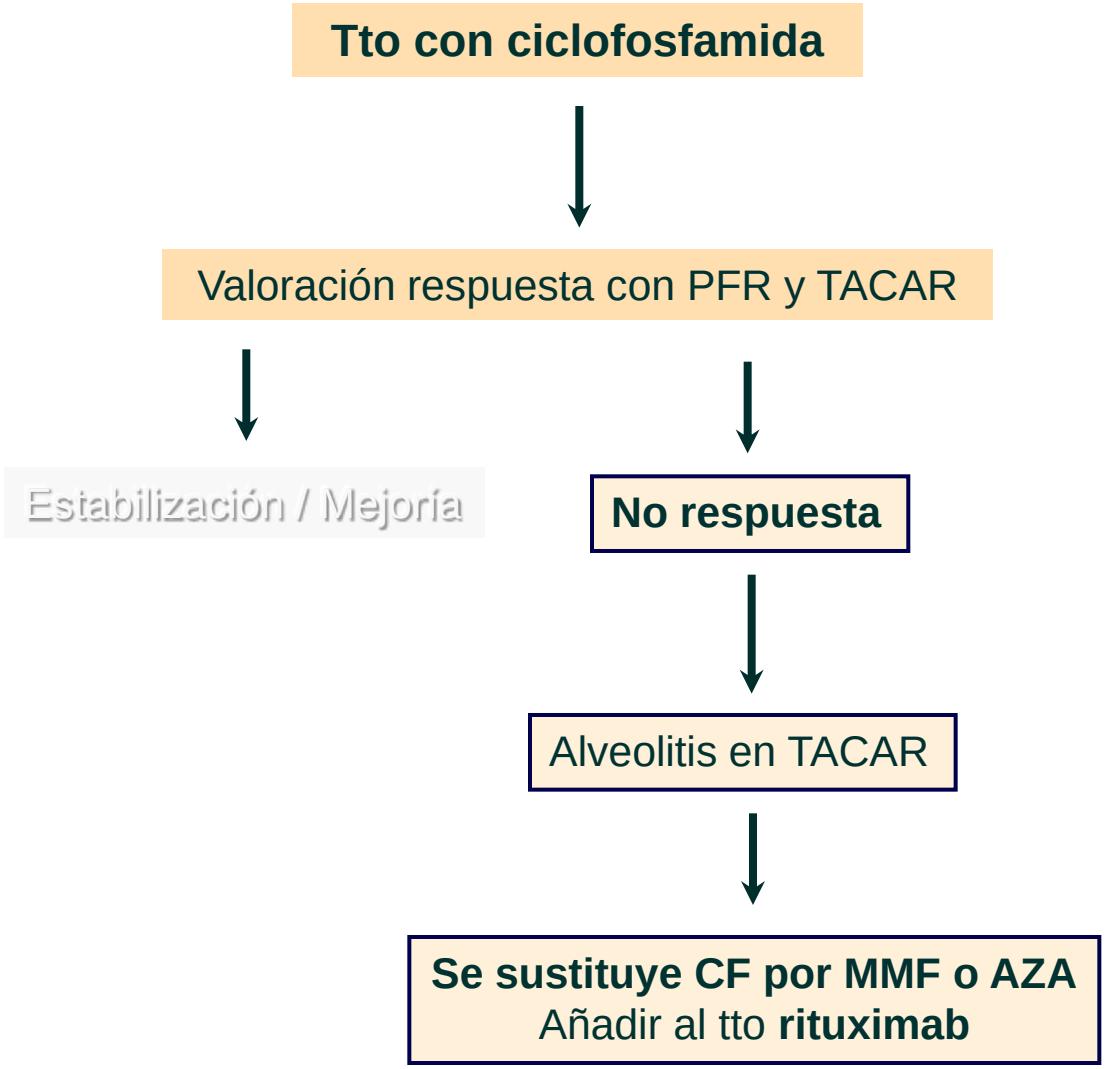
- Disnea (grado ≥ 2 en el índice de Mahler o ≥ 3 en la escala de Borg) tras excluir otras posibles causas.

- Edad < 70 años y no contraindicación para el tto con CF.

En caso de no indicación (afectación pulmonar leve-moderada) o contraindicación a la CF: **Micofenolato** (MMF) 2 g/día ó **ácido micofenólico** (750 mg/12 horas).

**Pauta de tto con CF:** pulsos mensuales de 750 mg/m2 de superficie corporal durante 6 meses (o 500 mg/m2 según tolerancia) y posteriormente de forma trimestral hasta completar 1 año.




