Τι νεότερο στη ρευματολογία Ι:
Ρευματολογικά νοσήματα και πνεύμονας

- Θεραπεία της διάμεσης πνευμονίας αυτοανόσων νοσημάτων: ποιά τα δεδομένα για MMF/Rituximab έναντι της κυκλοφωσφαμιδής; (Α. Αντωνίου)

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Λάρνακα, 24 Οκτωβρίου 2015

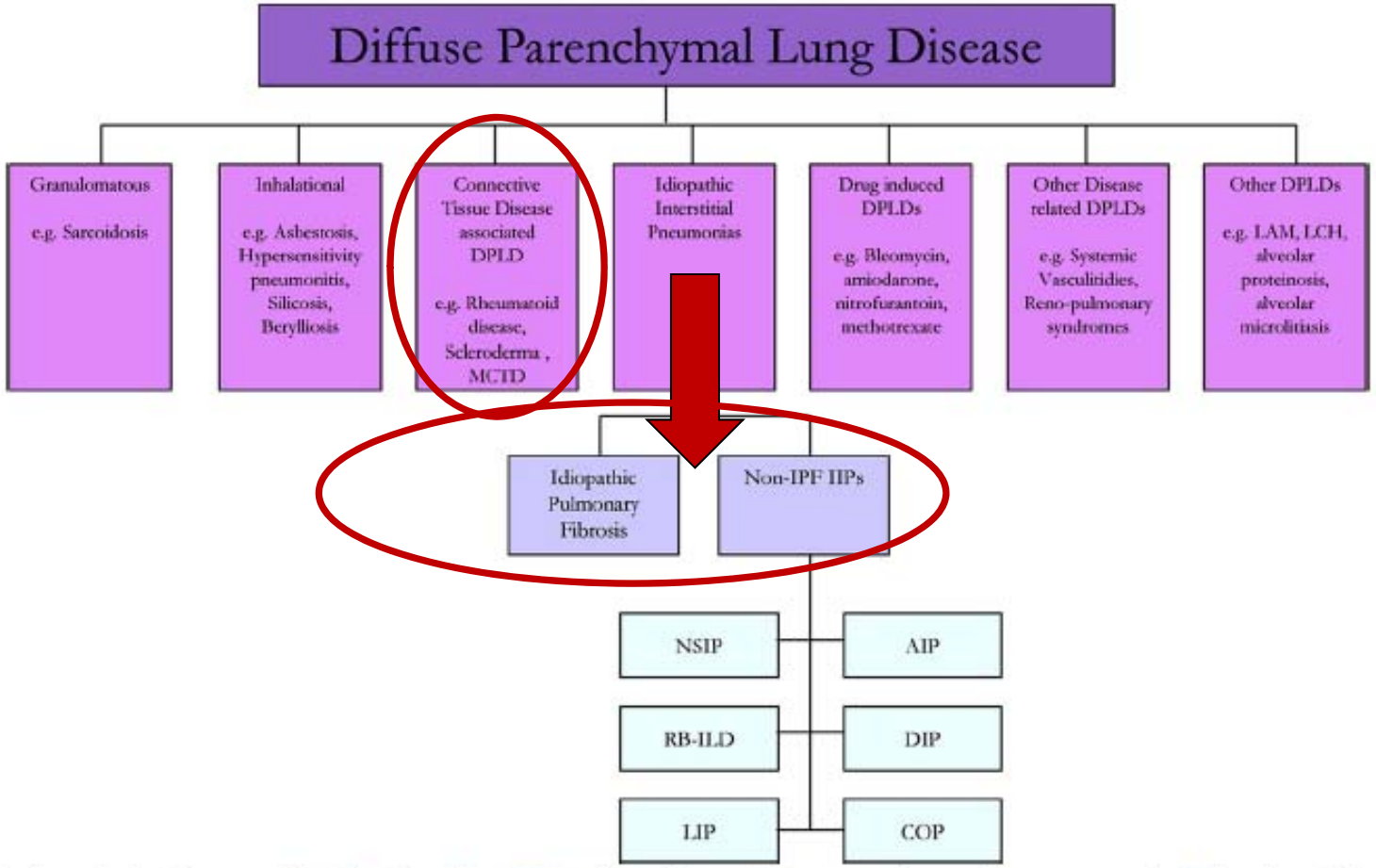


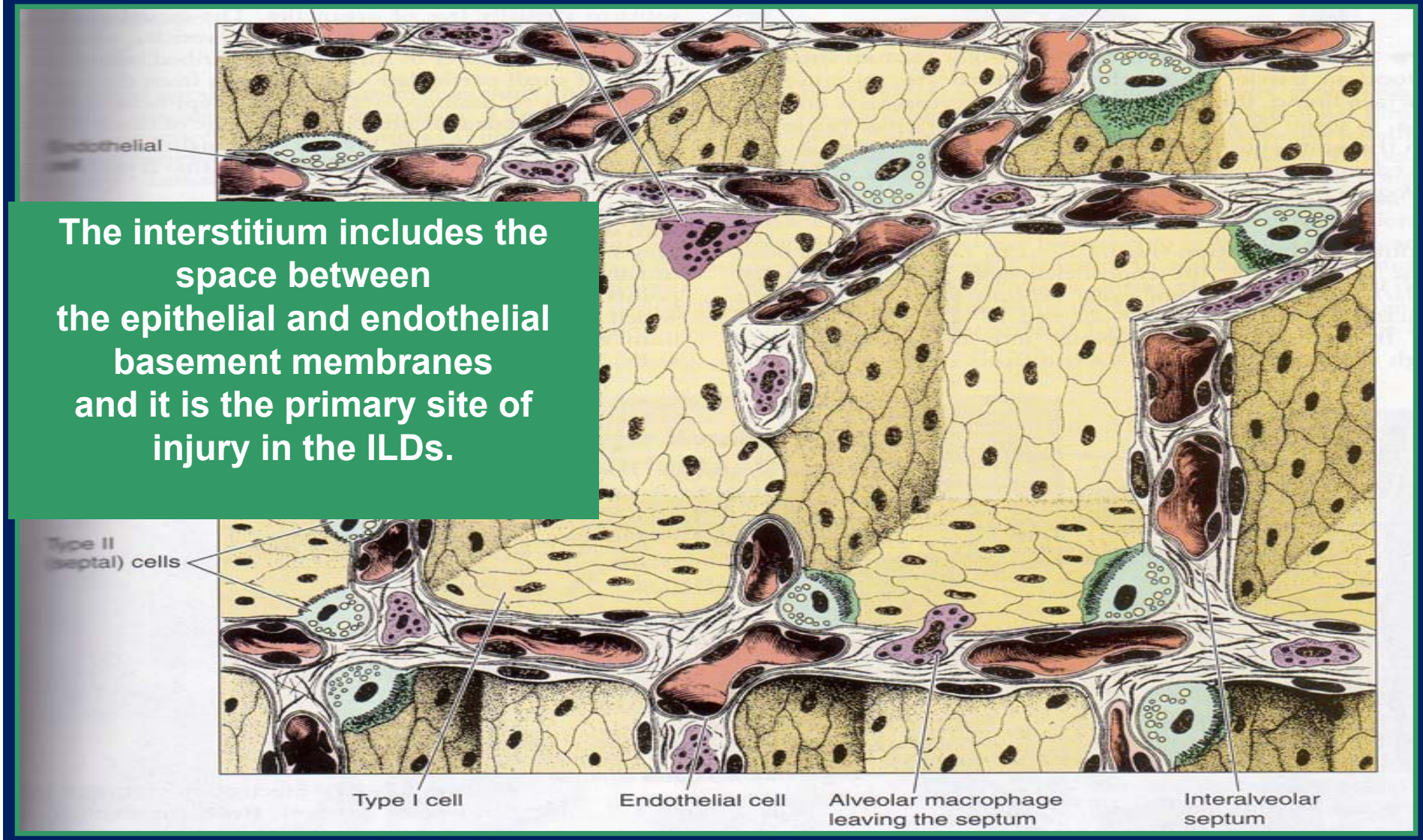
Fig. 1. A schematic for the general classification of the DPLDs. *Abbreviations:* COP, cryptogenic organizing pneumonia; LIP, lymphocytic interstitial pneumonia; MCTD, mixed connective tissue disease.

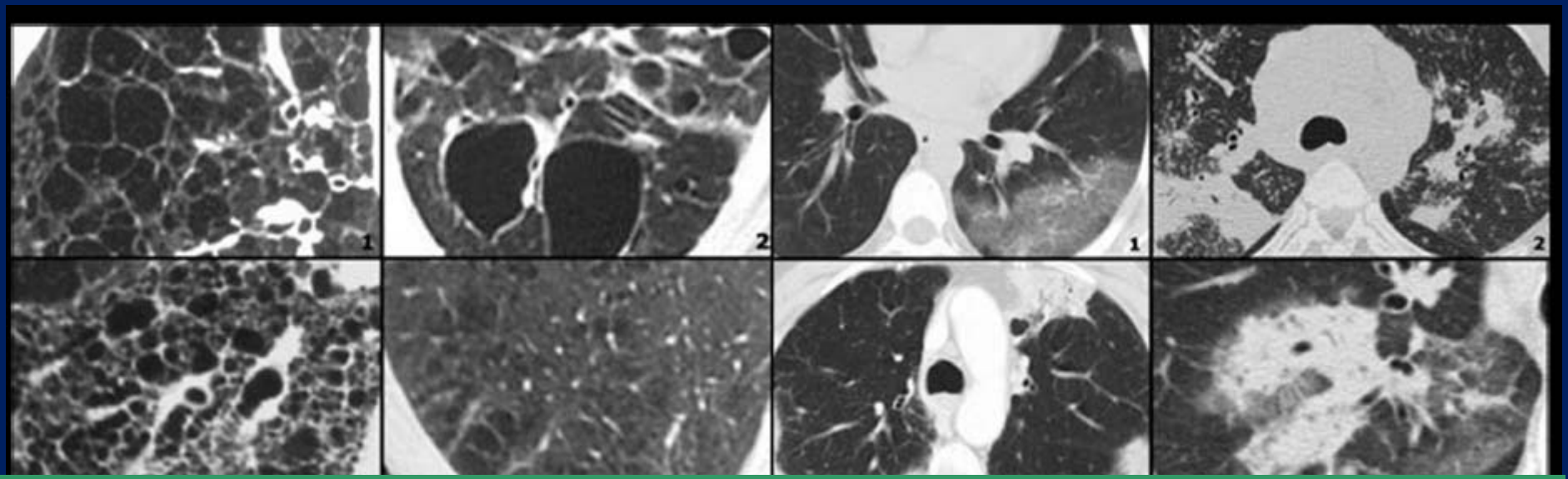
Maher TM. Immunol Allergy Clin N Am 2012; 453-472

The management of non-IPF ILDs

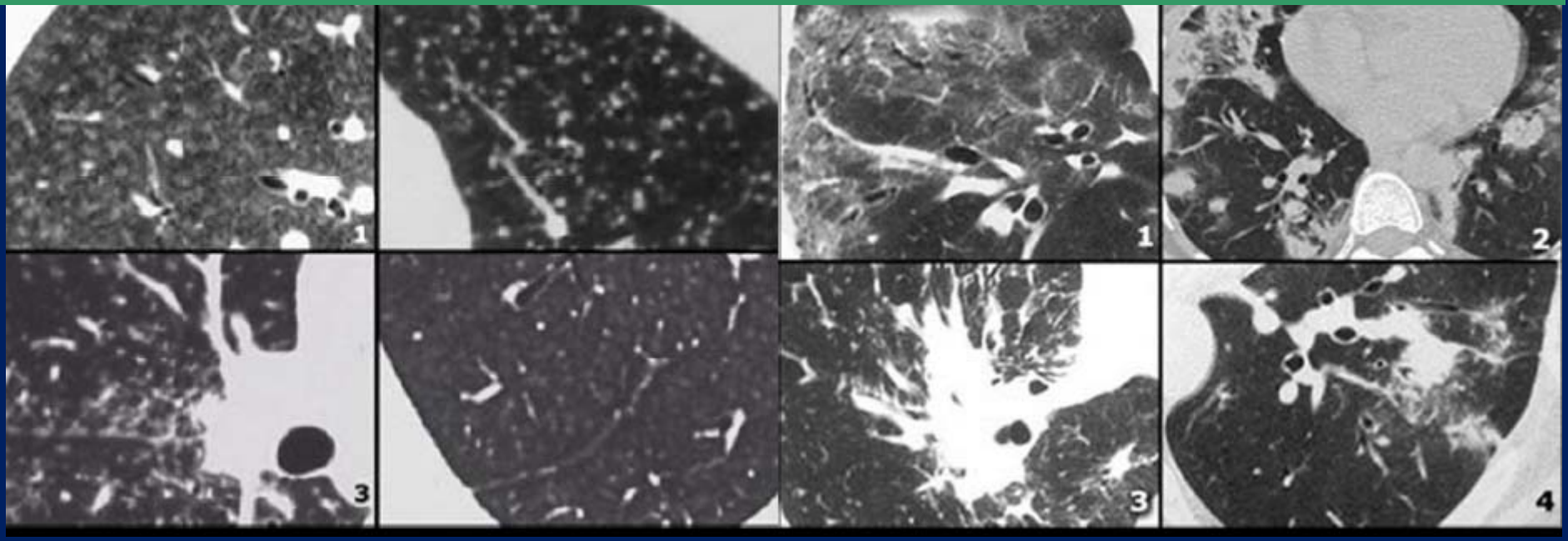
- Corticosteroids +/- immunosuppressive agents remain the mainstay of treatment in most non IPF ILDs
- The aim of treatment in many instances is that of stabilization in the face of previous progression
- CTD-ILD the most studied
- The only placebo-controlled trials in CTD-ILD have been performed in scleroderma-ILD (SSc-ILD)

The interstitium includes the space between the epithelial and endothelial basement membranes and it is the primary site of injury in the ILDs.





However, these disorders frequently affect also the airspaces, peripheral airways, and vessels along with their respective epithelial and endothelial linings



Connective Tissue Disease–related Thoracic Disease

Yutaka Tsuchiya, MD[a,b,*], Aryeh Fischer, MD[c], Joshua J. Solomon, MD[d], David A. Lynch, MB[a]

Box 1
Features of CTD-related thoracic disease

- Often asymptomatic
- May predate other manifestations
- Involves 1 or many lung compartments: interstitium, airway, vessels, pleura
- Type of involvement varies with specific type of CTD
- Clues to diagnosis may be apparent on chest radiograph or CT

Clin Chest Med ■ (2015)

Types of pulmonary involvement

- *When a patient with an underlying CTD presents with new signs or symptoms referable to the chest, a vast range of differential diagnostic possibilities exists:*

Eur Respir Mon, 2009

A.L. Olson, K.K. Brown*,#*

CONNECTIVE TISSUE DISEASE-ASSOCIATED DISORDERS

Eur Respir Mon, 2009

The connective tissue diseases (including rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, Sjögren's syndrome, polymyositis/dermatomyositis, and their associated overlap syndromes) are associated with a wide variety of pulmonary complications.

