Future Perspectives of Idiopathic Lung Disease(ILD) Treatment

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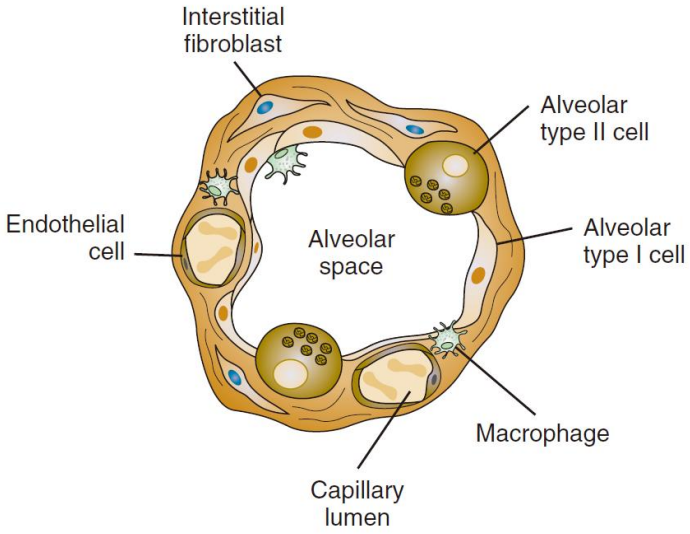
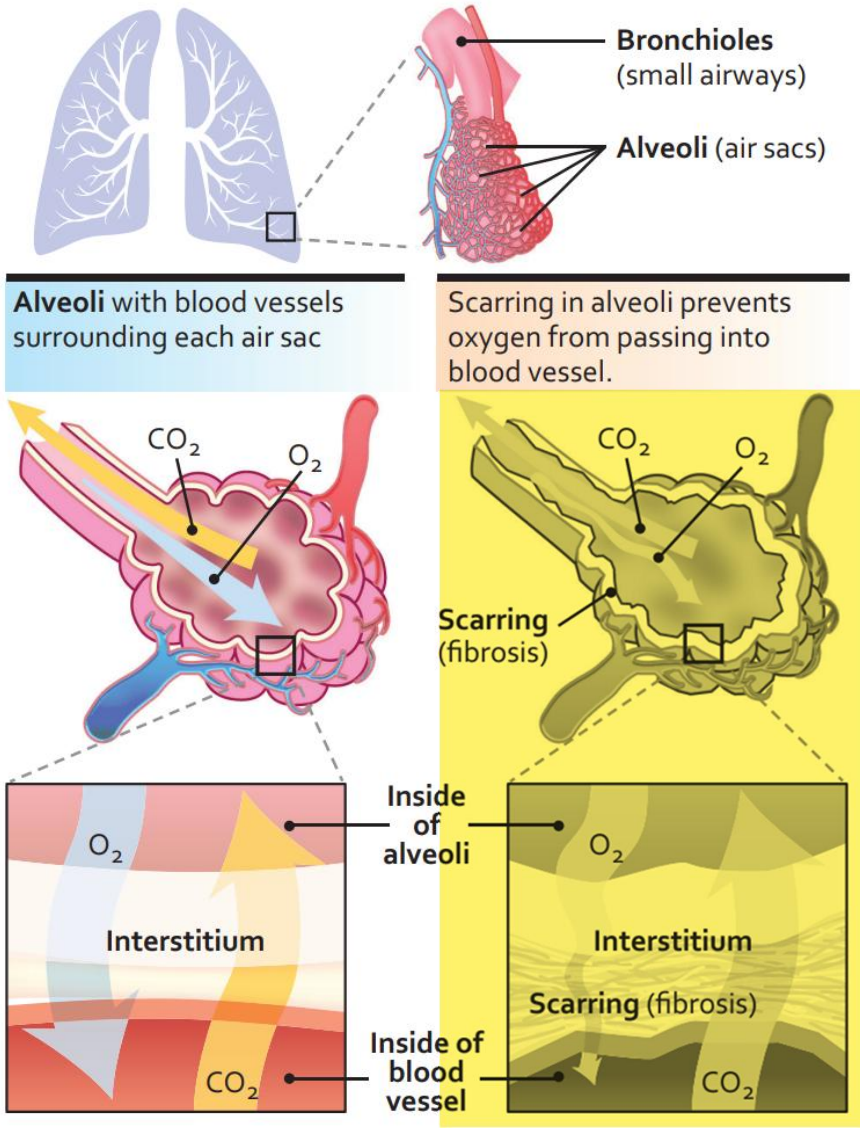
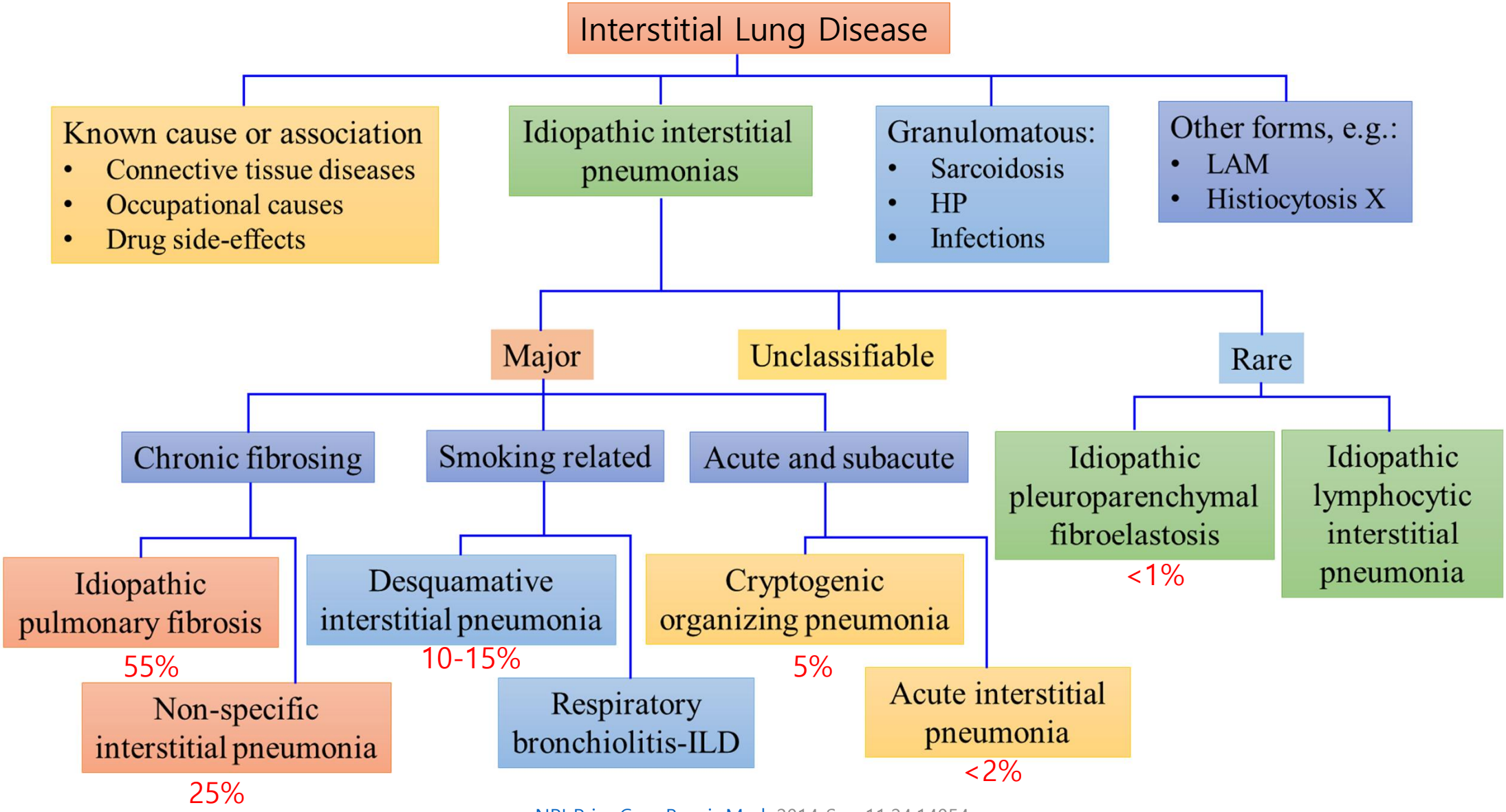
Interstitial lung diseases