Tto con ciclofosfamida
Valoración respuesta con PFR y TACAR
Estabilización / Mejoría
No respuesta
Alveolitis en TACAR
Se sustituye CF por MMF o AZA
Añadir al tto rituximab

# Rituximab

## Effect of long-term treatment with rituximab on pulmonary function and skin fibrosis in patients with diffuse systemic sclerosis

D. Daoussis[1], S.C. Liossis[1], A.C. Tsamandas[2], C. Kalogeropoulou[3], F. Paliogianni[4], C. Sirinian[2], G. Yiannopoulos[1], A.P. Andonopoulos[1]

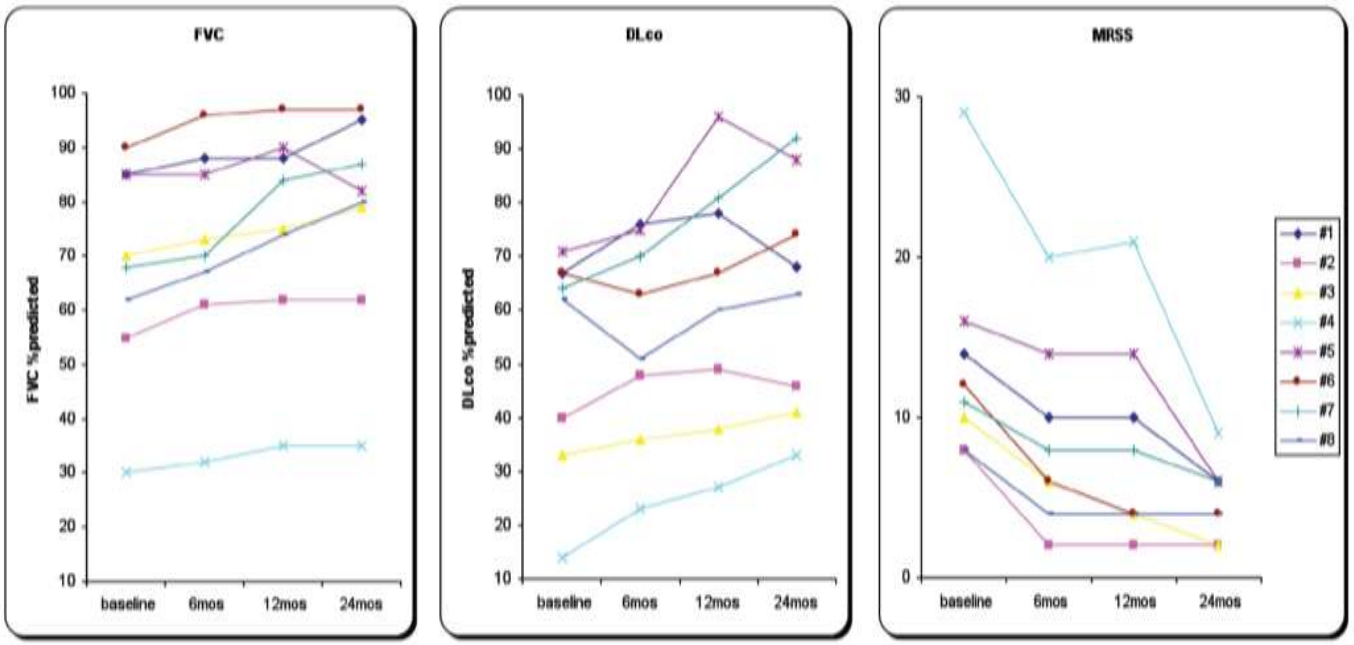


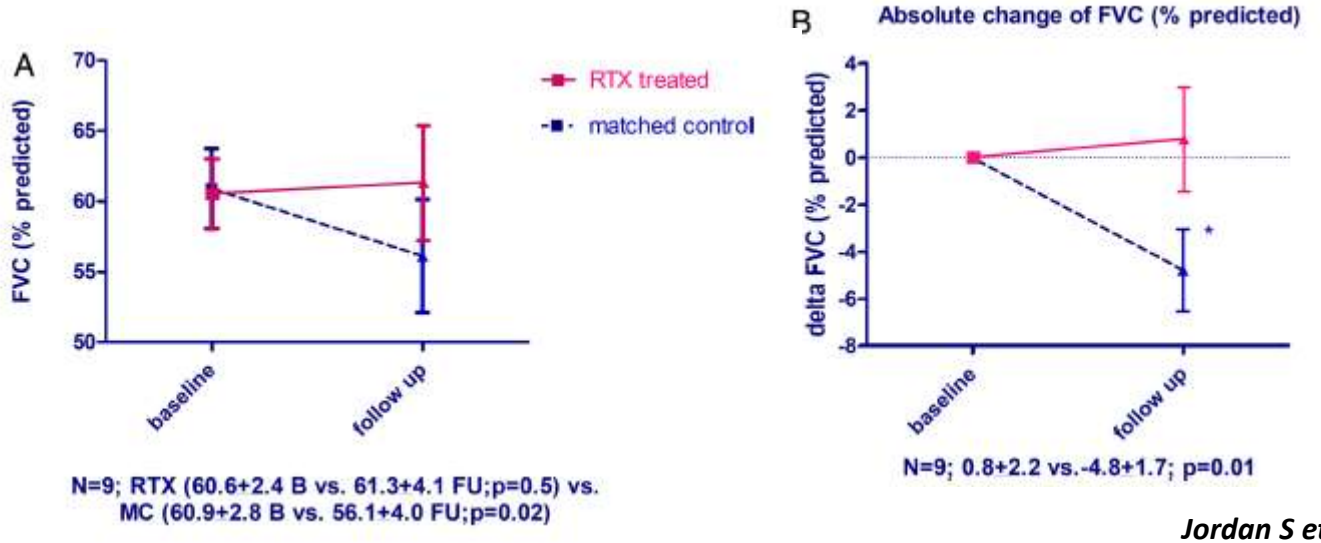

**Fig. 1.** Beneficial effect of long term RTX treatment on lung function and skin thickening in patients with SSc. RTX mediates a significant linear improvement of FVC ($p<0.0001$) and DLco ($p=0.0003$) during a 2-year follow-up (A and B, respectively). Similarly, skin thickening improved as indicated by a significant decline ($p<0.0001$) in MRSS (C).

*Clin Exp Rheumatol 2012; 30 (Suppl 71):S17-22*

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

**METHODS:** Inclusion criteria were fulfilment of American College of Rheumatology classification criteria for SSc, treatment with RTX and availability of follow-up data. RTX-treated patients were matched with control patients from the EUSTAR database not treated with RTX. Matching parameters for skin/lung fibrosis were the modified Rodnan Skin Score (mRSS), forced vital capacity (FVC), follow-up duration, scleroderma subtype, disease duration and immunosuppressive co-treatment. The primary analysis was mRSS change from baseline to follow-up in the RTX group compared with the control group. Secondary analyses included change of FVC and safety measures.

**RESULTS:** 63 patients treated with RTX were included in the analysis. The case-control analysis in patients with severe diffuse SSc showed that mRSS changes were larger in the RTX group versus matched controls (N=25; -24.0±5.2% vs -7.7±4.3%; p=0.03). Moreover, in RTX-treated patients, the mean mRSS was significantly reduced at follow-up compared with baseline (26.6±1.4 vs 20.3±1.8; p=0.0001). In addition, in patients with interstitial lung disease, RTX prevented significantly the further decline of FVC compared with matched controls (N=9; 0.4±4.4% vs -7.7±3.6%; p=0.02). Safety measures showed a good profile consistent with previous studies in autoimmune rheumatic diseases.