While specific connective tissue diseases are typically associated with particular pulmonary complications, virtually all complications can occur with any of the connective tissue diseases and may even present prior to the diagnosis of the underlying connective tissue disease.

KEY POINTS

- Understanding the prevalence of each entity and the characteristic imaging patterns of each connective tissue disease (CTD) manifestation helps to make the correct diagnosis for CTD-related thoracic disease.
- Drug-induced toxicity, pulmonary infection, and malignancy are frequently seen in patients with CTD. These complications should be excluded when thoracic involvement newly occurs.
- Innovative approaches for evaluating severity and therapeutic effect for patients with CTD-associated thoracic disease have been under development.

Clin Chest Med ■ (2015)

Types of pulmonary involvement

1. infection, drug toxicity, ***direct pulmonary complications (e.g. interstitial lung disease(ILD));***
2. indirect complications (e.g.hypoventilation secondary to myopathy);
3. cardiovascular complications (e.g. coronary artery disease or cardiomyopathy); and
4. unrelated disease

Eur Respir Mon, 2009

Interstitial lung disease in connective tissue disorders

Aryeh Fischer, Roland du Bois

	ILD	Airways	Pleural	Vascular	DAH
Systemic sclerosis	+++	–	–	+++	–
Rheumatoid arthritis	++	++	++	+	–
Primary Sjögren's syndrome	++	++	+	+	–
Mixed CTD	++	+	+	++	–
Polymyositis/ dermatomyositis	+++	–	–	+	–
Systemic lupus erythematosus	+	+	+++	+	++

The signs show prevalence of each manifestation (–=no prevalence; +=low prevalence; ++=medium prevalence; +++=high prevalence). ILD=interstitial lung disease. DAH=diffuse alveolar haemorrhage. CTD=connective tissue disease.

Table 1: **CTDs and common pulmonary manifestations**

Lancet

Vol 380 August 18, 2012

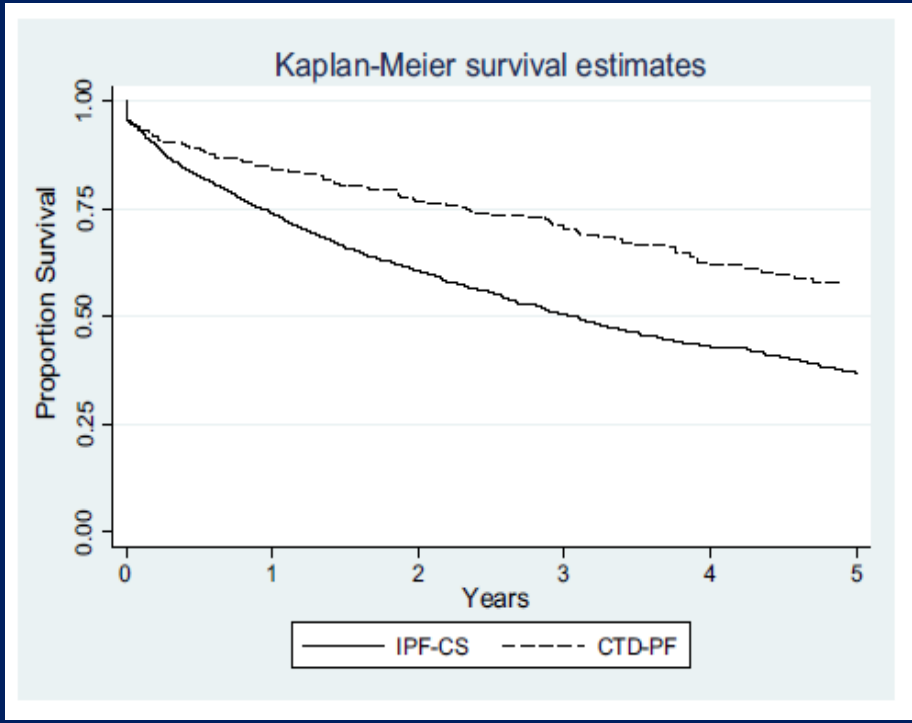
CATEGORIZATION OF MAJOR IDIOPATHIC INTERSTITIAL PNEUMONIAS, 2013,
All patterns may appear in patients with CTD-ILD

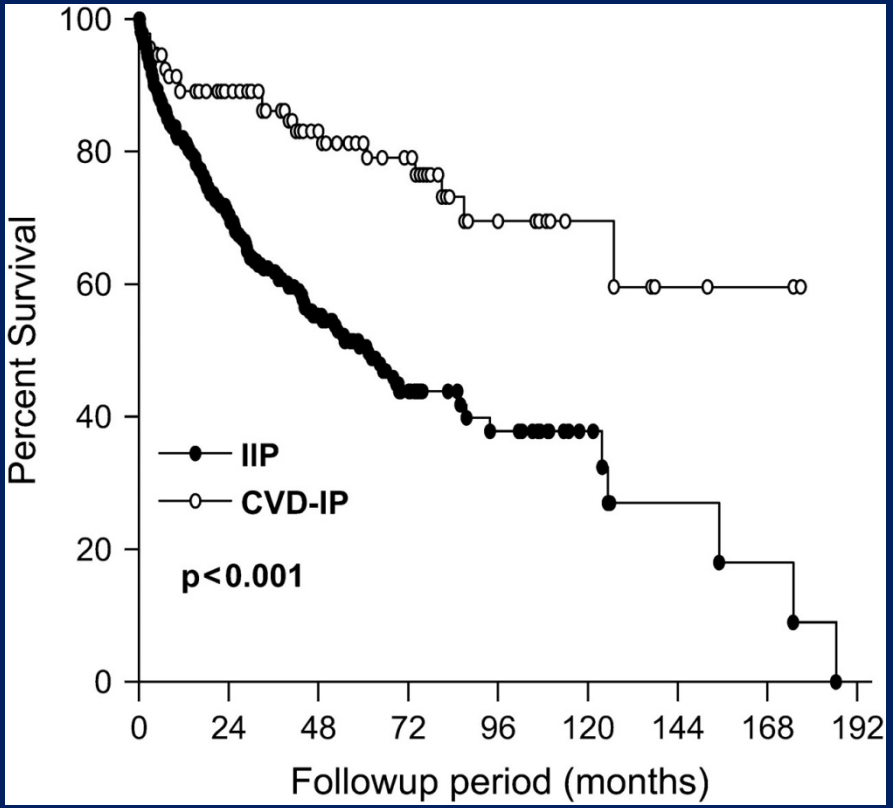
CATEGORY	CLINICAL-RADIOLOGIC- PATHOLOGIC DIAGNOSES	ASSOCIATED MORPHOLOGIC PATTERNS
Chronic Fibrosing IP	Idiopathic Pulmonary Fibrosis	**Usual Interstitial Pneumonia**
	Idiopathic Nonspecific Interstitial Pneumonia‡	**Nonspecific Interstitial Pneumonia**
Smoking-related IP †	Respiratory Bronchiolitis Interstitial Lung Disease	Respiratory Bronchiolitis
	Desquamative Interstitial Pneumonia	Desquamative Interstitial Pneumonia
Acute/subacute IP	Cryptogenic Organizing Pneumonia	Organizing Pneumonia
	Acute Interstitial Pneumonia	Diffuse Alveolar Damage

Histological patterns

- **Same spectrum of histological patterns in CTD as in the IIPs**
- **However, there is NOT the same proportion of individual patterns as there is in idiopathic disease**
- ***Patterns do NOT have the same prognostic significance***

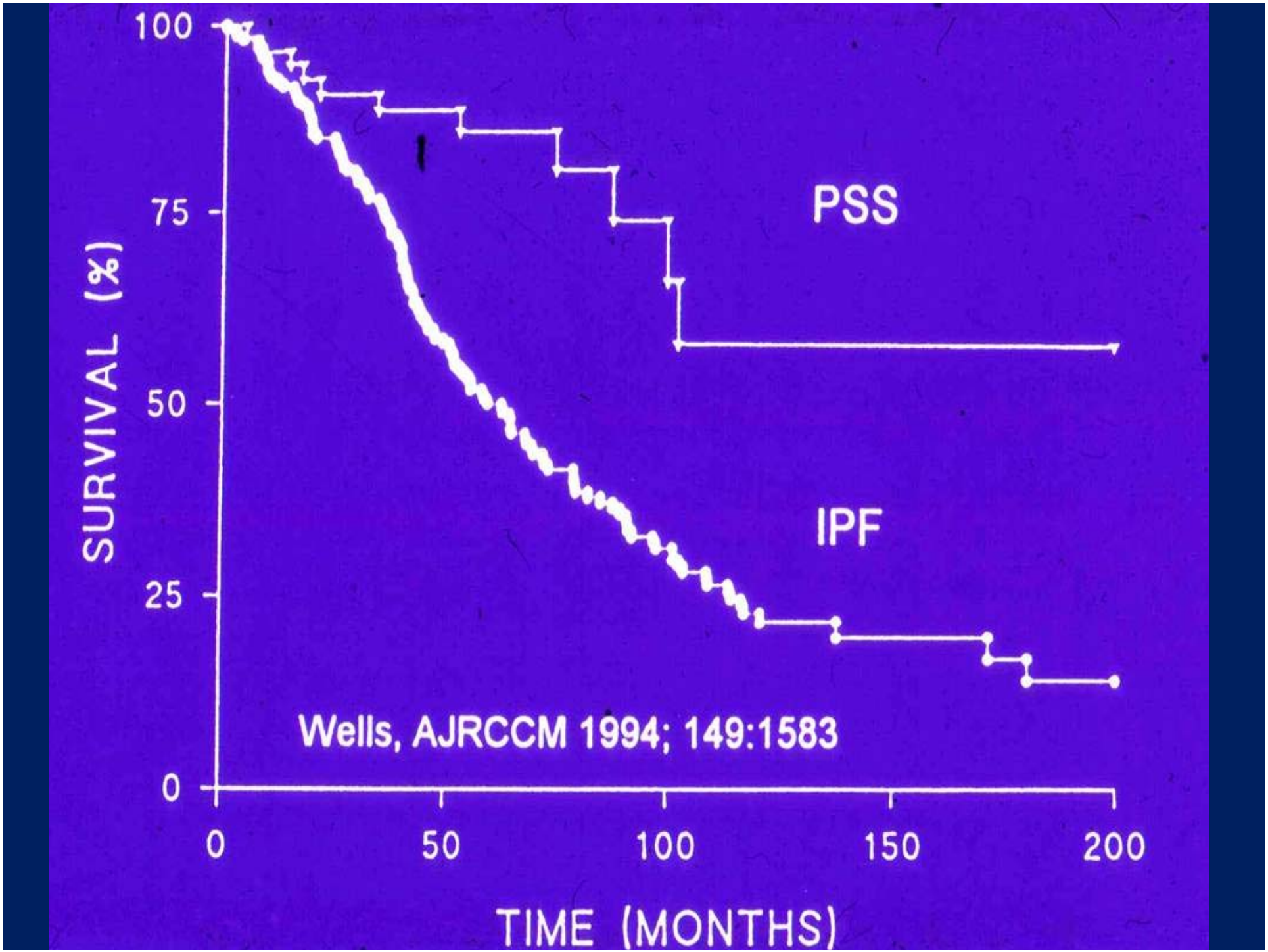
ILD with Autoimmune Findings
Impact on Prognosis