- Diffuse infiltrative lung diseases
- Heterogeneous group of disorders that predominantly affect the lung parenchyme
- Vary widely in etiology, clinicoradiologic presentation, histopathologic features, and clinical course



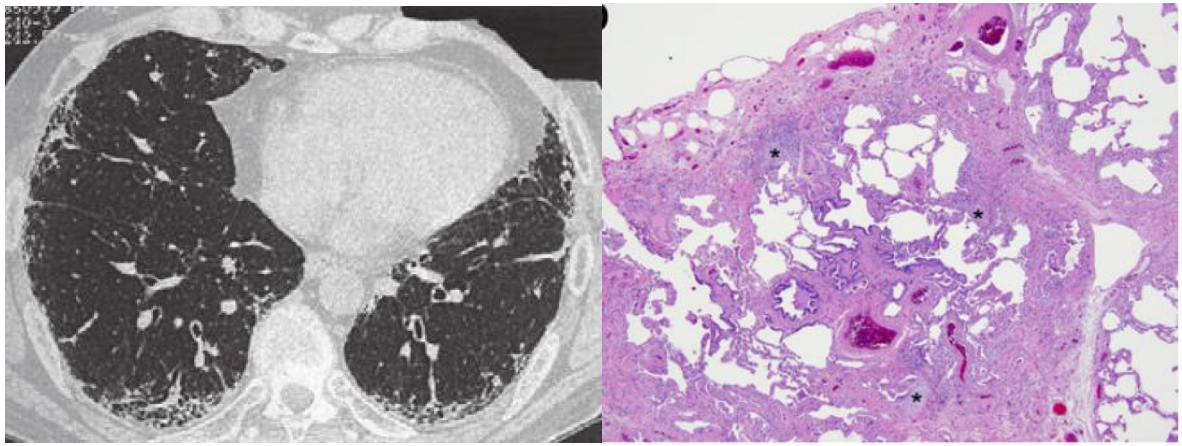
Mayo Clin Proc. 2007;82(8):976-986
Am J Respir Crit Care Med Vol. 203, P5-P6, 2021



NPJ Prim Care Respir Med. 2014 Sep 11;24:14054.

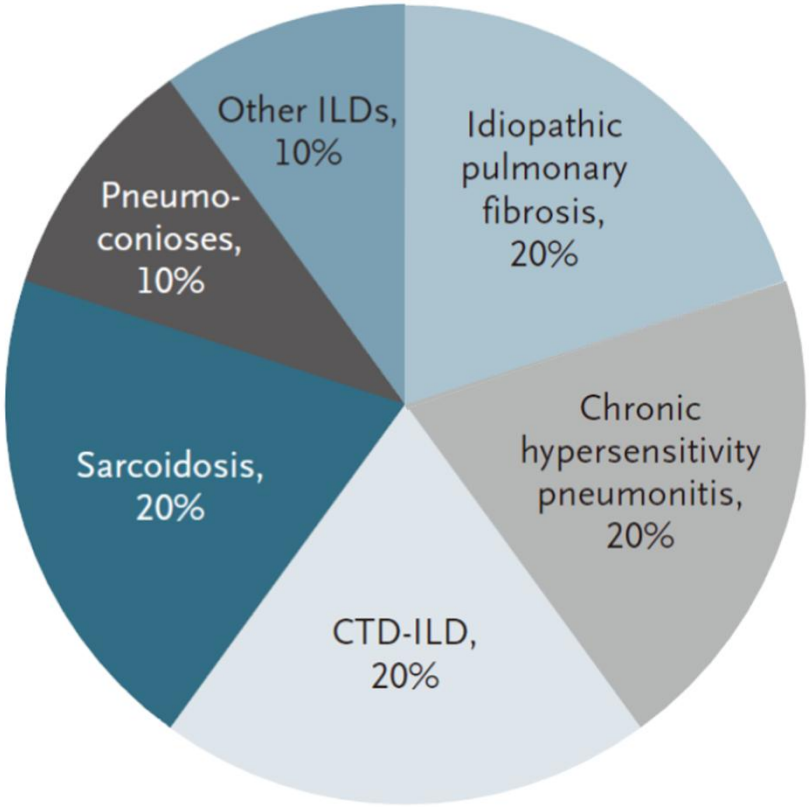
Idiopathic pulmonary fibrosis (IPF)

- A specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause
- Occurs in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP)



Am j Respir Crit Care Med 2011;183:788

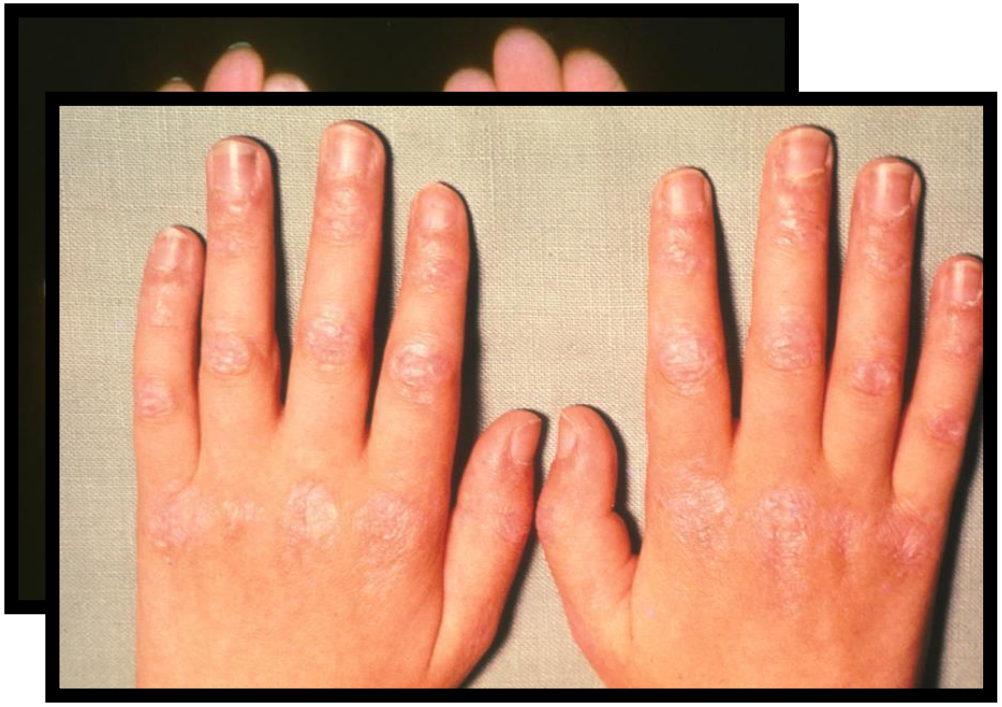
Estimated Relative Distribution of Specific Interstitial Lung Diseases



N Engl J Med 2018;378:1811-23.