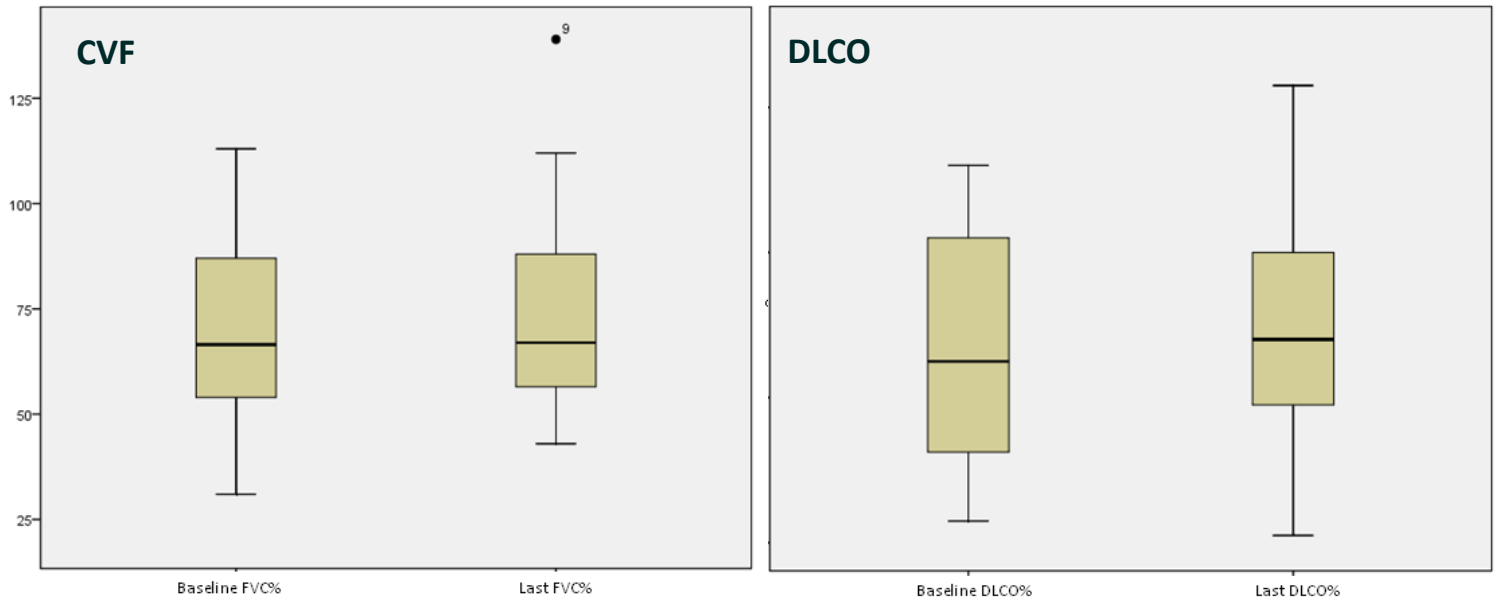



**DLCO:**
3.7 1.4 *vs* 6.2 6.2; p=0.9

*Jordan S et al. Ann Rheum Dis 2014 (en prensa)*

# Long-term efficacy of rituximab in SSc (ACR 2014)

- Estudio multicéntrico observacional
- 30 pacientes con SSc refractaria a " tto convencional" (CF 50%, MMF 47%).
- **Indicación clínica:** EPID (73%)
  Artritis (37%)
  Calcinosis (33%)
  Afección cutánea grave (20%)
- **T medio seguimiento:** 13 meses (1-43).



# Rituximab

**ClinicalTrials.gov**
A service of the U.S. National Institutes of Health

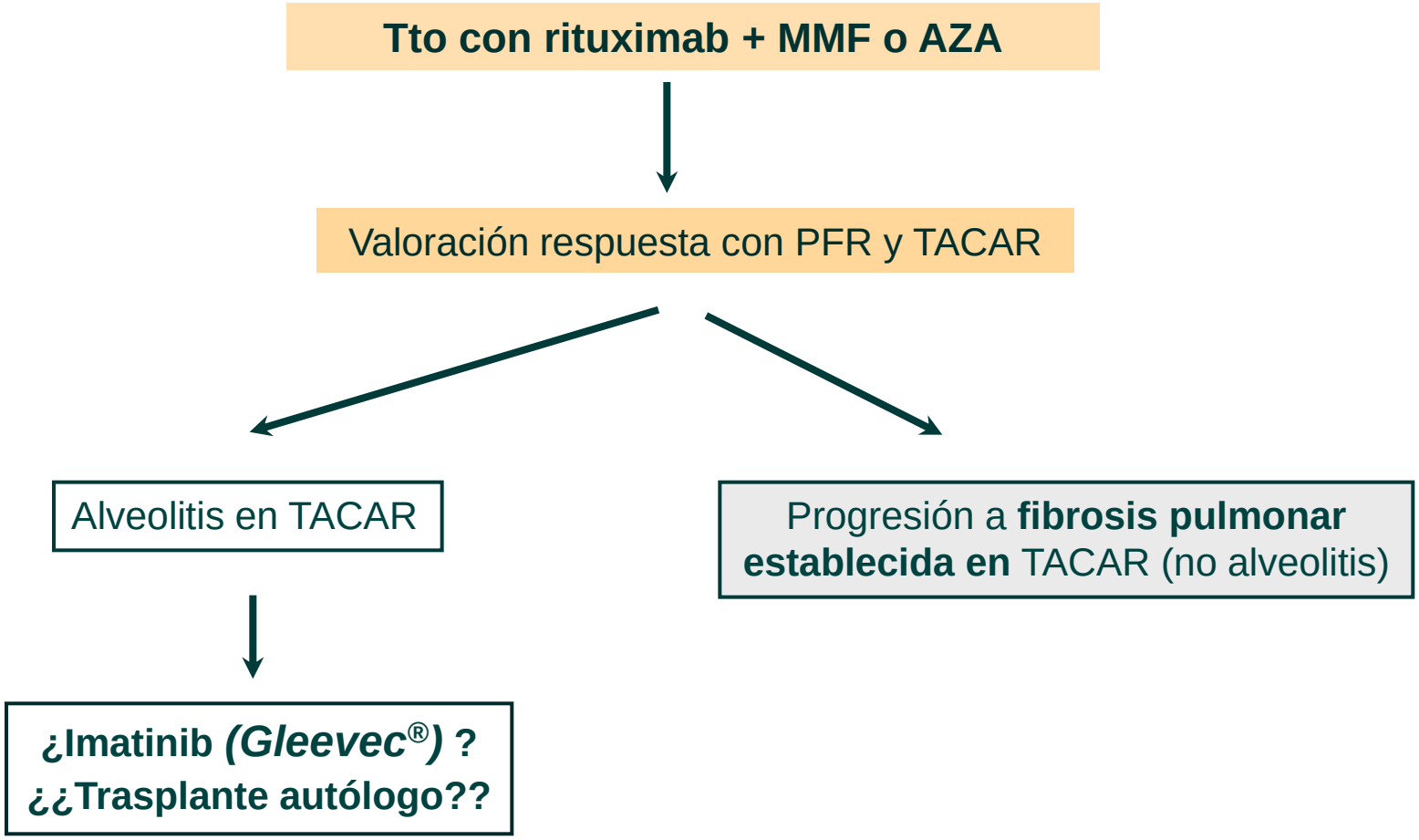
*Example: "Heart attack" AND "Los Angeles"*