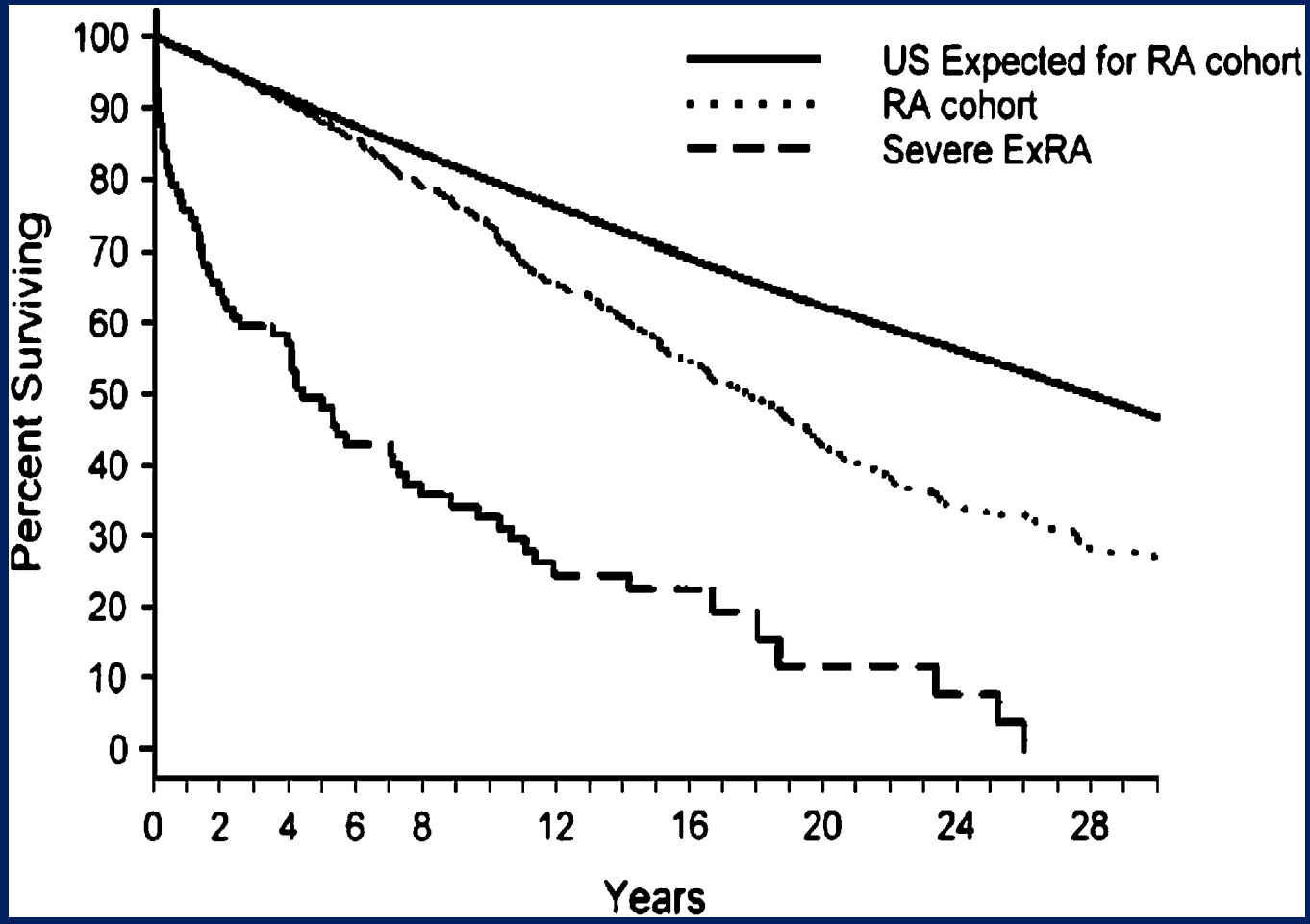


Navaratnan et al. Respir Med, 2011

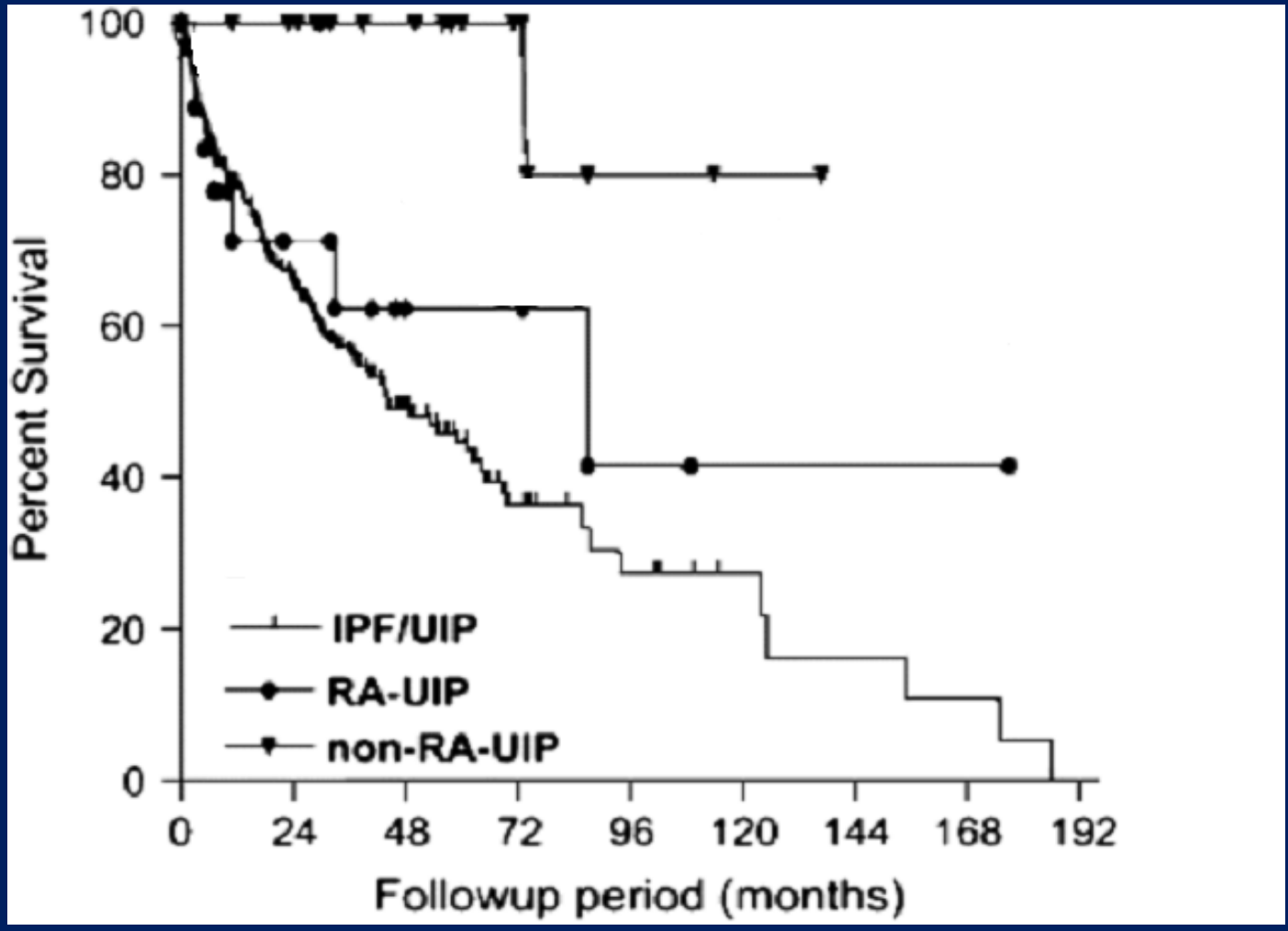
Park et al. Am J Respir Crit Care Med, 2007


100
75
50
25
0
SURVIVAL (%)
PSS
IPF
Wells, AJRCCM 1994; 149:1583
0
50
100
150
200
TIME (MONTHS)

Survival


US Expected for RA cohort
RA cohort
Severe ExRA
Percent Surviving
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
12
16
20
24
28
Years

Survival in RA –UIP



(Brown KK, PATS 2007)

A classification based on pragmatic management ...

- **Specific diagnosis**
- **Cause**
- **Predominant morphologic abnormality**
- **Severity**
- **Longitudinal behaviour**

Integrate *these as follows*

CLINICAL BEHAVIOR	TREATMENT GOAL	MONITORING STRATEGY
Reversible & self-limited (e.g. RBILD)	Remove possible cause	Short term (3-6 month) observation to confirm disease regression
Reversible disease with risk of progression (e.g. some NSIP, DIP, COP)	Initial response & then rationalize longer term therapy	Short term observation to confirm Rx response. Long term observation to ensure that gains are preserved
Stable with residual disease (e.g. some NSIP)	Maintain status	Long term observation to assess disease course
Progressive, irreversible disease with potential for stabilization (e.g. some fibrotic NSIP)	To prevent progression	Long term observation to assess disease course
Progressive, irreversible disease despite therapy (e.g. IPF, some fibrotic NSIP)	To slow progression	Long-term observation to assess disease course to assess need for transplant or effective palliation

Table 3 RA-associated interstitial pneumonias: classification according to disease behavior, adapted from Travis et al,[72] classification for the idiopathic interstitial pneumonias[a]

Clinical behavior	Treatment and treatment goal	Monitoring strategy
Potentially reversible with risk of irreversible disease (e.g., cases of drug-related lung disease in RA)	Remove cause, treat to obtain a response to reverse changes	Short-term (3–6 mo) observation to confirm disease regression, or occasionally need for palliation
Reversible disease with risk of progression (e.g., RA-cellular NSIP and some RA-fibrotic NSIP, RA-OP)	Treat to initially achieve response and then rationalize longer term therapy	Short-term observation to confirm treatment response. Long-term observation to ensure that gains are preserved
Stable with residual disease (e.g., some RA-fibrotic NSIP, some RA-UIP)	No treatment if stable, aiming to maintain status	Long-term observation to assess disease course
Progressive, irreversible disease with potential for stabilization (e.g., some RA-fibrotic NSIP, some RA-UIP)	Consider treatment trial to stabilize	Long-term observation to assess disease course
Progressive, irreversible disease despite therapy (e.g., RA-DAD, most RA-UIP, some RA-fibrotic NSIP)	In absence of contraindications, consider treatment trial in selected patients to slow progression	Short (DAD) or long-term observation to assess disease course, and need for transplant or effective palliation

Lake and Proudman. Semin Respir Crit Care Med 2014

The issue of limited versus extensive disease

- HRCT now widely used to screen for ILD in CTD patients
- Many CTD pts have limited/inherently stable ILD
- However, a substantial minority have progressive/severe disease

Should we treat? When?

- Current treatments all have a degree of toxicity

- In limited disease, especially if longstanding, risk /benefit favour careful observation

- Threshold for initiating treatment is definitely reduced in
  - severe ILD
  - ongoing progression based on lung function and symptoms
  - recent onset of systemic disease (at least in SSc)

Likelihood of progression: ILD severity is the strongest known predictor

- Severity: reduced lung function and extent fibrosis on CT
- Scleroderma the most studied

Prognostic Factors

Poorer survival predicted by

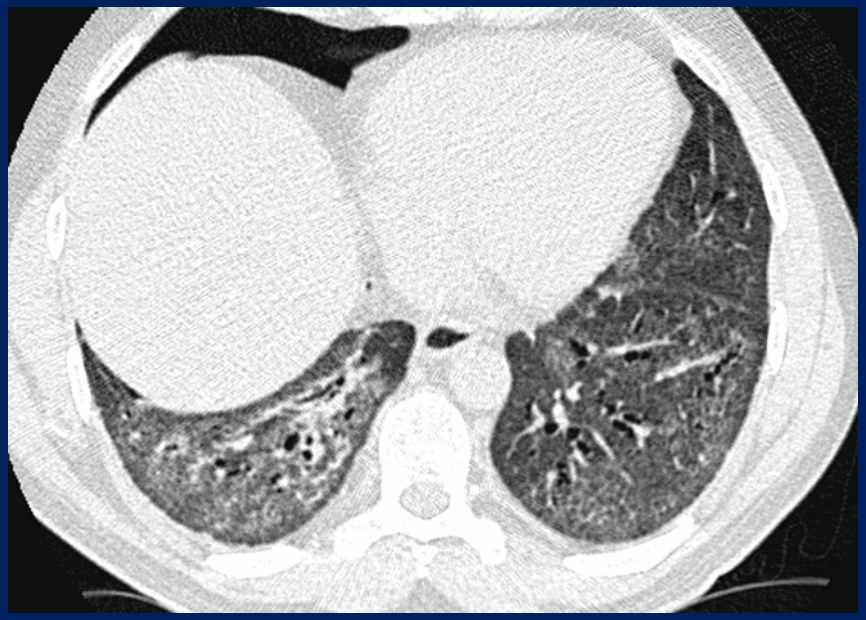
- Lower baseline DLCO
- Increased eosinophil count on BAL
- Deterioration in DLCO during 3 yrs of follow-up

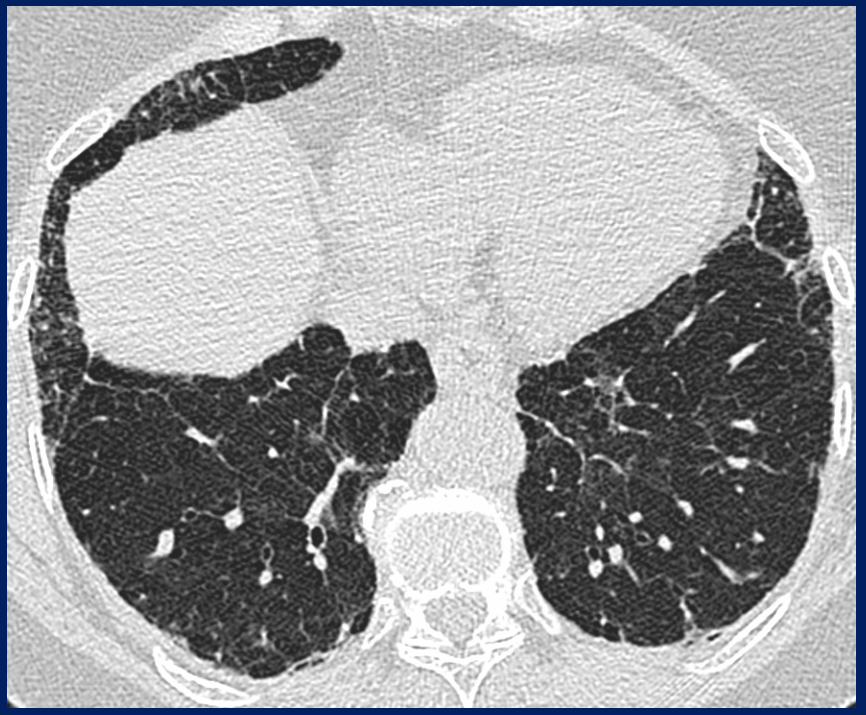
Bouros AJRCCM 2002

The key clinical dilemma

- We need to treat major pulmonary inflammation and progressive fibrosis.
- But we need to avoid unnecessary treatment in inherently stable disease.
- How to decide? A trend towards routine screening for pulmonary fibrosis in SSc has made this a frequent issue.

Sometimes the answer is obvious





Intensive treatment vs MICO therapy

“Indolent/stable disease”

MICO:

Masterful Inactivity

with Cat-like Observation

The role of the doctor is to amuse the patient while nature takes its course

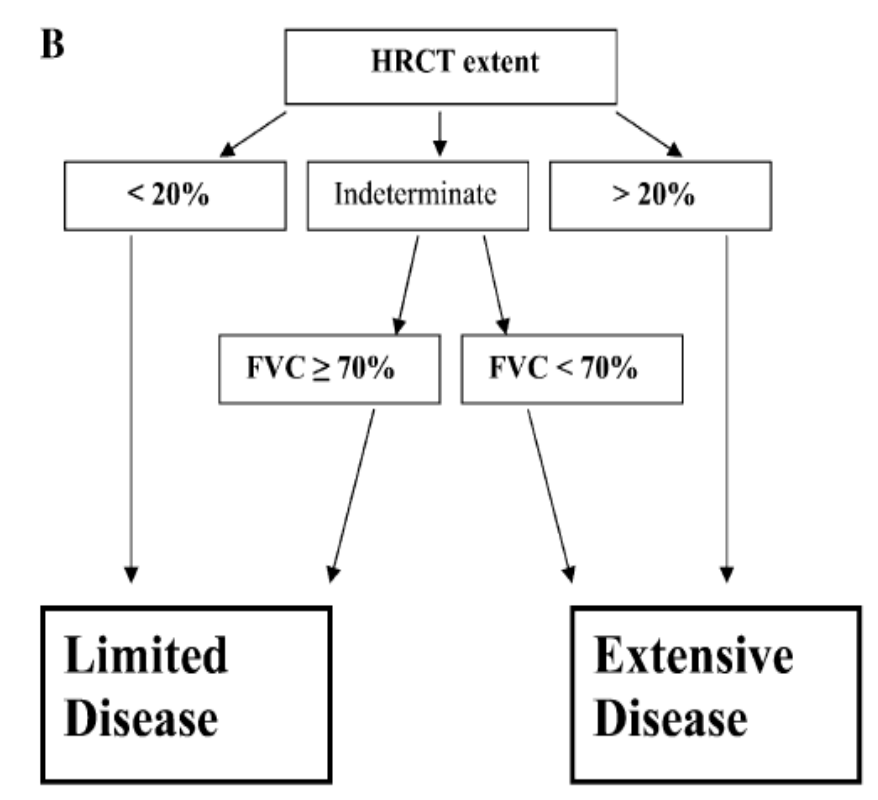
Voltaire

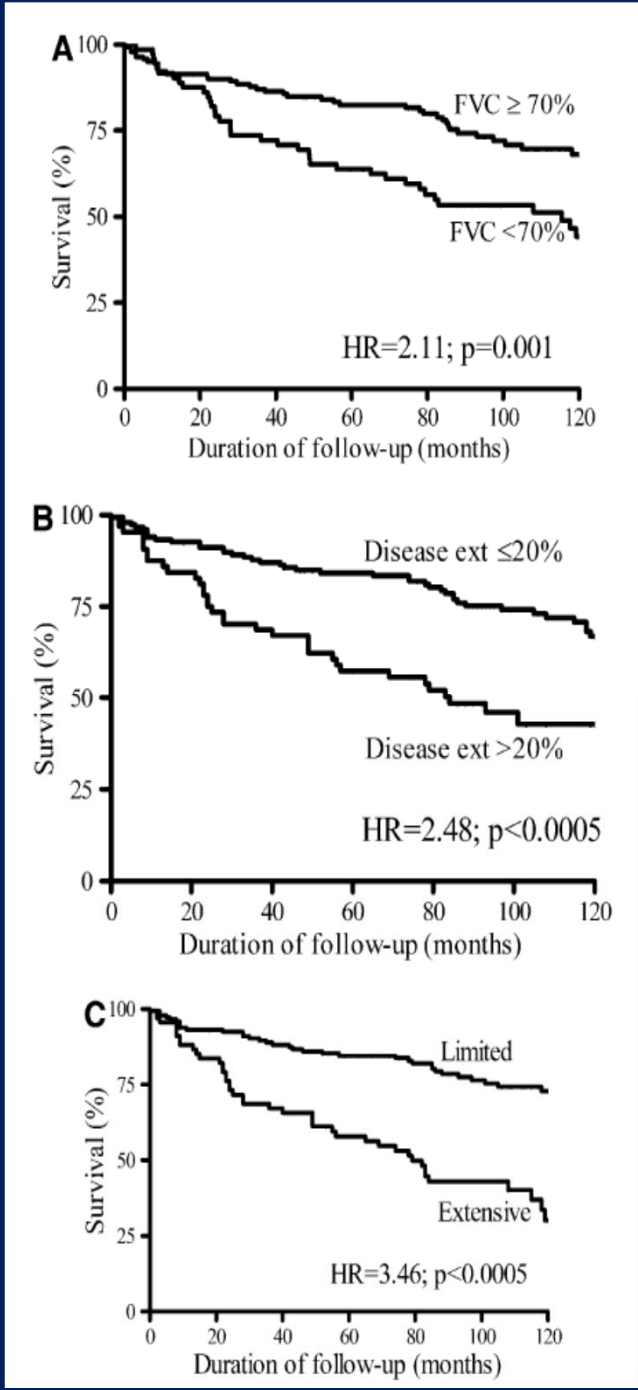
Often the answer is not obvious

Clinician needs

- Decisions are dichotomous: treat or not, enrol in treatment trial or not
- We need definition of high and low risk disease
- We need to STAGE lung disease

Combined HRCT/LFT score-SSc





Goh, AJRCCM 2008

Recommendations for treatment of RA-ILD

- MDD to confirm the diagnosis and review severity of ILD based on extent of fibrosis on HRCT and DLCO (< 54%).
- Unless severe symptomatic disease, monitor comprehensive lung function (spirometry, lung volumes, DLCO, and 6MWT) for 3 to 6 months if initial measurements are abnormal.
- Consider potential impact (positive or negative) of drugs required for joint disease (DMARDs) and monitor lung function during therapy.

Lake and Proudman. Semin Respir Crit Care Med 2014

Recommendations for treatment of RA-ILD

- Consider potential impact (positive or negative) of drugs required for joint disease (DMARDs) and monitor lung function during therapy.[105]
- Consider treatment if extensive disease (extent of fibrosis on HRCT $>$ 30%, DLCO $<$ 54%, desaturation with exercise), deteriorating (decrease from baseline in FVC by 10% or DLCO by 15%) or very symptomatic.
- Review age and comorbidities (obesity, osteoporosis, cardiovascular disease, infection risk, diabetes, coexisting lung disease such as chronic obstructive pulmonary disease [COPD]).
- Determine patient's informed wish.

Treatment may be considered, irrespective of whether the pattern of ILD is UIP or NSIP, if disease is clinically significant (symptoms, severity of abnormalities), progressive and if the patient is younger, has minimal comorbidities, and is keen for treatment.

In future clinical trials of patients with CTD-ILD

- Appropriate selection of patients, to increase the power to detect effects:
  - Selection of patients likely to decline off treatment (exclude patients with inherently stable disease)!
- In SSc-ILD, targeting of patients with “extensive” ILD, and/or recent worsening and early systemic disease
- In all CTDs, targeting patients with ILD based on severity and/or recent worsening of lung function

Randomized placebo-controlled clinical trials

- Scleroderma Lung Study (SLS): 1 yr of oral cyclophosphamide vs placebo: FVC change at 12 months (2.53%, p=0.03)

- FAST trial: monthly iv cyclo for six months followed by azathioprine and low dose pred for six months: similar changes in FVC (+2.4% in active vs -3.0% in placebo (p=0.07)

Tashkin et al NEJM 2006; Hoyles R et al A&R 2007

Cyclophosphamide versus Placebo in Scleroderma Lung Disease

D.P. Tashkin et al. for the Scleroderma Lung Study Research Group

New Engl J Med 2006; 354: 2655-66

Beneficial treatment effects at one year on FVC levels, dyspnoea, skin thickening and quality of life were statistically significant

The scleroderma lung study (SLS)

- Multi-centred, double-blind, randomised, placebo-controlled trial
- The effects of oral cyclophosphamide on lung function and health-related symptoms in patients with active alveolitis and SSc-ILD
- 145 patients completed at least 6 months of treatment

Tashkin DP, *et al*. *N Engl J Med* 2006; 354:2655-66.

The Scleroderma Lung Study
Cyclophosphamide *vs* placebo

	Forced vital capacity (FVC) % of predicted*	
	Cyclophosphamide *n* = 73	Placebo *n* = 72
Baseline value (mean ± SE)	67.6±1.3	68.3±1.5
Value at 12 months (mean ± SE)	66.6±1.7	65.6±1.6
Difference (mean ± SE)	−1.0±0.92	−2.6±0.9
p-value	*p* <0.05 after adjustment for baseline values in favour of cyclophosphamide	

*Primary endpoint

Tashkin DP, *et al*. *N Engl J Med* 2006; 354:2655-66.

Management

- The average FVC treatment effects in both trials was small (less than 5% of baseline values).
- SLS trial: the benefits came at the price of a significant prevalence of adverse effects.
- .The crucial conclusion, to be drawn from the SLS trial, is that ***in more typical lung disease, stabilisation of pulmonary fibrosis should be regarded as the primary treatment goal.***

Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease.

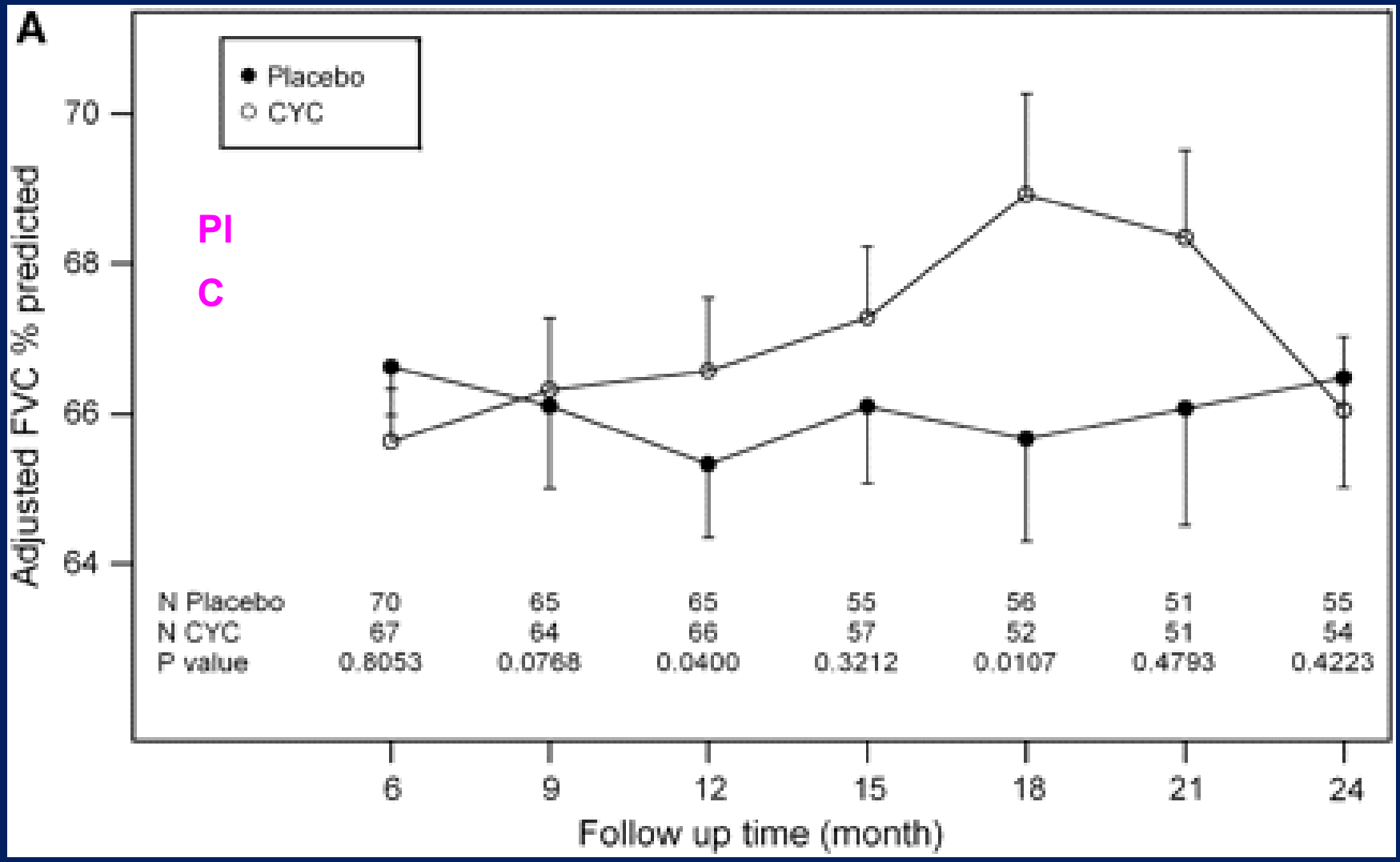
Tashkin DP, Elashoff R, Clements PJ et al (Scleroderma Lung Study Research Group)

Am J Respir Crit Care Med 2007; 176:1026-1034

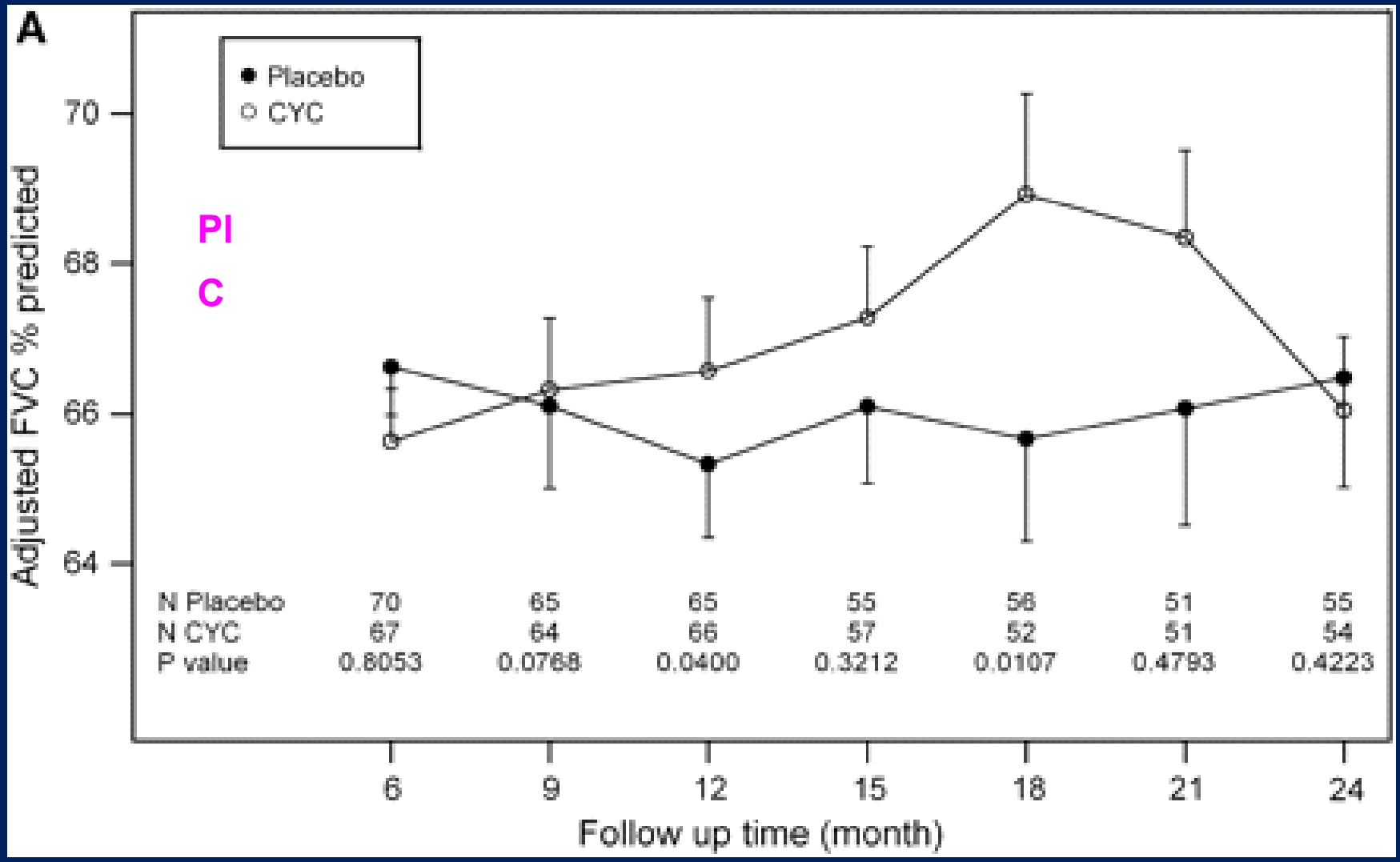
Background

- Effect favouring active treatment with cyclophosphamide in the scleroderma lung study
- Aim: to determine the length of the treatment effect
- Follow-up studies like this are novel and provide valuable insights

The major effect is prevention of progression



The amplitude of the treatment effect is small



Meaningless mean values...