Organ	Main manifestations to be evaluated
Peripheral circulation	Raynaud's phenomenon
Skin	Sclerodactyly
	Digital ulcerations or scars
	Telangiectasia
	Violaceous erythematous rash over the interphalangeal joints, knuckles, elbows and knees (Gottron's sign)
	Lilaceous rash of the eyelids
	Rash of the neck and upper chest and shoulders (heliotrope rash, e.g. photosensitivity)
	Mechanics' hands
Joints	Joint pain or swelling (arthritis, arthralgia)
	Morning stiffness lasting for more than 60 min
Muscle	Muscle pain, muscle weakness
Mouth and eyes	Dry mouth, dry eyes (sicca syndrome)

CTD를 의심할 수 있는 주요 증상들



Suggested categories of ILD patients that require further rheumatoid evaluation

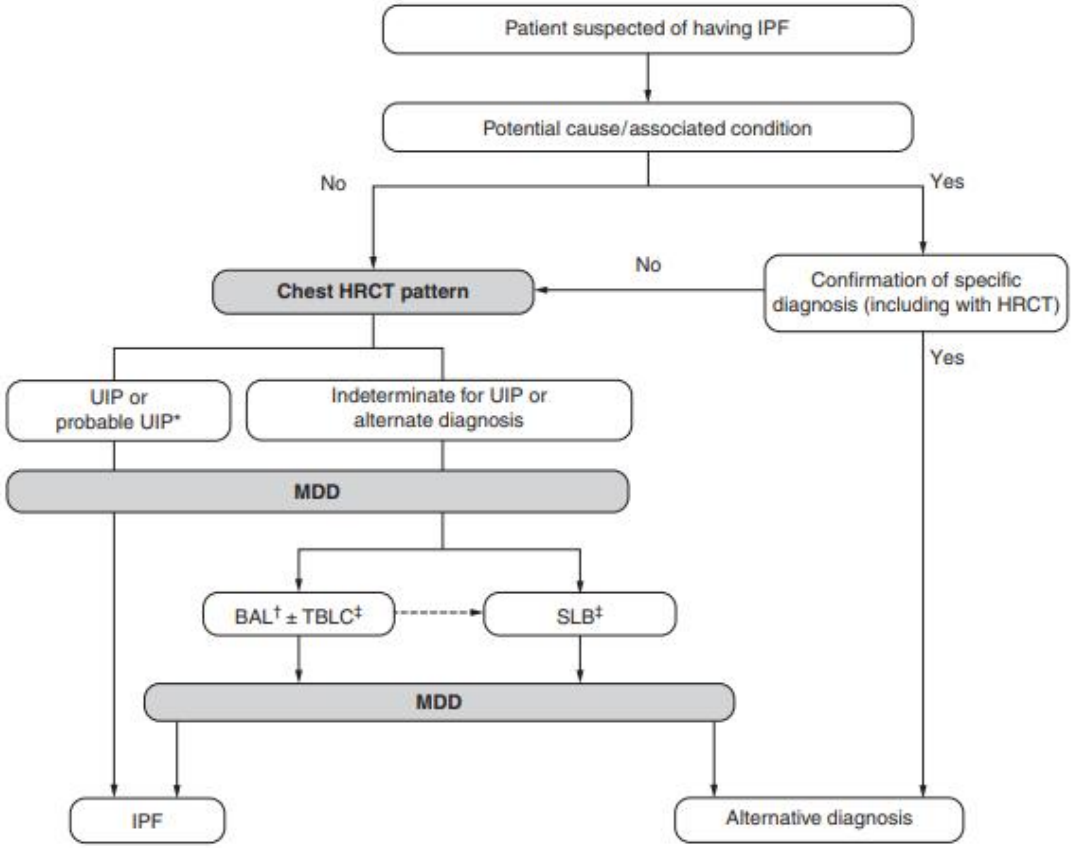
1. Women, particularly those younger than 50.
2. Any patient with extrathoracic manifestations is highly suggestive of CTD, that is, Raynaud phenomenon, esophageal hypomotility, inflammatory arthritis of the metacarpal–phalangeal joints or wrists, digital edema, or symptomatic keratoconjuctivitis sicca.
3. All cases of NSIP, LIP, or any ILD pattern with secondary histopathology features that might suggest CTD, that is, extensive pleuritis, dense perivascular collagen, lymphoid aggregates with germinal center formation, prominent plasmacytic infiltration.
4. Patients with a positive ANA or RF in high titer (generally considered to be ANA $>$ 1:320 or RF $>$ 60 IU/mL), a nucleolar-staining ANA at any titer, or any positive autoantibody specific as to a particular CTD, that is, anti-CCP, anti-Scl-70, anti-Ro, anti-La, anti-dsDNA, anti-Smith, anti-RNP, anti-tRNA synthetase.

- **50세 이내의 여성**
- **Raynoud phenomenon**
- **Esophageal hypomotility**
- **Hand and wrist arthritis**
- **Symptomatic keratoconjunctivitis sicca**
- **NSIP, LIP pattern**
- **High titer of ANA or RF**

Diffuse Lung Disease: A Practical Approach. 2nd ed. New York: Springer; 2012

Diagnostic algorithm for IPF

American thoracic society/European respiratory society



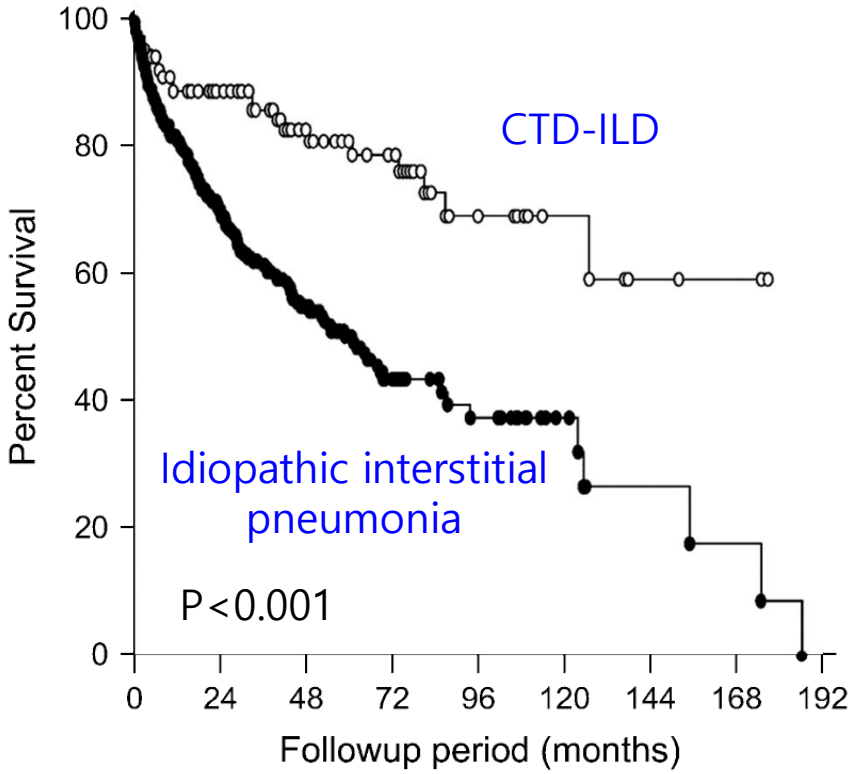
IPF diagnosis on the basis of HRCT and biopsy patterns