Search for studies: Search

Advanced Search | Help | Studies by Topic | Glossary

Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site

| Rank | Status | Study |
|---|---|---|
| 1 | Recruiting | Rituximab in Systemic Sclerosis (RECOVER Study)<br>**Condition:** Systemic Sclerosis<br>**Interventions:** Drug: Rituximab; Drug: Placebo (NaCl) |
| 2 | Recruiting | Rituximab for Treatment of Systemic Sclerosis-Associated Pulmonary Arterial Hypertension (SSc-PAH)<br>**Condition:** Systemic Sclerosis-Associated Pulmonary Arterial Hypertension<br>**Interventions:** Biological: Rituximab; Other: Placebo |
| 3 | Not yet recruiting | Rituximab Versus Cyclophosphamide in Connective Tissue Disease-ILD (RECITAL Study)<br>**Conditions:** Interstitial Lung Disease; Scleroderma; Idiopathic Inflammatory Myositis; Mixed Connective Tissue Disease<br>**Interventions:** Drug: Rituximab; Drug: Cyclophosphamide |
| | Active, not recruiting | A Protocol Based Treatment for Early and Severe Systemic Sclerosis With (Anti-CD20), Rituximab<br>**Condition:** Early and Severe Systemic Sclerosis<br>**Intervention:** Drug: Administration of rituximab and methylprednisolone |


Tto con rituximab + MMF o AZA
Valoración respuesta con PFR y TACAR
Alveolitis en TACAR
Progresión a **fibrosis pulmonar establecida en** TACAR (no alveolitis)
**¿Imatinib *(Gleevec®)* ?**
**¿¿Trasplante autólogo??**

RESEARCH ARTICLE Open Access

# Low-dose oral imatinib in the treatment of systemic sclerosis interstitial lung disease unresponsive to cyclophosphamide: a phase II pilot study


## Abstract

**Introduction:** Pulmonary involvement represents a major cause of death of systemic sclerosis (SSc) patients. Recent data suggest that tyrosine kinase inhibitors, such as imatinib, may be a therapeutic option for SSc patients. However, preliminary published clinical trials were inconclusive about imatinib efficacy and showed side effects. The purpose of this study was to verify efficacy and tolerability of low-dose imatinib on interstitial lung disease in a cohort of SSc patients unresponsive to cyclophosphamide therapy.

**Methods:** Thirty consecutive SSc patients with active pulmonary involvement, unresponsive to cyclophosphamide, were treated with imatinib 200 mg/day for 6 months followed by a 6-month follow-up. A "good response" was defined as an increase of forced vital capacity (FVC) by more of 15% and/or increase of diffusing capacity of carbon monoxide ($DL_{CO}$) >15% and $PaO_2$ > 90% of initial value and high-resolution computed tomography (HRCT)-scan pattern unchanged or improved.

**Results:** Twenty-six patients completed the study. Three patients died and one patient was lost to follow-up. Four patients (15.32%) had a good response, 7 worsened and 15 had a stabilized lung disease. Overall, 19 (73.07%) patients had an improved or stabilized lung disease. After a 6-month follow-up, 12 (54.5%) of the 22 patients showed an improved or stabilized lung disease.

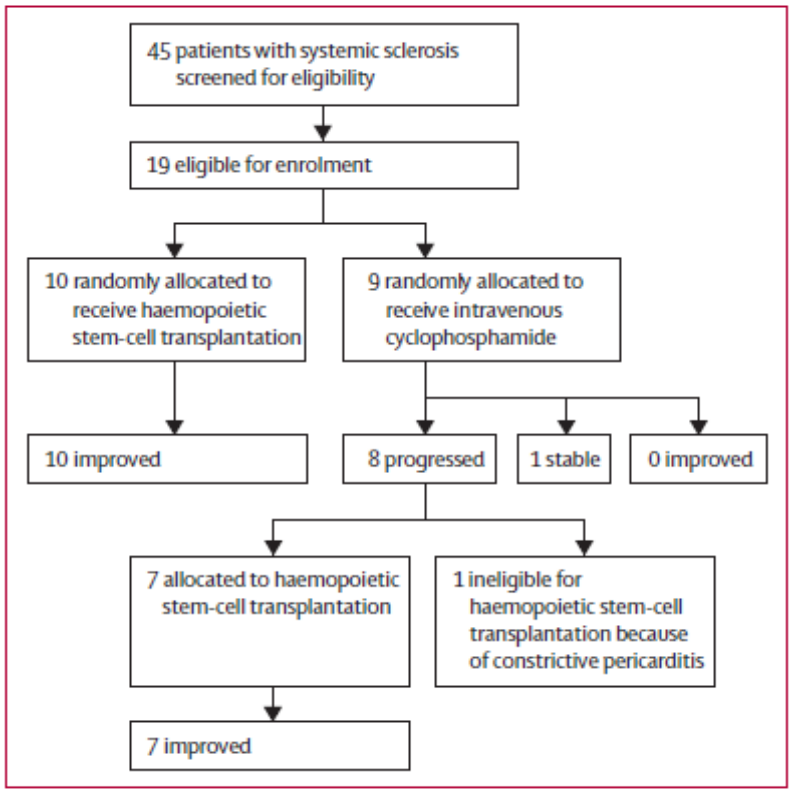
**Conclusions:** Lung function was stabilized in a large proportion of patients unresponsive to cyclophosphamide therapy and a beneficial outcome emerged from the analysis of HRCT lung scans. There was no significant improvement of skin involvement, and the low dose was well tolerated. These data provide useful suggestions to design future randomized clinical trials for SSc therapeutics.