- ***Only 15% of the whole cohort was considered to need open therapy in year 2***
- **Patients with less progressive disease recruited to the study. This is a CRUCIAL selection bias reflecting availability of open therapy**
- **To what extent does this apply to recent studies of sarcoidosis and IPF?**

These studies are major advances because

- They endorse the principle of preventing progression of fibrotic disease and this can be extrapolated to many other diseases
- They highlight the selection bias in placebo-controlled studies
- But also, they permit the definition of sub-groups with and, crucially, without treatment benefits

EULAR/EUSTAR recommendations for SSc-ILD

In view of the results from two high quality RCTs and despite its known toxicity, cyclophosphamide should be considered for treatment of SSc-ILD

Kowal-Bielecka O, *et al. Ann Rheum Dis* 2009; 68:620-8.

Follow up to the SLS study

- Benefits lost at 2 yrs
- Ongoing treatment to maintain stability
- Prospective assessment of less toxic maintenance; -RCT MMF vs cyclo nearing completion (Scleroderma Lung Study II - NCT00883129-estimated completion June 2015)

MMF for CTD-ILD

- Mycophenolate mofetil (MMF) is gaining popularity for the treatment of CTD-ILD
- Few published series in CTD-ILD
  - mostly scleroderma-ILD
  - all with few subjects
- MMF in CTD-ILD appears to be:
  - well-tolerated
  - associated with preservation of lung function

Swigris Chest 2006, Liossis Rheumatology 2006, Gerbino Chest 2008, Zamora Resp Med 2008, Saketkoo Am J Med Sci 2009, Koutroumpas Clin Rheum 2010, Simeon-Aznar Clin Rheum 2011

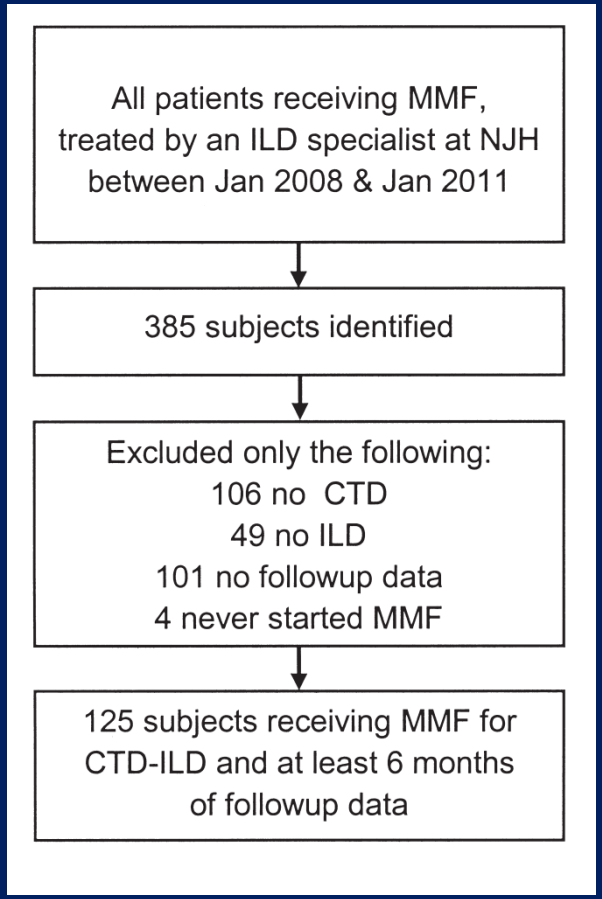
Mycophenolate Mofetil (MMF) for CTD-ILD

- Retrospective observational study from Denver
- 28 pt treated with MMF over 35.9 patient-years: scleroderma n=9, PM/DM n=5, Sjögren n=4
- Prednisone reduction from 15 to 10 mg (p=0.09)
- FVC %pred increased by 2.3%, DLCO by 2.6%

Swigris et al, Chest 2006;130:30

MMF in CTD-ILD

- Experience of MMF
- Well tolerated
- 10% of patients discontinued
- 2.5 years median follow-up



Fischer A et al. J Rheumatol 2013; 40:640-6

Main Results

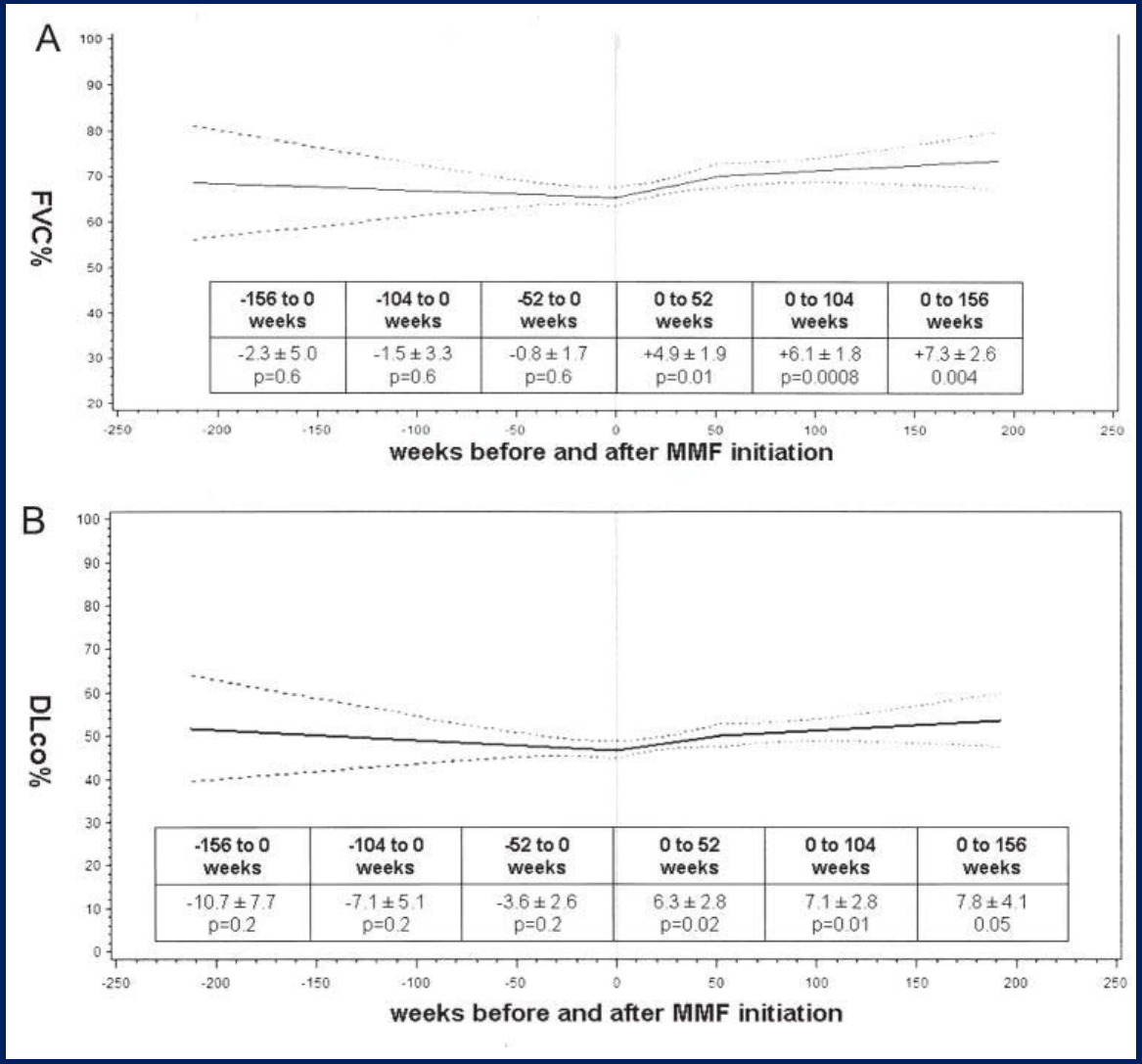
- MMF was discontinued in 13 subjects
- MMF was associated with significant improvements in estimated percentage of predicted (FVC%) from MMF initiation to 52, 104, and 156 weeks.); and
- in estimated percentage predicted DLCO% from MMF initiation to 52 and 104 weeks (6.3% ± 2.8%, p = 0.02; 7.1% ± 2.8%, p = 0.01).

Results

- A mean age of 60.4 11.6 years; 42% were women and most were treated with MMF

  3 g/d over a 3-year period.
- MMF treatment was associated with effective CS dose tapering (from a median of
- 20 mg/d to 5 mg/d of prednisone at 12 months from MMF initiation [P<.0001]).
- MMF also associated with longitudinal improvements in FVC and DLCO.

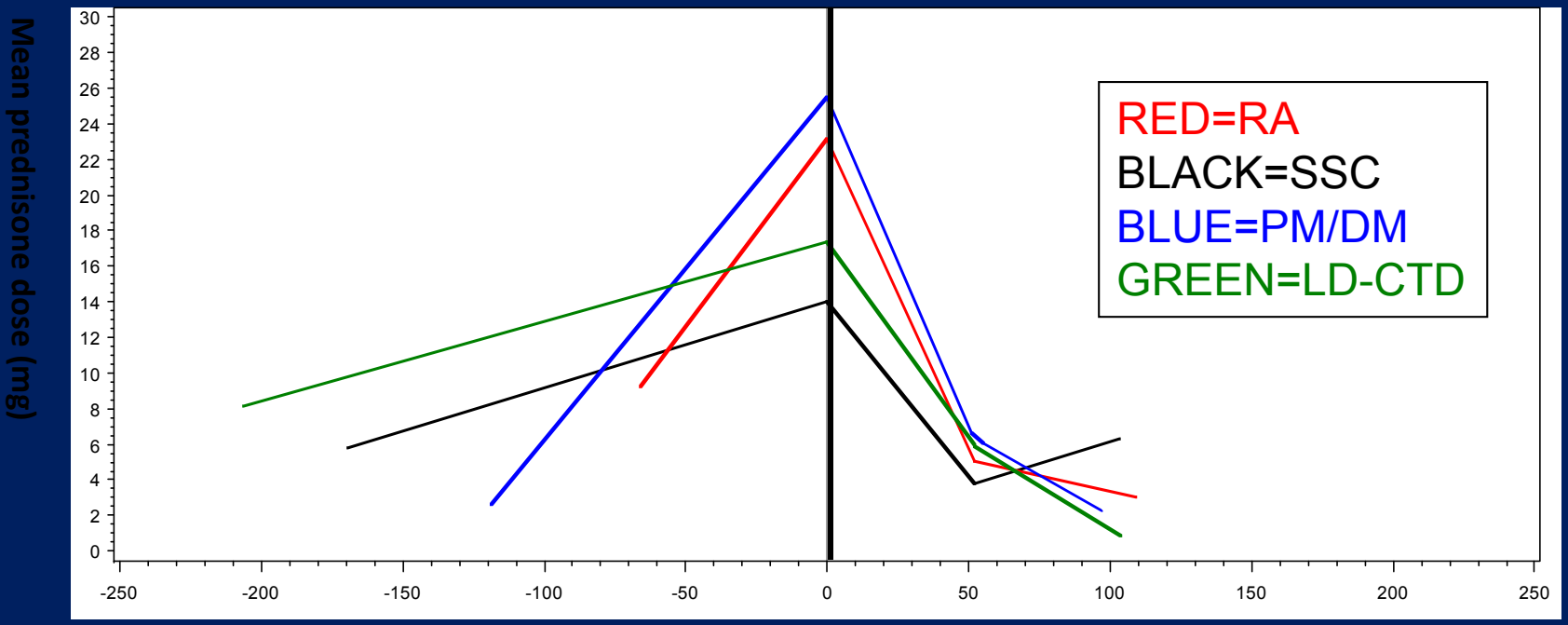
FVC an DLCO over time in the entire cohort pe- and post-mycophenolate



Fischer A et al. J Rheumatol 2013; 40:640-6

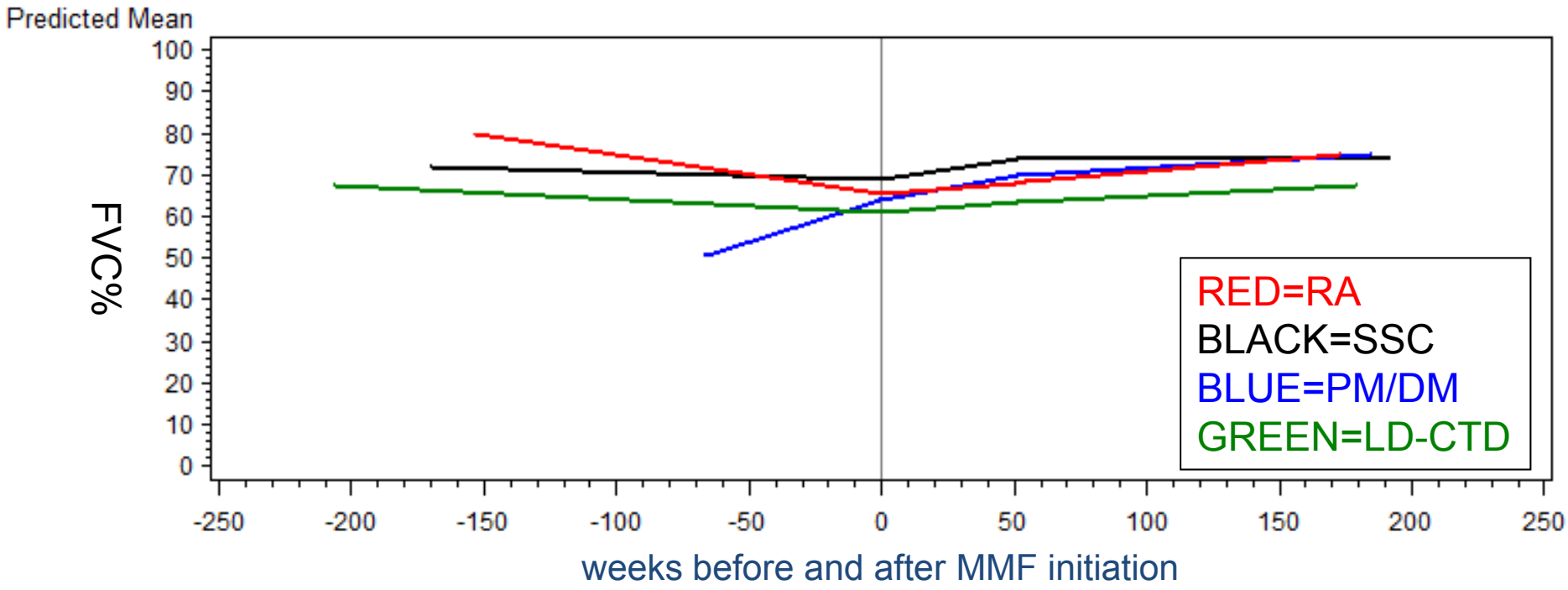
MMF was associated with steroid tapering effects

median prednisone dose:
at MMF initiation: 20 mg qd
after 9-12 months on MMF: 5 mg qd ($p<0.0001$)