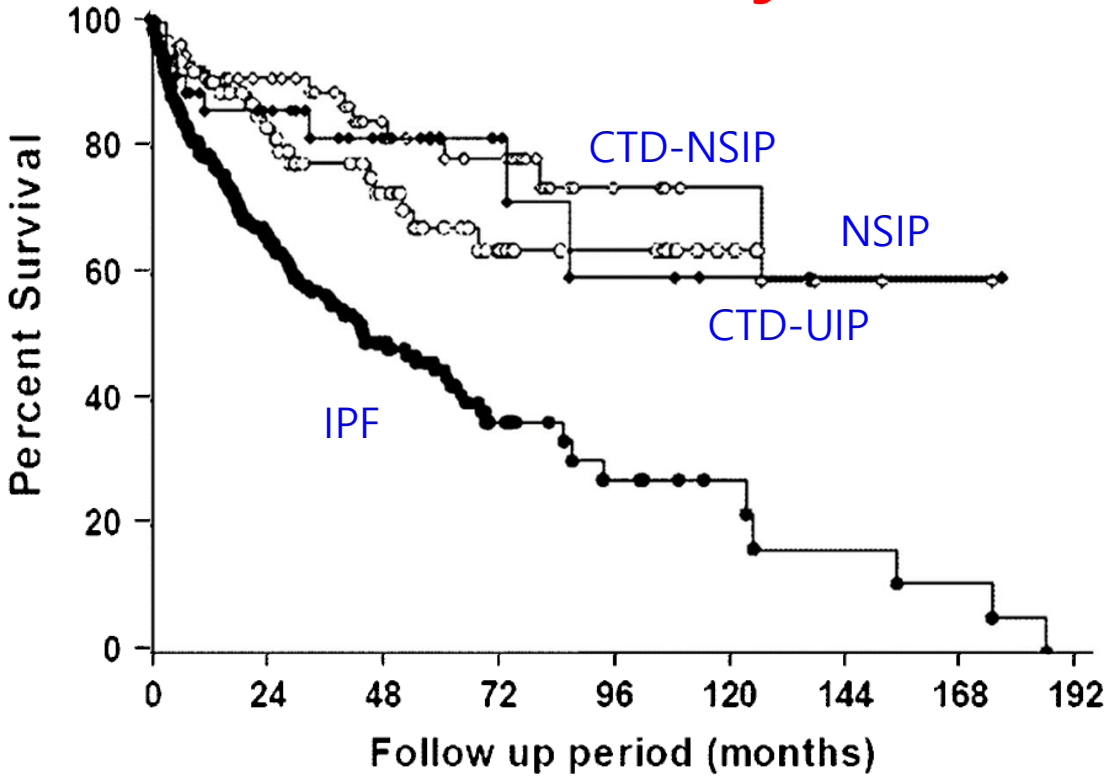
IPF suspected*		Histopathology pattern†			
		UIP	Probable UIP	Indeterminate for UIP or biopsy not performed	Alternative diagnosis
HRCT pattern	UIP	IPF	IPF	IPF	Non-IPF dx
	Probable UIP	IPF	IPF	IPF (Likely)‡	Non-IPF dx
	Indeterminate	IPF	IPF (Likely)‡	Indeterminate§	Non-IPF dx
	Alternative diagnosis	IPF (Likely)‡	Indeterminate§	Non-IPF dx	Non-IPF dx

Am J Respir Crit Care Med Vol 205, Iss 9, pp e18–e47, May 1, 2022

Prognosis of interstitial lung disease

median survival of IPF: 3~5 years





CTD: connective tissue disease
ILD: interstitial lung disease
UIP: usual interstitial pneumonia

Am J Respir Crit Care Med Vol 175. pp 705–711, 2007

TABLE 4 Possible preventive and therapeutic measures in acute exacerbations of idiopathic pulmonary fibrosis (AE-IPF)

Therapeutics	**Recommendation**
Ventilation	
• Low tidal volume ventilation	+
• Noninvasive ventilation	+
• High-flow nasal cannula oxygen therapy	+/–
Pharmacology	
• Corticosteroid	+
• Empiric antibiotics	+/–
• Immunosuppressant[#]	–/+
• Thrombomodulin	–/+
Lung transplantation	+/–
Others	
• Extracorporeal membrane oxygenation	–[§]
• Polymixin B haemoperfusion	–/+
• Rituximab, plasma exchange, intravenous immunoglobulin	–
• Non-steroid approach[¶]	–

- ***Question*:** Should patients with acute exacerbation of IPF be treated with corticosteroids?

  Although high-dose corticosteroids are commonly prescribed for the treatment of acute exacerbation of IPF (143, 144, 147–149, 152, 153, 155, 157, 300), there are no controlled trials on which to judge efficacy. Cyclosporin A and anticoagulation have also been used without conclusive results (152, 241, 301).

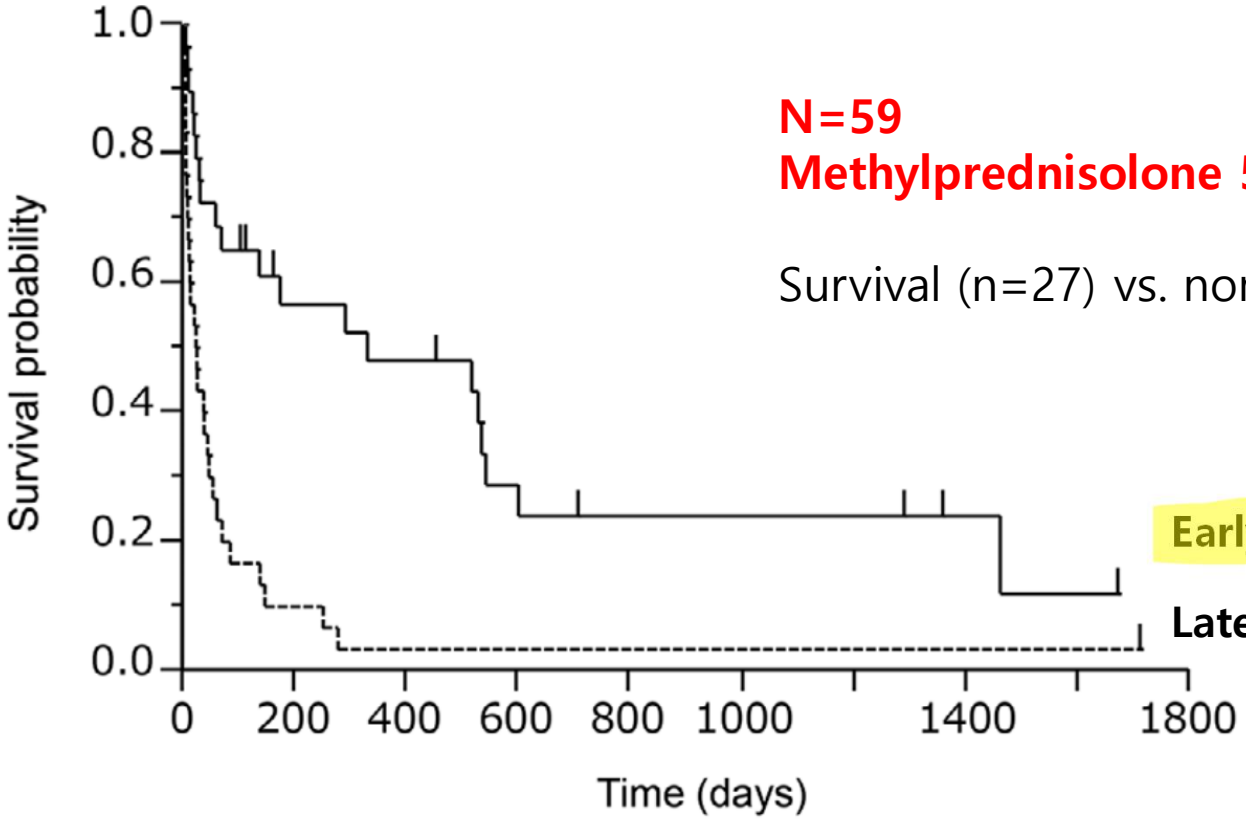
2011 ATS/ERS/JRS/ALAT statement

Recommendation: The majority of patients with acute exacerbation of IPF should be treated with corticosteroids, but corticosteroids may not be reasonable in a minority (weak recommendation, very low-quality evidence).Values: This recommendation places a high value on anecdotal reports of benefit and the high mortality of acute exacerbation of IPF.

Remarks: Specific recommendations regarding the dose, route, and duration of corticosteroid therapy cannot be made. Intravenous corticosteroids up to a gram per day have been reported in a few case series. There was consensus that supportive care is the mainstay of therapy for acute exacerbation of IPF. (Vote: 14 for use, 5 against use, 1 abstention, 11 absent.)