**Trial registration:** ClinicalTrials.gov NCT00573326. Registered 13 December 2007.


*Fraticelli P et al. Arthritis Res Ther 2014 Jul 8;16:R144*

# Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial

**Findings** Between Jan 18, 2006, and Nov 10, 2009 we enrolled 19 patients. All ten patients randomly allocated to receive HSCT improved at or before 12 months' follow-up, compared with none of nine allocated to cyclophosphamide (odds ratio 110, 95% CI 14·04–∞; p=0·00001). Eight of nine controls had disease progression (without interval improvement) compared with no patients treated by HSCT (p=0·0001), and seven patients switched to HSCT. Compared with baseline, data for 11 patients with follow-up to 2 years after HSCT suggested that improvements in mRSS (p<0·0001) and forced vital capacity (p<0·03) persisted.




*Burt RK et al. Lancet 2011;378:498-506*

Research

Original Investigation

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

## A Randomized Clinical Trial


**IMPORTANCE** High-dose immunosuppressive therapy and autologous hematopoietic stem cell transplantation (HSCT) have shown efficacy in systemic sclerosis in phase 1 and small phase 2 trials.

**OBJECTIVE** To compare efficacy and safety of HSCT vs 12 successive monthly intravenous pulses of cyclophosphamide.

**DESIGN, SETTING, AND PARTICIPANTS** The Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial, a phase 3, multicenter, randomized (1:1), open-label, parallel-group, clinical trial conducted in 10 countries at 29 centers with access to a European Group for Blood and Marrow Transplantation–registered transplant facility. From March 2001 to October 2009, 156 patients with early diffuse cutaneous systemic sclerosis were recruited and followed up until October 31, 2013.

**INTERVENTIONS** HSCT vs intravenous pulse cyclophosphamide.

**MAIN OUTCOMES AND MEASURES** The primary end point was event-free survival, defined as time from randomization until the occurrence of death or persistent major organ failure.

**RESULTS** A total of 156 patients were randomly assigned to receive HSCT (n = 79) or cyclophosphamide (n = 77). During a median follow-up of 5.8 years, 53 events occurred: 22 in the HSCT group (19 deaths and 3 irreversible organ failures) and 31 in the control group (23 deaths and 8 irreversible organ failures). During the first year, there were more events in the HSCT group (13 events [16.5%], including 8 treatment-related deaths) than in the control group (8 events [10.4%], with no treatment-related deaths). At 2 years, 14 events (17.7%) had occurred cumulatively in the HSCT group vs 14 events (18.2%) in the control group; at 4 years, 15 events (19%) had occurred cumulatively in the HSCT group vs 20 events (26%) in the control group. Time-varying hazard ratios (modeled with treatment × time interaction) for event-free survival were 0.35 (95% CI, 0.16-0.74) at 2 years and 0.34 (95% CI, 0.16-0.74) at 4 years.

**CONCLUSIONS AND RELEVANCE** Among patients with early diffuse cutaneous systemic sclerosis, HSCT was associated with increased treatment-related mortality in the first year after treatment. However, HCST conferred a significant long-term event-free survival benefit.


*Van Laar J et al. EBMT/EULAR Scleroderma Study Group. JAMA 2014; 311:2490-8*

**Tto con rituximab + MMF o AZA**

↓

Valoración respuesta con PFR y TACAR

↓

Progresión a **fibrosis pulmonar establecida en** TACAR (no alveolitis)