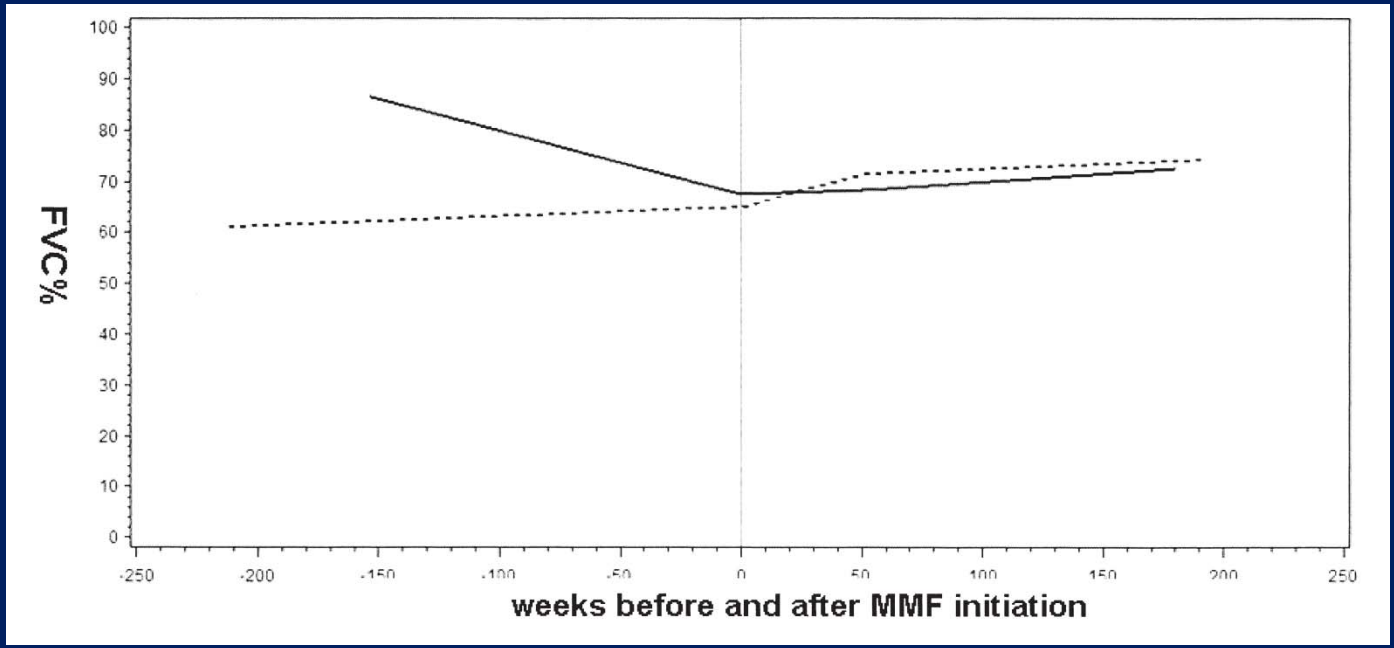
Fischer et al. J Rheumatol 2013

Plot of mixed-effects model estimates for FVC% by CTD type



UIP (n=32) compared to non-UIP

- FVC shown before and after MMF
- UIP = solid line (biopsy, n=15; HRCT, n=17)



Fischer A et al. J Rheumatol 2013; 40:640-6

MMF in CTD-ILD

- Well tolerated
- Low rate (10%) of discontinuation
- Effective corticosteroid tapering
- Associated with stabilization or improvement in lung function
- A longer term option (than CYC)

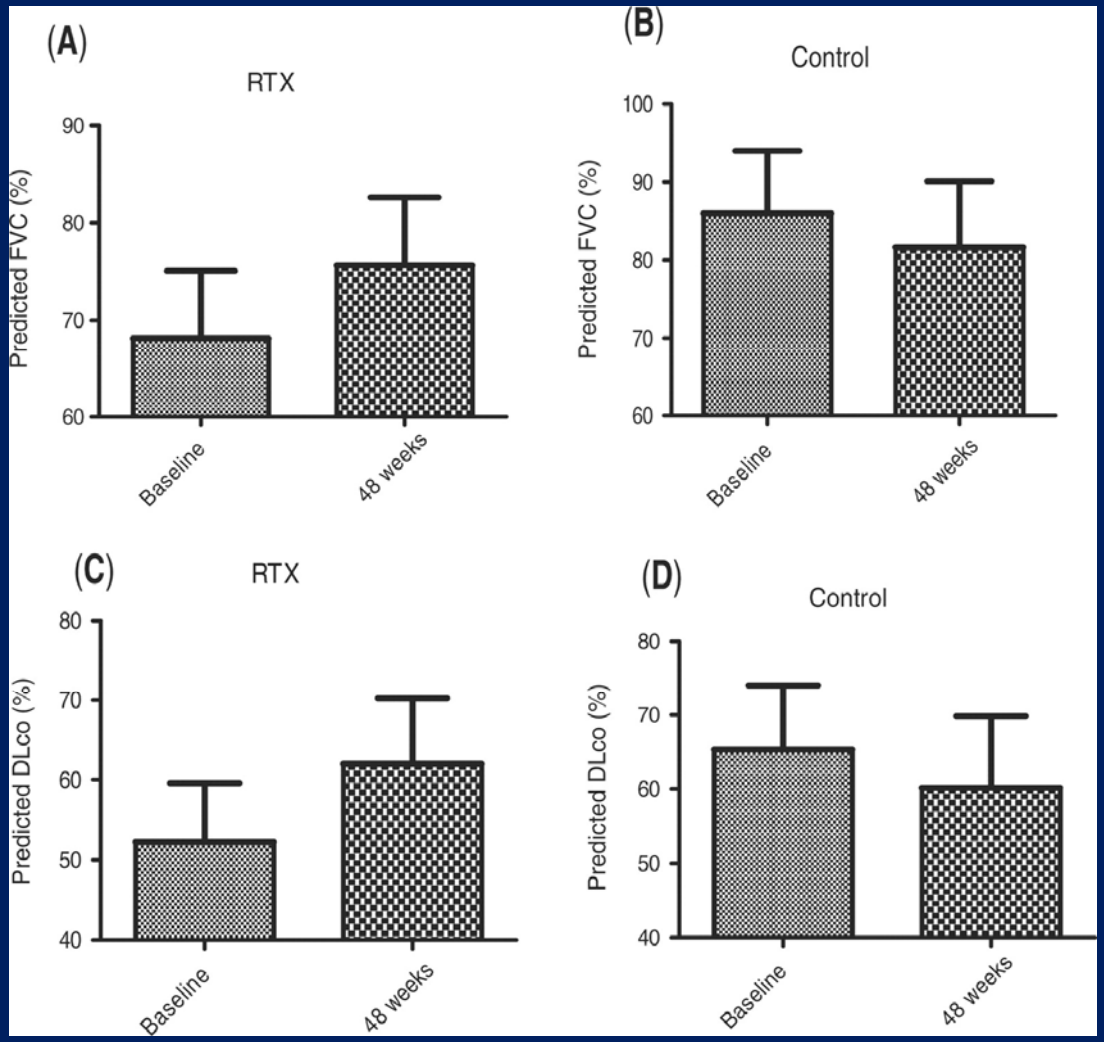
- Warrants prospective study
  - SLS II

Fischer et al. J Rheumatol 2013

Unmet clinical need in ILD-CTD: severe unresponsive disease

- A proportion of CTD-ILD patients is refractory to intense immunosuppression, including iv cyclophosphamide

Rituximab in SSc-ILD



14 SSc-ILD pts all stable prior to starting treatment;

- **8 received Rituximab +standard treatment**
- **6 standard treatment alone**

Rituximab treatment performed at baseline and 24 weeks

Daoussis, D. et al. Rheumatology 2010

Main results

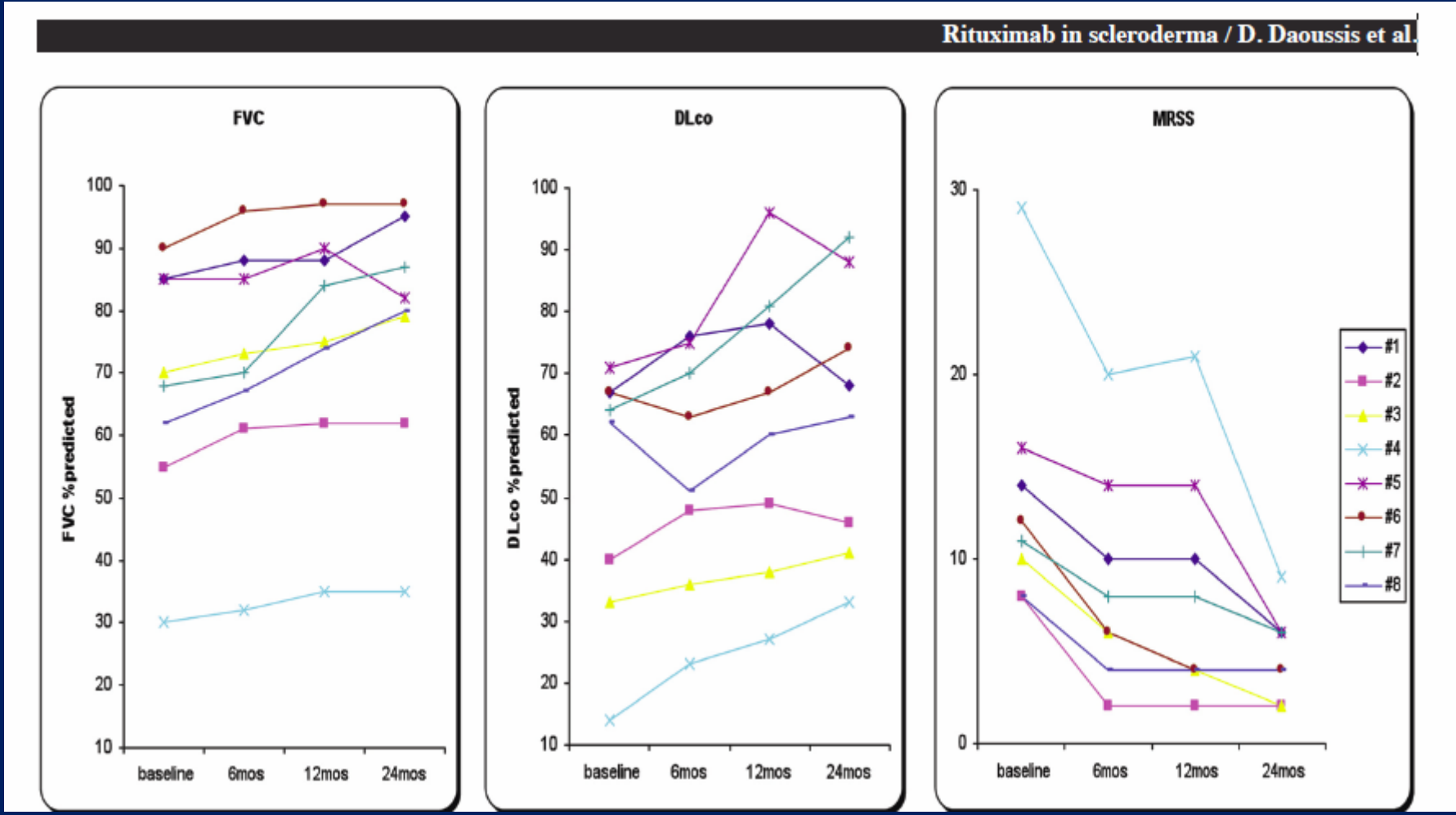
- Vasculitis protocol (375 mg/m2 weekly for 4 weeks) and then again 6 months later compared with 6 subjects receiving standard treatment (including prednisone, MMF, CYC, and bosentan).

- At 1 year, the FVC in the RTX group increased by 10.3% compared with the control group losing 5.0%.

- The DLCO also improved by 9.7% compared with a decrease of 7.5% in the control group.

Daoussis, D. et al. Rheumatology 2010

Follow up study of same pts treated for 2 yrs



Daoussis Clin Exp Rheumatol 2012

Eur Respir J 2012; 40: 641–648
DOI: 10.1183/09031936.00163911

Severe interstitial lung disease in connective tissue disease: rituximab as rescue therapy

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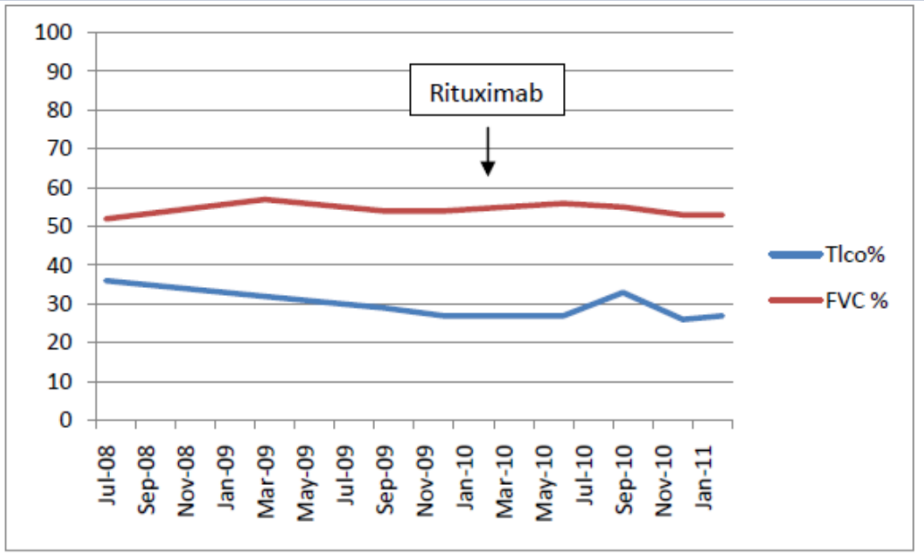
Age/sex	*HRCT*	*Serology*	*Pre-Ritux treatment*
Polymyositis/dermatomyositis			
45/M	OP/DAD	ENA, Ro+	IV MP
60/M	NSIP	Jo1	MMF, pred, iv Cyclo
60/F	NSIP	Jo1,RF	MMF, Pred, iv Cyclo
29/F	NSIP	Jo1	MMF, Pred, iv Cyclo
51/M	NSIP	Jo1	MMF, Pred, iv Cyclo
Undifferentiated CTD			
49/M	NSIP	ANA +++	MMF, Pred, iv Cyclo
37/F	OP	CCP, Ro	Iv MP
Systemic sclerosis			
63/M	NSIP	Scl70	MMF, pred, cyclo intolerant