2011 ATS/ERS/JRS/ALAT statement

The initiation of corticosteroid pulse therapy may be an independent prognostic factor in AE-IPF



N=59
Methylprednisolone 500~1000 mg/day for 3days

Survival (n=27) vs. non-survival (n=32)

Early treatment <5 days (n=29)

Late treatment ≥5 days (n=30)

Log-rank test; P<0.0001

Intern Med. 2018 Mar 1;57(5):655-661

Japanese guidelines

- 5.10. Clinical Question 10: Should patients with acute exacerbation of IPF be treated with corticosteroids including pulse therapy?

- We suggest that patients with acute exacerbation of IPF should be treated with corticosteroids including pulse therapy. (strength of recommendation 2, quality of evidence D)

- Corticosteroid pulse therapy at 1 g/day for 3 days (repeated 1–4 times at weekly intervals while observing reaction) and subsequent corticosteroid treatment maintained at 0.5–1 mg/kg, with dose reduction every 2–4 weeks by 5 mg at a time depending on patient condition.

Respir Investig. 2018 Jul;56(4):268-291

Korean guidelines

7. 급성악화

요 약

2016년 개정된 급성악화 진단기준은 새로운 양측성 폐침윤을 동반한 급성, 중증의 호흡 악화로 1) 특발성폐섬유증이 이미 진단되었거나 현재 진단된 경우로, 2) 전형적으로는 최근 한달 내 호흡곤란이 새로 발생하거나 악화되고, 3) 흉부 CT 상 통상형 간질성 폐렴양상(usual interstitial pneumonia, UIP pattern)을 보이면서 간유리음영이나 경화가 양폐에 새롭게 관찰되며, 4) 이러한 이상소견이 심부전이나 수액과다로 충분히 설명되지 않는 경우 진단된다. 이전과 마찬가지로 급성악화가 의심되나 상기 조건을 하나라도 만족하지 못하는 경우 `급성악화의증(suspected acute exacerbation)'으로 정의한다. 주로 진행된 환자에게서 드물지 않게 발생하는 치명적 합병증으로 산소치료 등 보존적 치료와 고용량의 스테로이드 치료가 시행되나 아직 효과가 입증된 치료는 없다.

Treatment during AEIPF and in-hospital outcomes

Treatment regimen	Cases	Survival	p-value
Steroid pulse[#]	13 (14.4)	7 (53.8)	0.933
Steroid pulse[#] plus cytotoxic agent[¶]	8 (8.9)	4 (50.0)	
High-dose steroid[+]	46 (51.1)	19 (41.3)	
High-dose steroid[+] plus cytotoxic agent[¶]	14 (15.6)	11 (78.6)	
Low-dose steroid[§]	6 (6.7)	3 (50.0)	
Low-dose steroid[§] plus cytotoxic agent[¶]	1 (1.1)	1 (100.0)	
No treatment	2 (2.2)	0	
Total	90 (100)	45 (50)	

Steroid pulse
≥ 500 mg/day of Methylprednisolone for 3 days → ≥ 0.5 mg/kg/day of prednisolone

High-dose steroid
≥ 0.5 mg/kg/day of prednisolone

Low-dose steroid
≤ 0.5 mg/kg/day of prednisolone

Cycotoxic agents
Azathioprine, Cyclosporine, Cyclophophamide

Song JW, Eur Respir J. 2011 Feb;37(2):356-63.