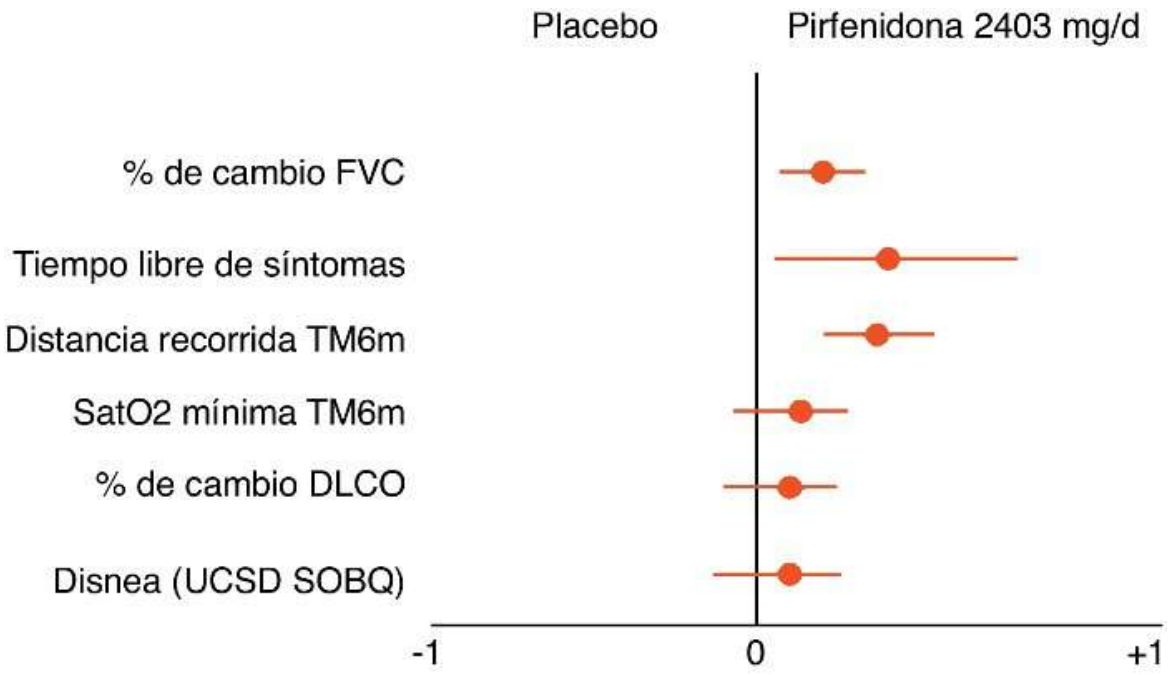
↓

**Suspender tto inmunosupresor**
Sólo medidas generales
Valorar **Pirfenidona** (NIU) o **trasplante pulmonar**

# Pirfenidona *(Esbriet®)*

**Propiedades antiinflamatorias y antifibróticas**: inhibe la proliferación de fibroblastos, la biosíntesis aumentada de colágeno, la acumulación de matriz extracelular estimulada por el factor TGF-β , y la producción de citoquinas profibróticas y factores de crecimiento (TGF- β, TNF-α e IL-1).

Su eficacia clínica en la **fibrosis pulmonar idiopática (FPI)** se he demostrado en 3 ECA *(estudios CAPACITY).*



# Safety and Tolerability of Pirfenidone in Patients With Systemic Sclerosis-Related Interstitial Lung Disease (SSc-ILD) (LOTUSS)

**This study is currently recruiting participants.**

*Verified August 2013 by InterMune*

**Sponsor:**
InterMune

**Information provided by (Responsible Party):**
InterMune

**ClinicalTrials.gov Identifier:**
NCT01933334

First received: August 23, 2013
Last updated: August 30, 2013
Last verified: August 2013
History of Changes

The LOTUSS Trial: An Open-Label, Randomized, Phase 2 Study of the Safety and Tolerability of **Pirfenidone** When Administered to Patients With **Systemic Sclerosis**-Related Interstitial Lung Disease (SSc-ILD) (LOTUSS)

**Criteria**
Inclusion Criteria:

1. Diagnosis of SSc confirmed by the American College of Rheumatology classification criteria of systemic sclerosis (Masi 1980); duration of diagnosis <7 years
2. Diagnosis of SSc-ILD based on an HRCT scan
3. Screening FVC ≥50% of the predicted value, and screening DLCO ≥40% of the predicted value
4. At study entry, the patient either is not taking SSc-ILD medication or is taking cyclophosphamide or mycophenolate mofetil

ARCHIVOS DE BRONCONEUMOLOGIA

Arch Bronconeumol. 2013;49(8):343–353

Normativa SEPAR

# Normativa sobre el diagnóstico y tratamiento de la fibrosis pulmonar idiopática

Antoni Xaubet[a,b,*,1], Julio Ancochea[c,1], Elena Bollo[d], Estrella Fernández-Fabrellas[e], Tomás Franquet[f], Maria Molina-Molina[b,g], Maria Angeles Montero[h] y Anna Serrano-Mollar[b,i]

Recomendaciones basadas en la evidencia para el tratamiento farmacológico de la fibrosis pulmonar idiopática (FPI)†

| Agente | Mecanismo de acción | Recomendaciones |
|---|---|---|
| *Recomendado en pacientes seleccionados* | | |
| Pirfenidona | Antifibrótico + antiinflamatorio + antioxidante + anti TGF β1 | Sí, recomendación débil[a] |
| NAC en monoterapia | Antioxidante | No, recomendación débil |
| *No recomendados* | | |
| Esteroides + Azatioprina + NAC | Inmunosupresor + antioxidante + antiinflamatorio | No utilizar |
| Anticoagulación | Anticoagulante | No utilizar |
| Bosentán | Antagonismo dual del receptor de la endotelina | No utilizar |
| Esteroides en monoterapia | Inmunosupresor | No utilizar |
| Esteroides + terapia inmunomoduladora | Inmunosupresor | No utilizar |
| Colchicina | Inhibidor proliferación/síntesis de colágeno | No utilizar |
| Ciclosporina A | Inmunosupresor | No utilizar |
| Etanercept | Anti TNF alfa | No utilizar |
| Interferón gamma | Antifibrótico e inmunomodulador | No utilizar |

[a] En pacientes con FPI leve/moderada.