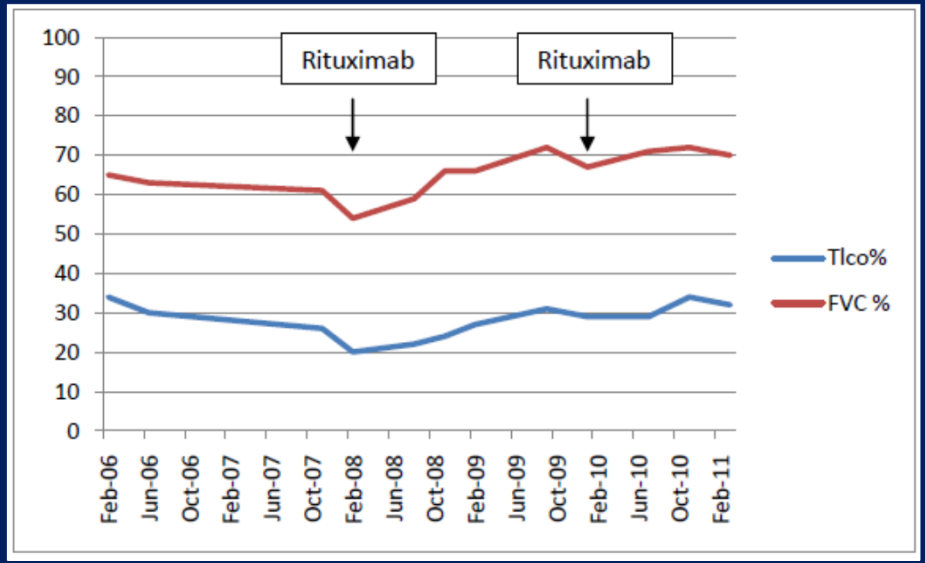
Rituximab as rescue therapy

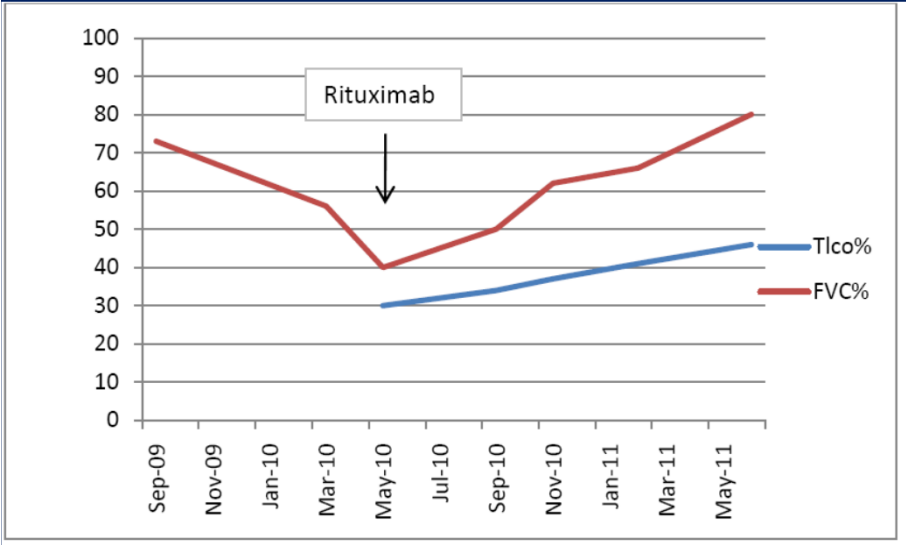
- 8 cases of CTD-ILD (5 IIM-ILD; median FVC, 45% of predicted; median DLCO, 25% of pred
- 6 of these patients had serial pulmonary function tests (PFTs):
- before RTX infusion,all had decline in FVC and DLCO, and after RTX infusion,
- a median DLCO improvement of 22% (P = .04) and a median FVC improvement of 18% (P= .03) were noted.

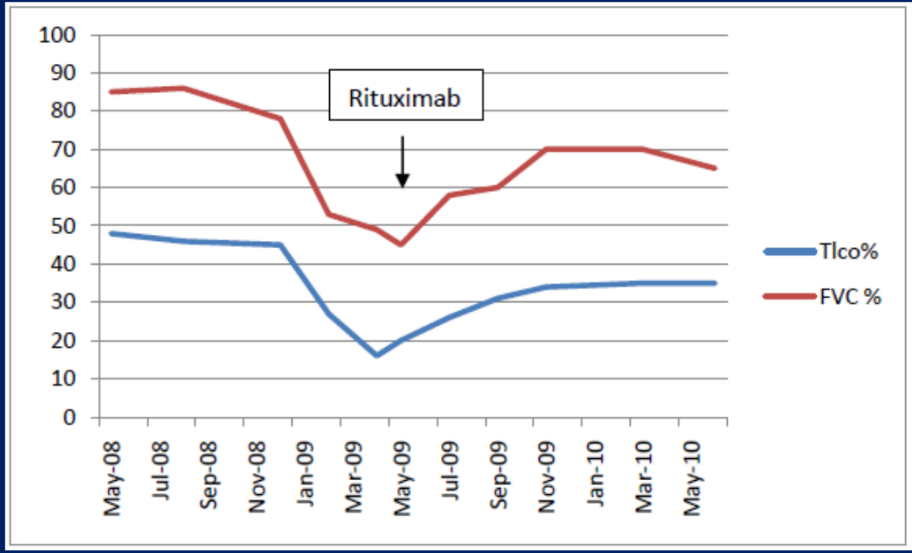
	Fall 6-9 months pre-Ritux	Nadir	Improvement 6-9 months post- Ritux
DLCO median (range)	-17.5% (-8-62)	25% (16-32)	+22.5% (9-114%)
FVC median (range)	-11% (-3-45)	45% (37-59%)	+18% (0-100)

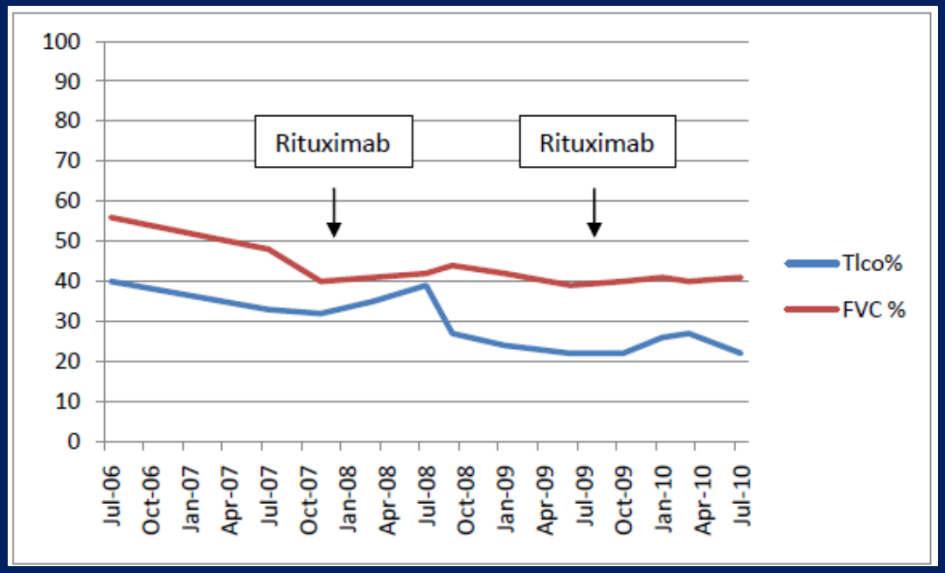
PM/DM patients










100
90
80
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20
10
0
Rituximab
Rituximab
Tlco%
FVC %
Jul-06
Oct-06
Jan-07
Apr-07
Jul-07
Oct-07
Jan-08
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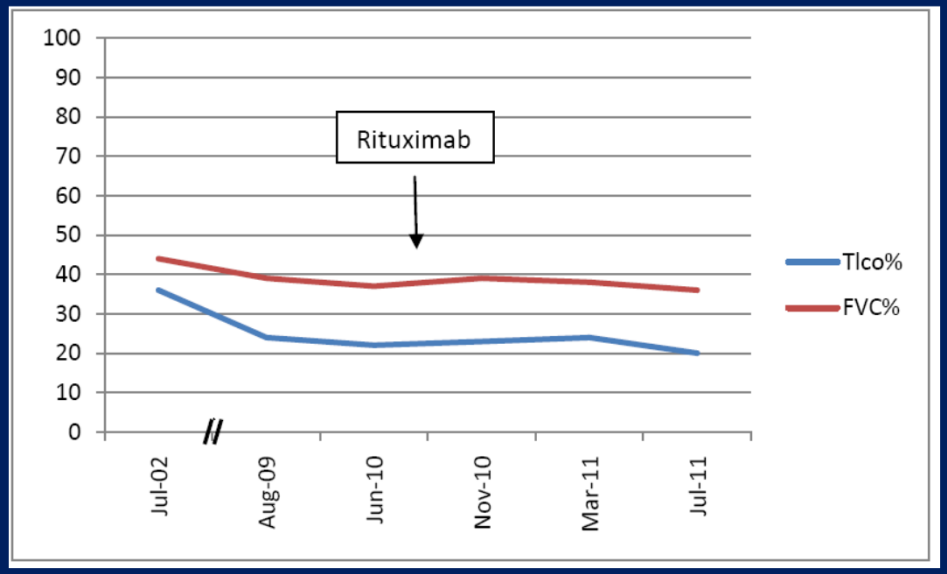
Jul-09
Oct-09
Jan-10
Apr-10
Jul-10

UCTD


100
90
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40
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10
0
Rituximab
Tlco%
FVC%
Jul-02
Aug-09
Jun-10
Nov-10
Mar-11
Jul-11

SSc

Recent audit of Rituximab use as rescue therapy in ILD

- 50 patients treated from 2007-April 2012
  - 35 CTD-ILD
  - 6 fibrotic HP
  - 3 drug induced
  - 2 DIP
  - 1 AIP, 1 OP, 2 unclassifiable
- Follow up of at least six months

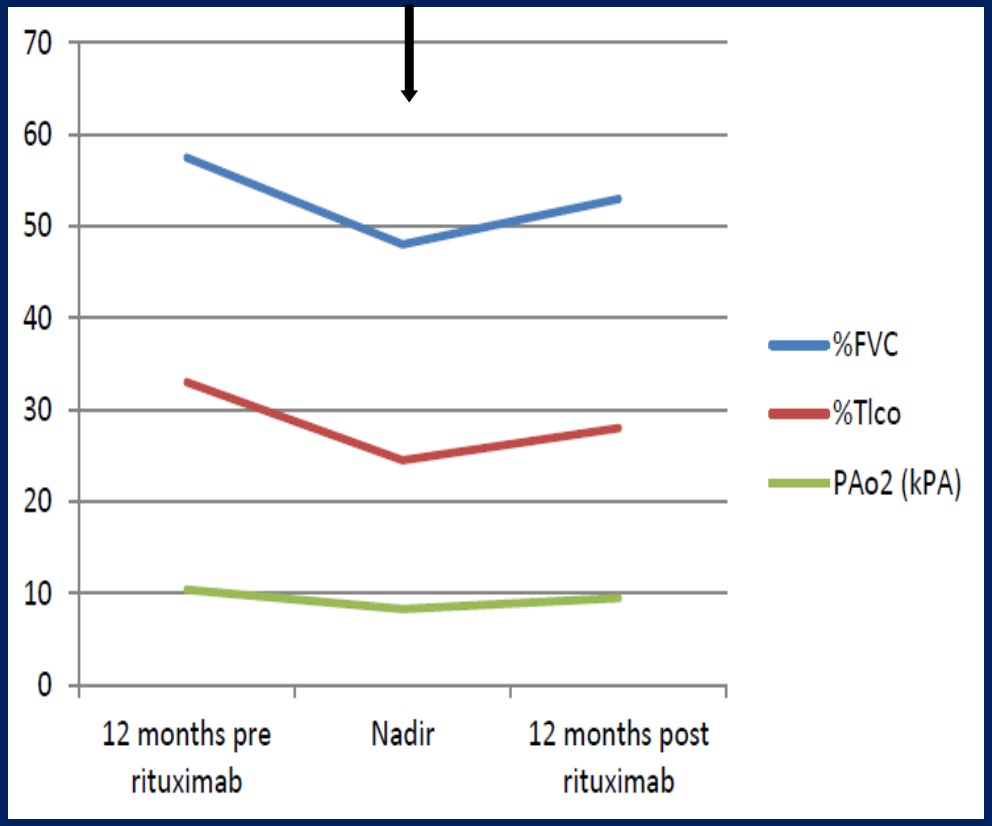
Keir et al Respirology 2014

Underlying disease	n=50
Connective tissue disease	
- Idiopathic inflammatory myopathy (PM/DM)	14
- Systemic sclerosis	6
- Mixed CTD	2
- Undifferentiated CTD	8
- Rheumatoid arthritis ILD	1
- Overlap syndromes	4
Pulmonary vasculitis	3
Hypersensitivity pneumonitis	5
Idiopathic NSIP/cryptogenic OP	1
Desquamative interstitial pneumonia	2
Drug induced ILD	2
Undifferentiated	2

	N=50
ILD severity	
FVC	48% (31-99)
DLCO	25.9% (14-56)
Treated course previous 12 months	
Δ DLCO	↓ 19% (0-67)
Δ FVC	↓ 18% (0-47)
Previous immunosuppression	
iv cyclo	42
aza/MMF	4
iv methylpred	4

Keir et al Respirology 2014

Rituximab



median FVC%	57.5 (34-110)	48.0 (31-99)	53.0 (32-105)
median Tlco %	33.0 (18-63)	25.9 (14-67)	28.0 (14-62)
median $Pa0_2$	10.4 (6.3-12.6)	8.3 (6.1-11.9)	9.5 (5.6-12.2)

Keir et al Respirology 2014

Results

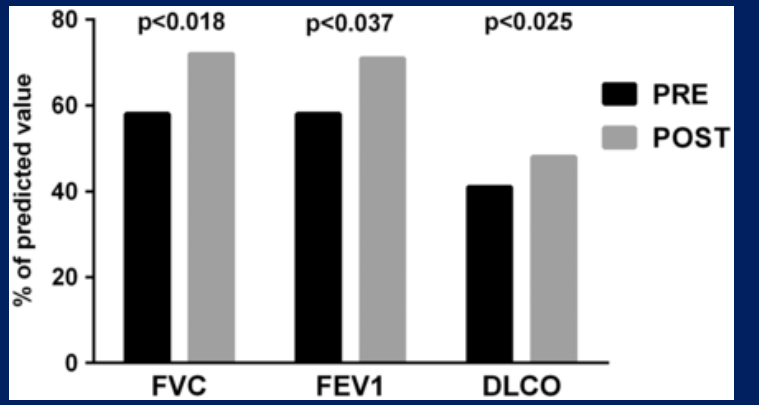
- In the CTD-ILD subgroup, 85% of the patients (most with IIM) were classified as responders
- In the 6 to 12 months before RTX, a
- ***median decline in FVC of 13.3% and in DLCO of 18.8% were noted compared with***
- ***the 6 to 12 months after RTX therapy, in which an improvement of 8.9% of the FVC***
- ***(P<.01) and a stabilization of the DLCO (P<.01) were noted.***