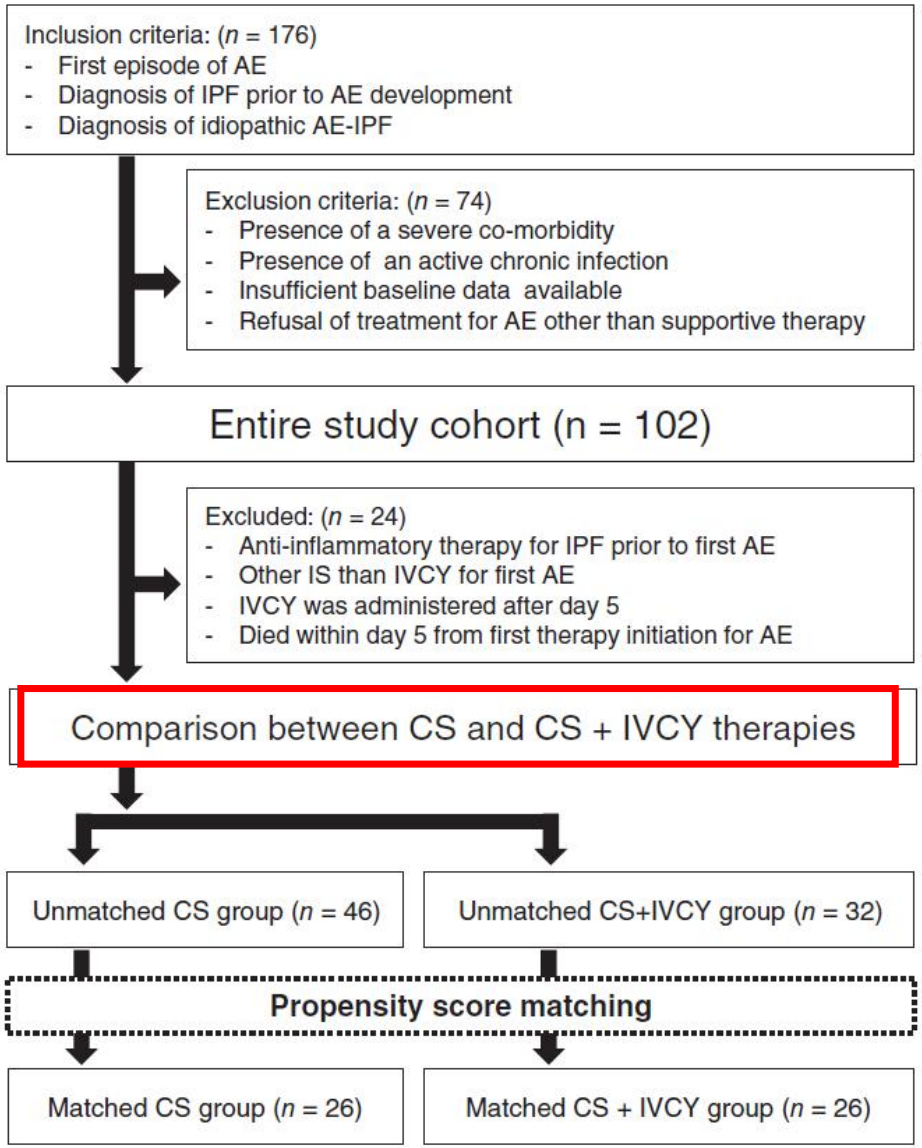
ORIGINAL ARTICLE

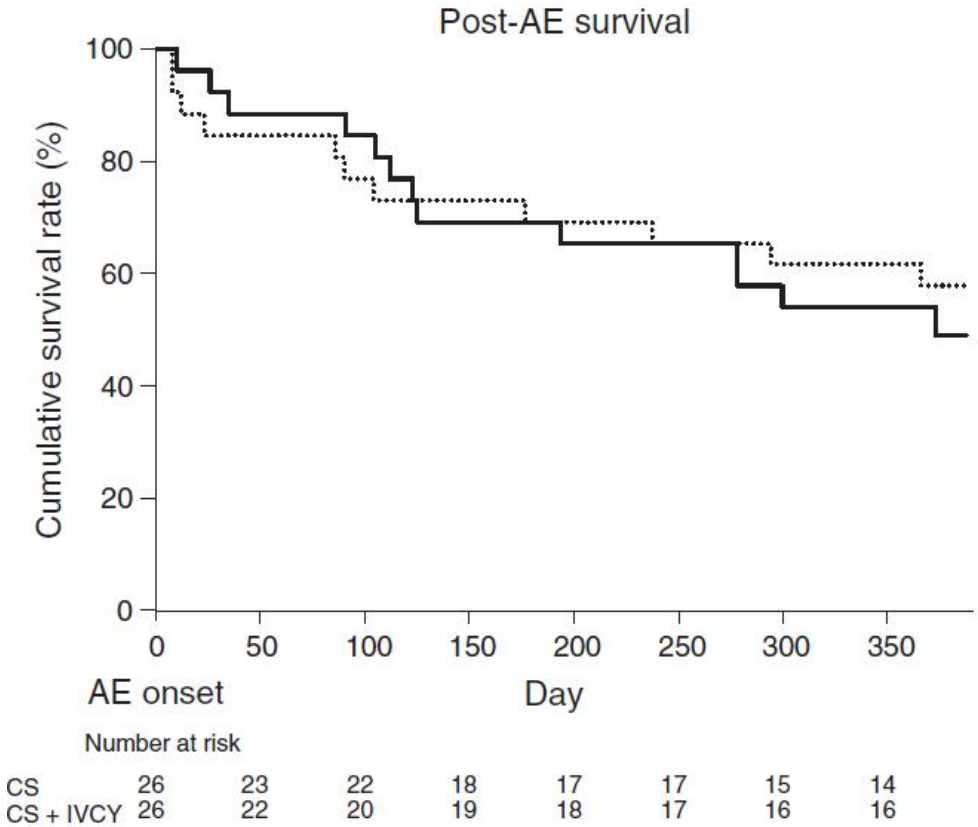
Efficacy of corticosteroid and intravenous cyclophosphamide in acute exacerbation of idiopathic pulmonary fibrosis: A propensity score-matched analysis

Hironao HOZUMI,[1] Hirotsugu HASEGAWA,[2] Koichi MIYASHITA,[3] Hideki YASUI,[1] Yuzo SUZUKI,[1] Masato KONO,[3] Masato KARAYAMA,[1] Kazuki FURUHASHI,[1] Dai HASHIMOTO,[3] Noriyuki ENOMOTO,[1] Tomoyuki FUJISAWA,[1] Naoki INUI,[1,4] Yutaro NAKAMURA,[1] Koshi YOKOMURA,[2] Hidenori NAKAMURA[3] AND Takafumi SUDA[1]

[1]*Second Division, Department of Internal Medicine, Hamamatsu University School of Medicine, Hamamatsu, Japan;* [2]*Department of Respiratory Medicine, Seirei Mikatahara General Hospital, Hamamatsu, Japan;* [3]*Department of Respiratory Medicine, Seirei Hamamatsu General Hospital, Hamamatsu, Japan;* [4]*Department of Clinical Pharmacology and Therapeutics, Hamamatsu University School of Medicine, Hamamatsu, Japan*

Respirology (2019) 24, 792–798





CS + IVCY therapy did not significantly improve post-AE survival in patients with AE-IPF

Respirology (2019) 24, 792–798

Official Journal of the Asian Pacific Society of Respirology
Respirology

ORIGINAL ARTICLE

Corticosteroid use is not associated with improved outcomes in acute exacerbation of IPF

ERICA FARRAND,[1] ERIC VITTINGHOFF,[2] BRETT LEY,[1] ATUL J. BUTTE[3] AND HAROLD R. COLLARD[1]

[1]*Department of Medicine, University of California San Francisco, San Francisco, CA, USA;* [2]*Department of Biostatistics and Epidemiology, University of California San Francisco, San Francisco, CA, USA;* [3]*Bakar Computational Health Sciences Institute, University of California San Francisco, San Francisco, CA, USA*

- US, retrospective, 2010-2018
- AE-IPF: corticosteroid (37) vs. no corticosteroid (45)
- Corticosteroid use: pulse ≥ mPRD 500 mg/day or PRD ≥0.5 mg/kg for 2 days or more

In-hospital mortality

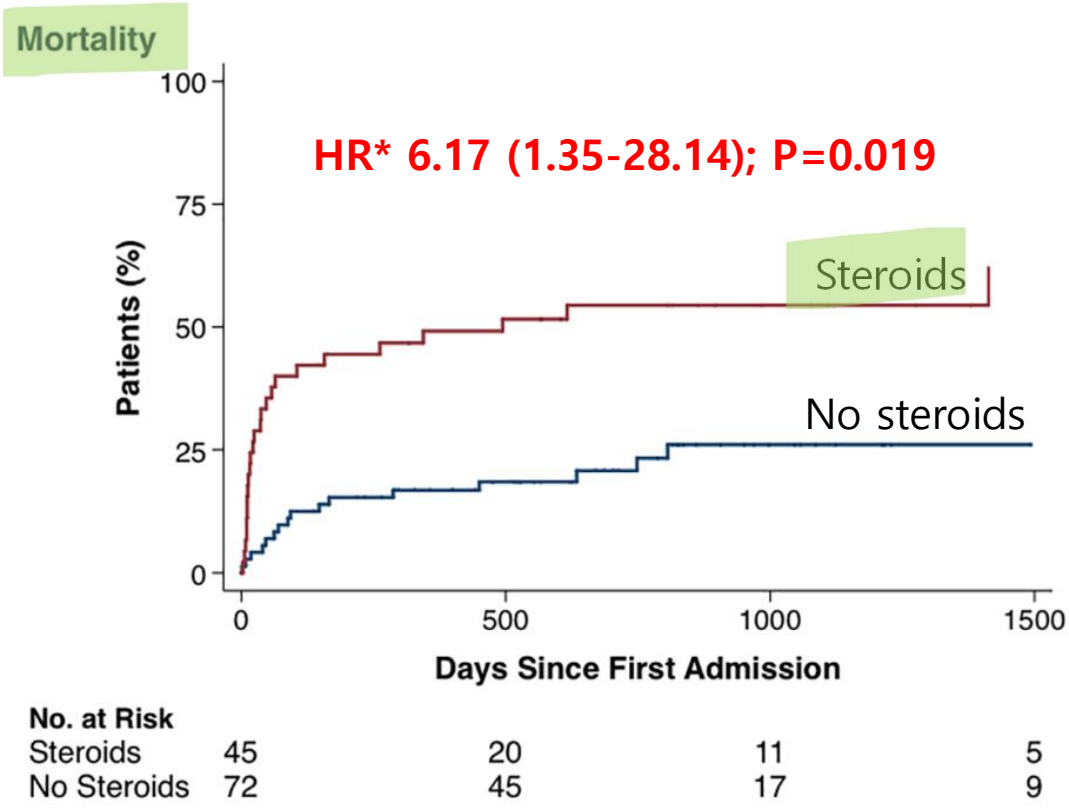
Table 2 Risk of in-hospital mortality in corticosteroid-treated subjects versus subjects receiving usual care, unadjusted, adjusted and treatment propensity-adjusted models

	HR	95% CI	*P*-value
Unadjusted	2.67	0.74–9.64	0.13
Adjusted[†]	1.52	0.37–6.18	0.56
Propensity score weighted[‡]	1.31	0.26–6.55	0.74

[†]Model adjusted for mechanical ventilation and ICU admission as time-dependent covariates.

[‡]Propensity score model adjusted for initial admission location, oxygen use at baseline, do not resuscitate order at admission, body mass index and antibiotic therapy. ICU admission and mechanical ventilation are included as time-dependent covariates.

HR, hazard ratio; ICU, intensive care unit.