†*Spagnolo P et al. Non-steroid agents for idiopathic pulmonary fibrosis. Cochrane Database Syst Rev.2010;(9):CD003134.*

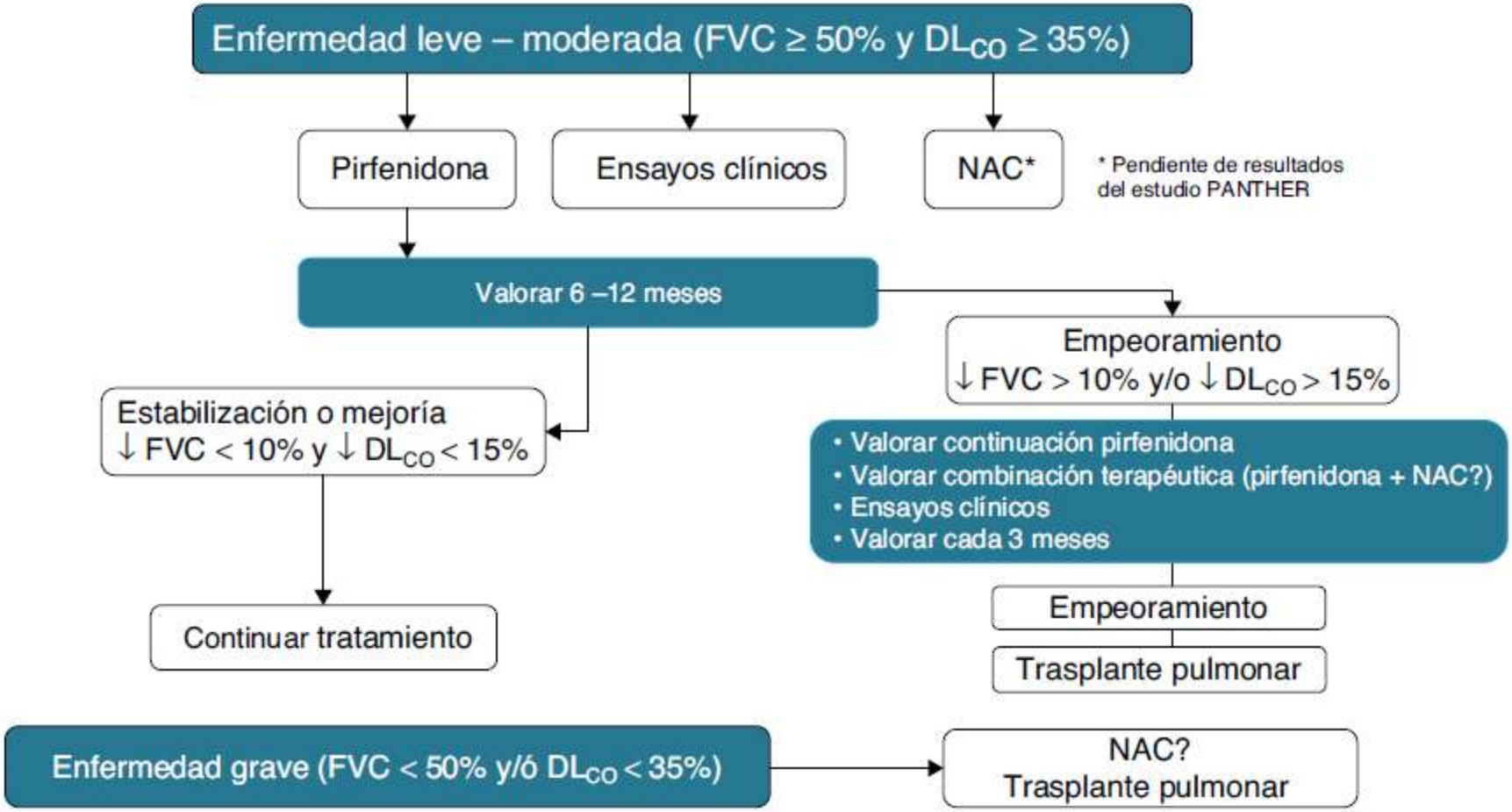



**Figura 6.** Tratamiento farmacológico de la fibrosis pulmonar idiopática.

*Xaubet A et al. Arch Bronconeumol 2013;49:343-53*

# Trasplante pulmonar

Datos de 47 pacientes con esclerodermia trasplantados por fibrosis pulmonar terminal.

- Supervivencia al año: 68%.
- Supervivencia a los 3 años: 46%.

**La supervivencia es similar a la de los pacientes transplantados por otras enfermedades**

*Massad MG et al. World J Surg 2005;29:1510-15*

Muchas gracias