Long-term experience with rituximab in anti-synthetase syndrome (ASS) - related interstitial lung disease

- Retrospective review of 34 pts, of which 24 ASS+ ILD resistant to conventional therapy with>12 months follow up (median of 52 m)

- Most striking effects in pts with subacute/acute presentation and/or <12 months disease duration

- During follow-up, 7/34 (21%) Rtx-treated ASS patients died; 6/7 deaths were related to infections (one PCP). Six non fatal infections also observed (three with PCP). Most pts had concomitant immuno suppressive drugs. Mortality rates did not differ vs non Rtx treated ASS+ pts same hospital

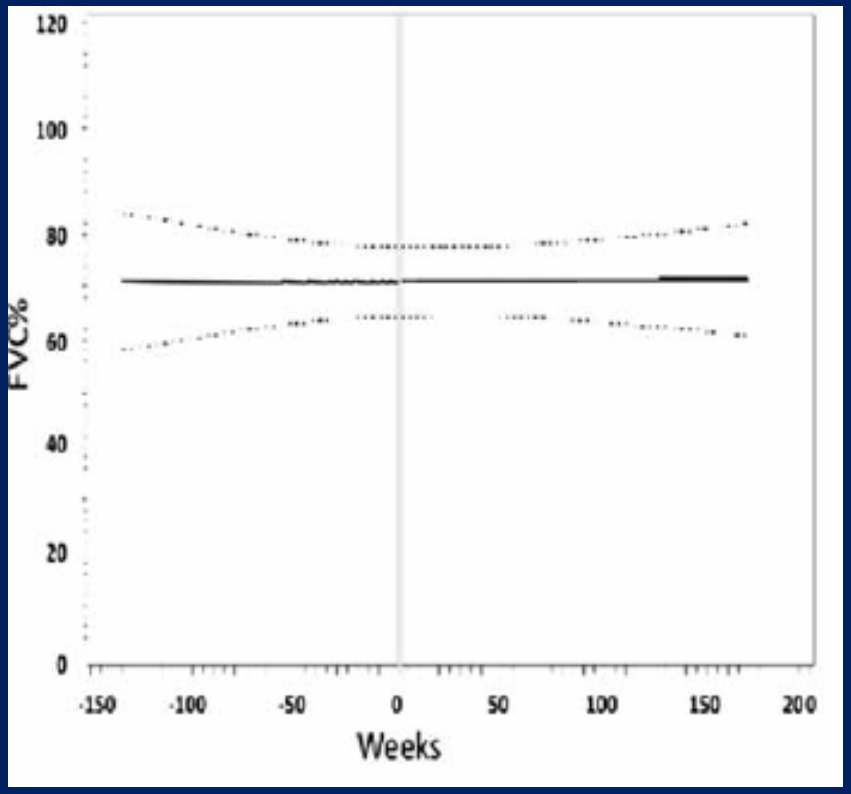


Andersson et al 2015 Rheumatology

Rituximab for the treatment of connective tissue disease-associated interstitial lung disease

Abstract. *Objective:* To describe our experience with rituximab (RTX) as treatment for a diverse spectrum of chronic connective tissue disease-associated interstitial lung disease (CTD-ILD). *Methods:* Twenty-four subjects with CTD-ILD were included. All had pulmonary function testing before and after their first RTX infusion. Each subject was evaluated in a multidisciplinary autoimmune and ILD outpatient clinic. Data were extracted by retrospective review of complete medical records. *Results:* Most subjects were middle-aged white women with rheumatoid arthritis (RA) (n=15) and a nonspecific interstitial pneumonia (NSIP) pattern on high-resolution chest computed tomography scans (n=17). Sixteen subjects received a corticosteroid-sparing agent at the time of RTX initiation; mostly mycophenolate mofetil (n=8). RTX administration was not associated with corticosteroid-sparing effects: 13 subjects were on prednisone at the time of the initial RTX cycle, and 9 remained on prednisone at 6 months after (mean daily dosage 10.2±16.2 mg before vs. 5.6±11.0 mg after, p=0.27). RTX had no appreciable effect on pulmonary physiology; however, individual trajectories for percentage predicted forced vital capacity (FVC%) were highly variable. The underlying CTD (RA vs. non-RA) and ILD pattern did not appear to affect response to RTX. Among 14 subjects who received multiple RTX cycles, FVC% trajectories were variable: FVC% increased in eight and declined in six. Respiratory infections were the most common post-RTX adverse event. *Conclusion:* In this small, retrospective study of chronic CTD-ILD, RTX was not associated with changes in FVC% or corticosteroid-sparing effects. Controlled, prospective studies are needed to more confidently define the effects of RTX in CTD-ILD. *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32: 00-00)*

SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2015;


120
100
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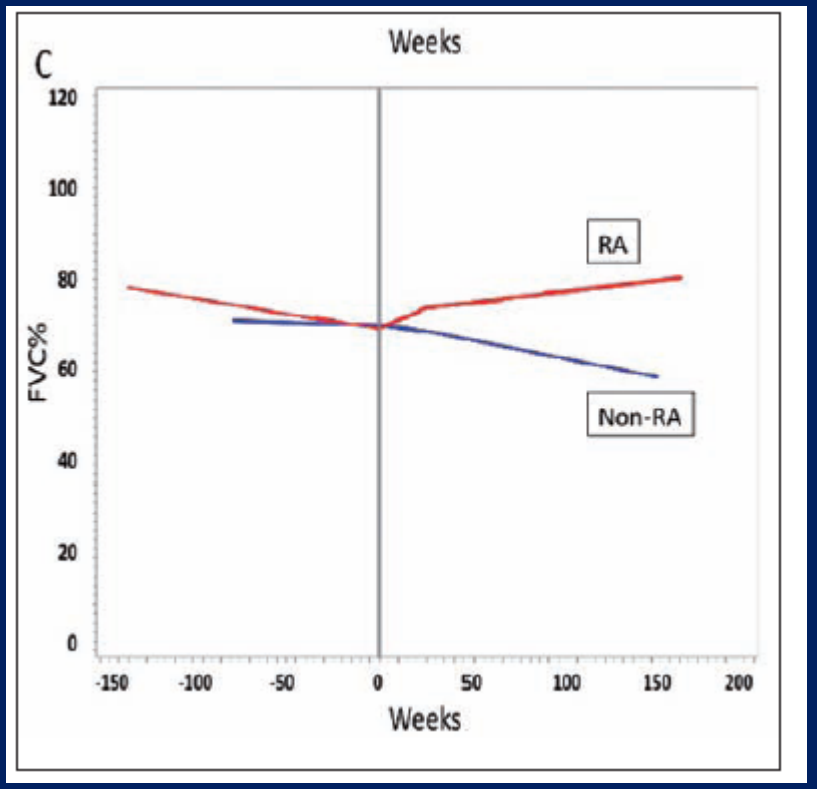
60
40
20
0
FVC%
-150
-100
-50
0
50
100
150
200
Weeks


C
Weeks
120
100
80
60
40
20
0
FVC%
RA
Non-RA
-150
-100
-50
0
50
100
150
200
Weeks

10 pts with RA-ILD (4UIP,6NSIP)

- baseline FVC 68%, DLCO, 48%
- Of the 7 subjects with data at baseline and 48 weeks, FVC and DLCO:
- worsened in 1 subject,
- ***stabilized in 4, and***
- ***improved by greater than 10% in 2 (at 48 weeks, FVC 75% [range, 50%–102%] and DLCO, 52% [range, 30%–75%]).***

Matteson E, et al. Open J Rheumatol Autoimmune Dis 2012

UK study: Palmer E,et al. Rheumatology 2014

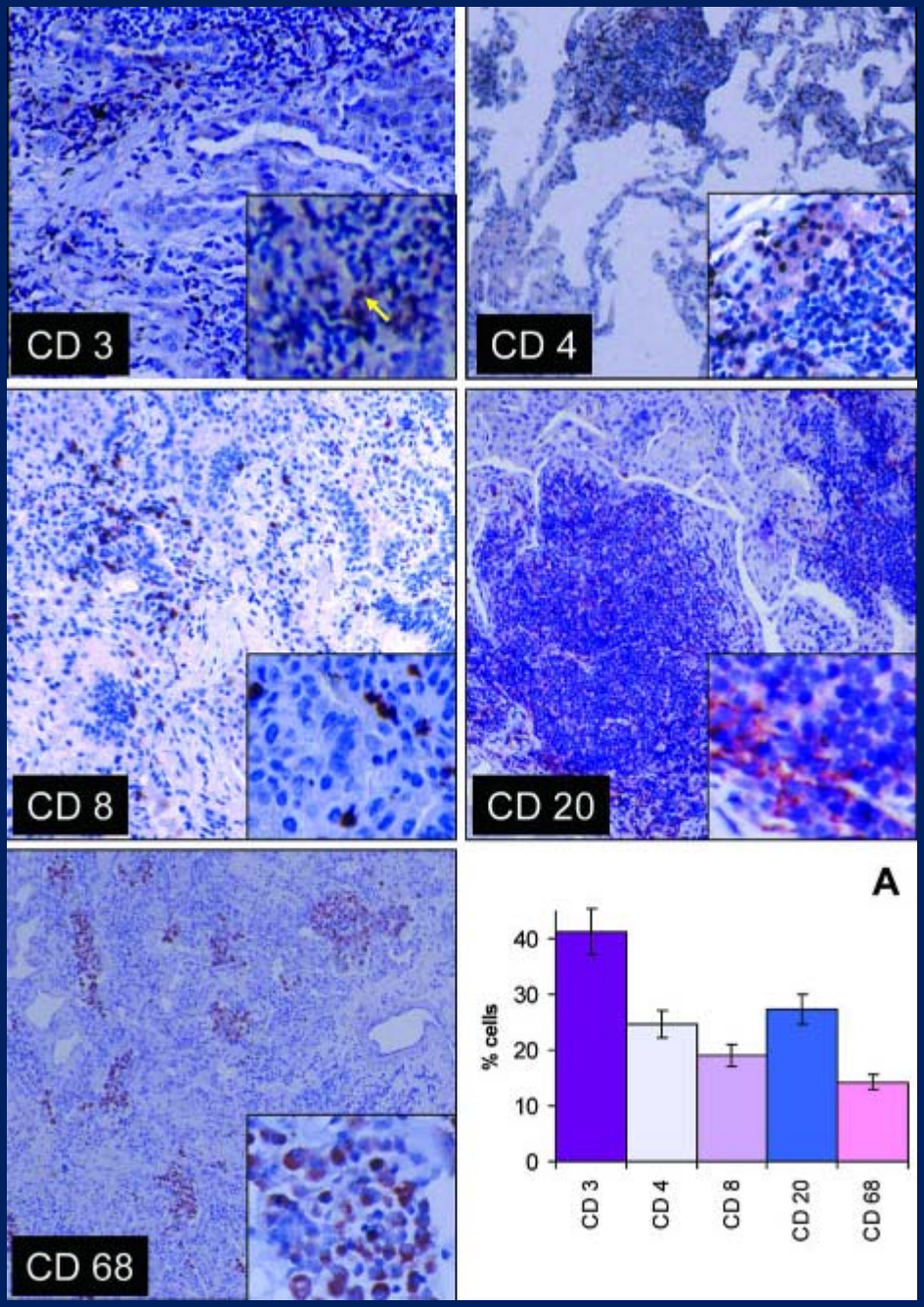
- 188 patients with RA-ILD in 16 centers across the United Kingdom during
- a 25-year period (65% UIP),
- 57 patients were treated with a biologic agent.
- No difference in all-cause or respiratory mortality was noted in patients treated with biologics versus other agents.

- ***A statistically significant difference in respiratory mortality between patients treated with anti-TNF (n = 30) versus RTX***
- ***(n =27) (15% vs 4%;) and***
- ***in all-cause mortality in 31% of patients treated with anti-TNF versus 8% of patients treated with RTX (P= 0 .03) in the UIP subgroup***

- In non-IPF ILD, activation of immune system, including B cells, likely to play a major role in driving fibrosis, regardless of diagnosis

- Rituximab as salvage therapy in severe interstitial lung disease (non IPF) unresponsive to standard intense immunosuppression

The role of RTX for CTD-ILD remains to be defined. This agent may have a role in specific subsets of CTD-ILD, such as the antisynthetase syndrome and those cases in which lung biopsy suggests a role of B cells in the ILD pathogenesis. Further studies are needed to more precisely define its role in CTD-ILD.



Large proportion of B lymphocytes in idiopathic NSIP

Keogh et al 2005

RBH trial:

- Rituximab (1 gr x2) vs iv cyclophosphamide (monthly for six months) in CTD-ILD (*NCT01862926*)
  - Systemic Sclerosis
  - Mixed Connective Tissue Disease
  - Idiopathic Inflammatory Myositis

Primary outcome: FVC change at twelve months

PI: Toby Maher RBH

Mechanisms potentially involved…

- Removal of pathogenic antibodies
- Removal of immune complexes
- Reduced antigen presentation to T cells, thereby activating autoreactive T cells
- Effect of B cells on mesenchymal cells

Future Directions in the Pharmacologic Treatment of Connective Tissue Disease–associated Interstitial Lung Disease

There have been several novel antifibrotic therapies studied in ILD but these have almost exclusively been limited to clinical trials for patients with IPF. The only antifibrotic agent studied in CTD-ILD was bosentan for SSc-ILD in the BUILD-2 trial,[53] which showed that bosentan is ineffective for the ILD in SSc. Recent studies of pirfenidone and nintedanib have shown a positive impact on disease progression in patients with IPF[54–56]; however, there are currently no data to support their use in CTD-ILD. There is an ongoing phase II study addressing safety and tolerability of pirfenidone for SSc-ILD (LOTUSS trial; NCT01933334).

Management of Connective Tissue Disease–associated Interstitial Lung Disease

Sandra Chartrand, MD, FRCPC[a,b], Aryeh Fischer, MD[c,*]

Clin Chest Med ■ (2015)

KEY POINTS

- Connective tissue disease (CTD)–associated interstitial lung disease (ILD) reflects a heterogeneous spectrum of diverse CTDs and a variety of patterns of interstitial pneumonia. Other than a few controlled trials in scleroderma-ILD, there are few studies to reliably inform an evidence-based approach to managing CTD-ILD, and, in general, clinicians are left with experience-based approaches.
- The management of CTD-ILD is limited to cases with progressive and/or clinically significant disease.
- Immunosuppression with corticosteroids and cytotoxic medications are the mainstay of pharmacologic treatment.
- Extrathoracic manifestations of the CTD need to be assessed and may also affect choice and intensity of immunosuppressive therapies.
- Nonpharmacologic approaches to treatment should be considered for each patient with CTD-ILD.

Clin Chest Med ■ (2015)