*adjusted for corticosteroid use, MV, ICU, Charlson index, PFT)

Respirology(2020) 25, 629–635

scientific reports

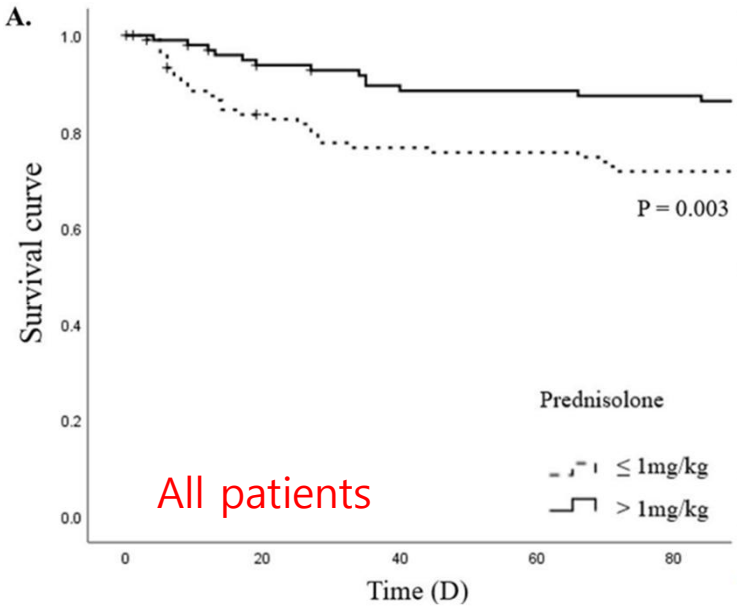
Check for updates

OPEN

Corticosteroid responsiveness in patients with acute exacerbation of interstitial lung disease admitted to the emergency department

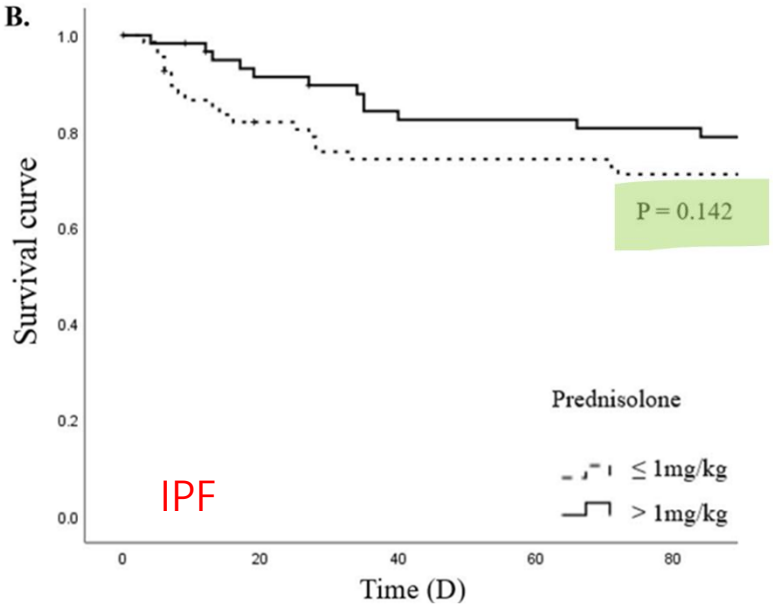
Hye Jin Jang, Seung Hyun Yong, Ah Young Leem, Su Hwan Lee, Song Yee Kim, Sang Hoon Lee, Eun Young Kim, Kyung Soo Chung, Ji Ye Jung, Young Ae Kang, Young Sam Kim, Joon Chang & Moo Suk Park✉

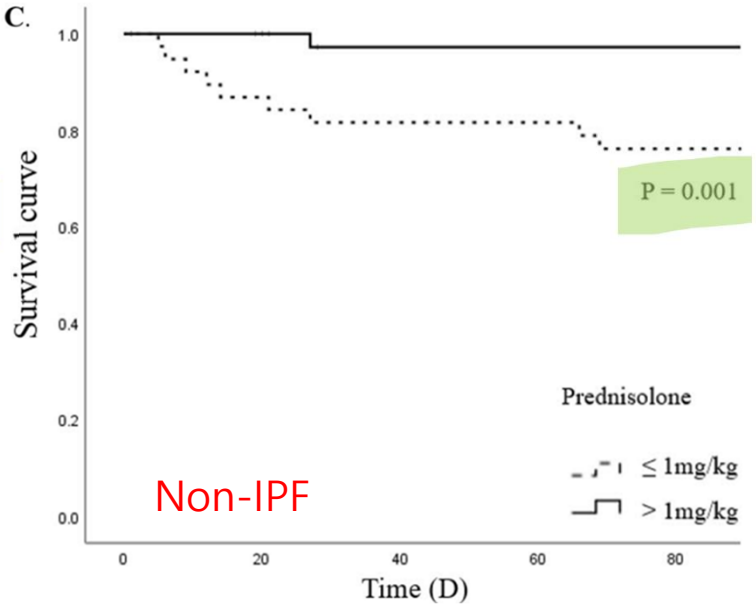
- Severance Hospital, 2016-2018
- Retrospective
- Total 182 patients = IPF (117), non-IPF (65)
- Corticosteroids are usually administered at doses ranging from 0.5 to 2 mg/kg, depending on the clinical situation.
- Steroid pulse therapy was not usually applied except for cases of vasculitis or dermatomyositis-associated rapid progressive ILD.



Variable	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Age, years	0.993	0.968–1.019	0.603	0.989	0.957–1.009	0.200
Sex, male	1.228	0.624–2.415	0.552	0.777	0.377–1.599	0.493
Initial P/F ratio	0.998	0.998–1.001	0.241	0.995	0.992–0.999	0.006
FVC (%), predicted	0.994	0.975–1.014	0.540			
DLco (%), predicted	0.976	0.952–1.001	0.059			
Prednisolone > 1 mg/kg	0.380	0.193–0.747	0.005	0.221	0.102–0.480	< 0.001
Use of vasopressors within 3 days	1.852	0.881–3.890	0.104	1.451	0.630–3.340	0.382
Need for mechanical ventilator	3.877	2.068–7.267	< 0.001	4.205	2.059–8.589	< 0.001

Table 5. Cox regression analysis of risk factors related to 90-day mortality in AE-ILD.





90-day mortality
Totoal: 22%
IPF: 25.6%
Non-IPF: 15.4%

Steroid를 쓸 것인가? 말 것인가?

- AE-IPF를 명확히 진단
- 쓴다면 초기에 사용 (증상 발생 5일 이내?)
- 용량은 적어도 high-dose (PRD 0.5~1 mg/kg/day)를 사용
- Tapering 기간은 잘 모름.

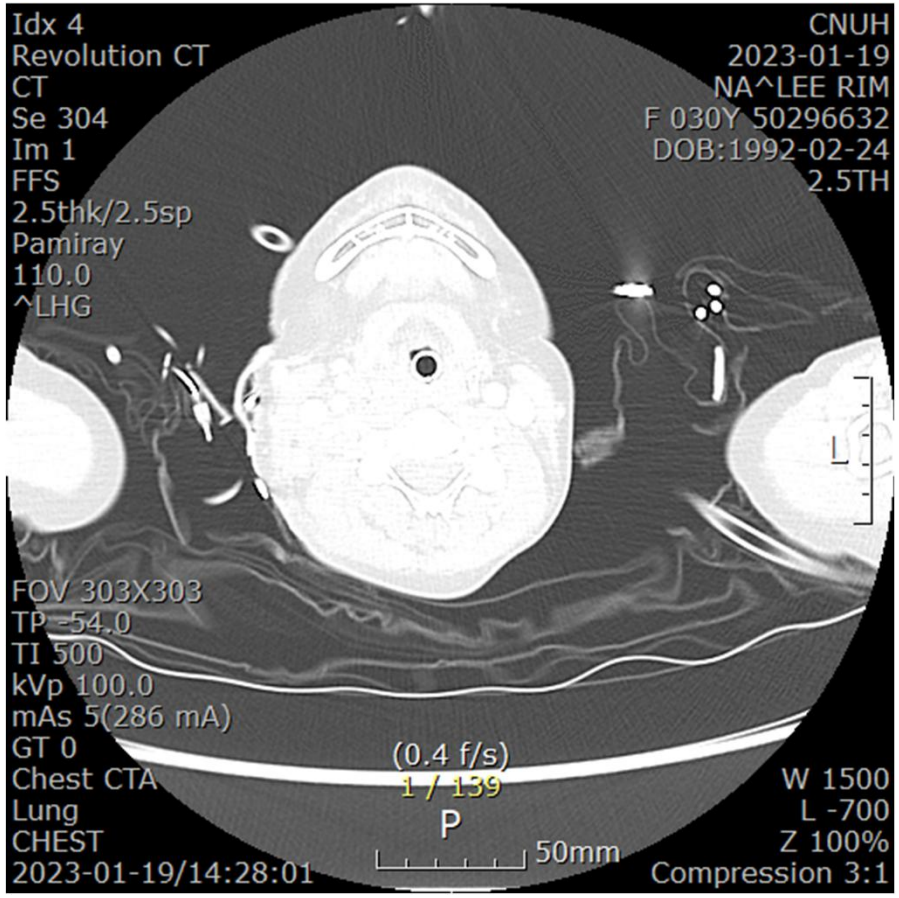
31/F

C/C) hemoptysis

P/I) r/o SLE, hepatitis 로 본원 RHD, GI f/u loss된 자로, 2-3년 전부터 발생한 복수 및 황달 증상이 호전과 악화 반복하던 중 내원 1주 전부터 hemoptysis 동반한 general weakness 있어 본원 응급실 내원함.

Initial ABGA>

pH	7.49
PCO2	37
PO2	60
Hct	27
Na+	119
K+	3.5
Ca++	0.92
Hgb	9.2
HCO3	28.2
O2 SAT	93



Autoimmune markers>

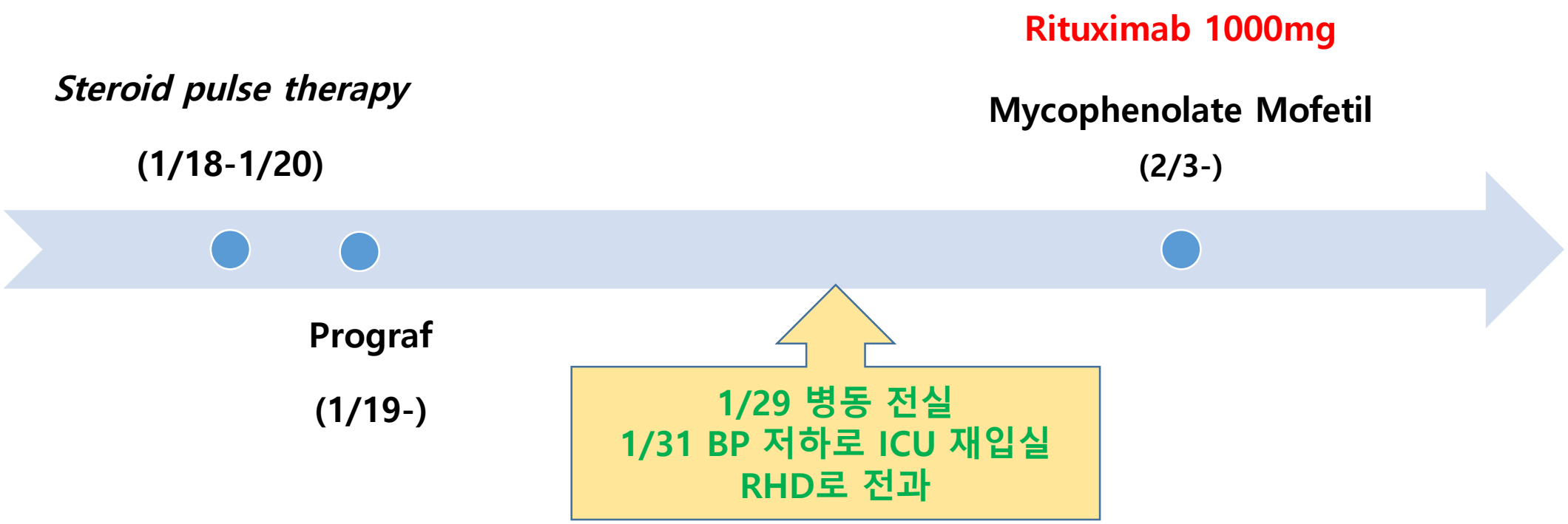
ANA titer 1:80 positive

ENA neg.

Ig G 1518.4 (normal)

IV steroid (1/16~)

Mechanical ventilation (1/17~)



SLE lab>

Anti-β2 IgM, IgG neg.

Anti cardiolipin IgM, IgG neg.

Cryoglobulin neg.

TABLE 4 Possible preventive and therapeutic measures in acute exacerbations of idiopathic pulmonary fibrosis (AE-IPF)

Therapeutics	Recommendation
Ventilation	
• Low tidal volume ventilation	+
• Noninvasive ventilation	+
• High-flow nasal cannula oxygen therapy	+/–
Pharmacology	
• Corticosteroid	+
• Empiric antibiotics	+/–
• Immunosuppressant[#]	–/+
• Thrombomodulin	–/+
Lung transplantation	+/–
Others	
• Extracorporeal membrane oxygenation	–[§]
• Polymixin B haemoperfusion	–/+
• Rituximab, plasma exchange, intravenous immunoglobulin	–
• Non-steroid approach[¶]	–

P201 **RITUXIMAB AS RESCUE THERAPY IN INTERSTITIAL LUNG DISEASE REFRACTORY TO CONVENTIONAL IMMUNOSUPPRESSION**

RR Abdullah, D Ming, GJ Keir, TM Maher, AU Wells, EA Renzoni; *Interstitial Lung Disease Unit, Royal Brompton Hospital, London, UK*

10.1136/thoraxjnl-2013-204457.353

Background Rituximab, a B cell-depleting monoclonal antibody, may offer an effective rescue therapy in a subgroup of patients with severe interstitial lung disease (ILD), progressing despite conventional immunosuppression.

Methods Retrospective assessment of 50 patients with severe, progressive ILD treated with rituximab between 2010 and 2012. This included 33 with connective tissue disease-associated ILD (CTD-ILD), 6 with fibrotic hypersensitivity pneumonitis, 3 with likely drug-induced ILD, 2 with desquamative interstitial pneumonia (DIP) and the rest with miscellaneous ILD patterns, excluding idiopathic pulmonary fibrosis. At the time of rituximab treatment, mean FVC was 49.1% (+ 17.6) and DLco 25.5% (+ 9.9). Four patients were mechanically ventilated. Prior to rituximab, all patients except one had received immunosuppressive treatment, including IV cyclophosphamide in 44 patients. Change in pulmonary function tests, as compared to pre-rituximab levels, was assessed at six to twelve months post-treatment and analysed by Wilcoxon signed rank test. Categorical trends (improvement, stability, deterioration) before and after treatment were defined using either ≥10% change in forced vital capacity (FVC) or ≥15% change in diffusing capacity for carbon monoxide (DLco) as threshold values.

Immunomodulatory Therapy :

When & How to Use It in the ILD AE Patient?

Thorax 2013;68(Suppl 3):A1–A220 A167

Results In the six to twelve months following rituximab treatment, a median improvement in FVC of 5.7% ($p < 0.01$) and stability of DLco ($p < 0.01$) was observed. This was in contrast to a median decline in FVC and DLco of 14.6% and 18.8% respectively, in the six *to twelve months prior to rituximab therapy* ($p < 0.01$). Patients with CTD-ILD were most represented in this *cohort* and were more likely to improve or stabilise following Rituximab (28/33), than those with non CTD-related ILD (8/17) ($p = 0.008$, Fisher exact test). However, of the four patients requiring invasive ventilation, improvement to extubation was observed in three patients with non CTD-ILD (one DIP, one acute interstitial pneumonia, one unclassifiable ILD). Two patients developed serious infections (pneumonia) requiring hospitalisation following rituximab, and ten patients died, all from progression of underlying ILD, *a median of 5.1 months after treatment.*

Conclusions Rituximab may offer a safe and effective therapeutic intervention in a subgroup of patients with severe, progressive ILD unresponsive to conventional immunosuppression. Future prospective, controlled trials are warranted to validate these findings.

Thorax 2013;68(Suppl 3):A1–A220 A167

Biological treatments

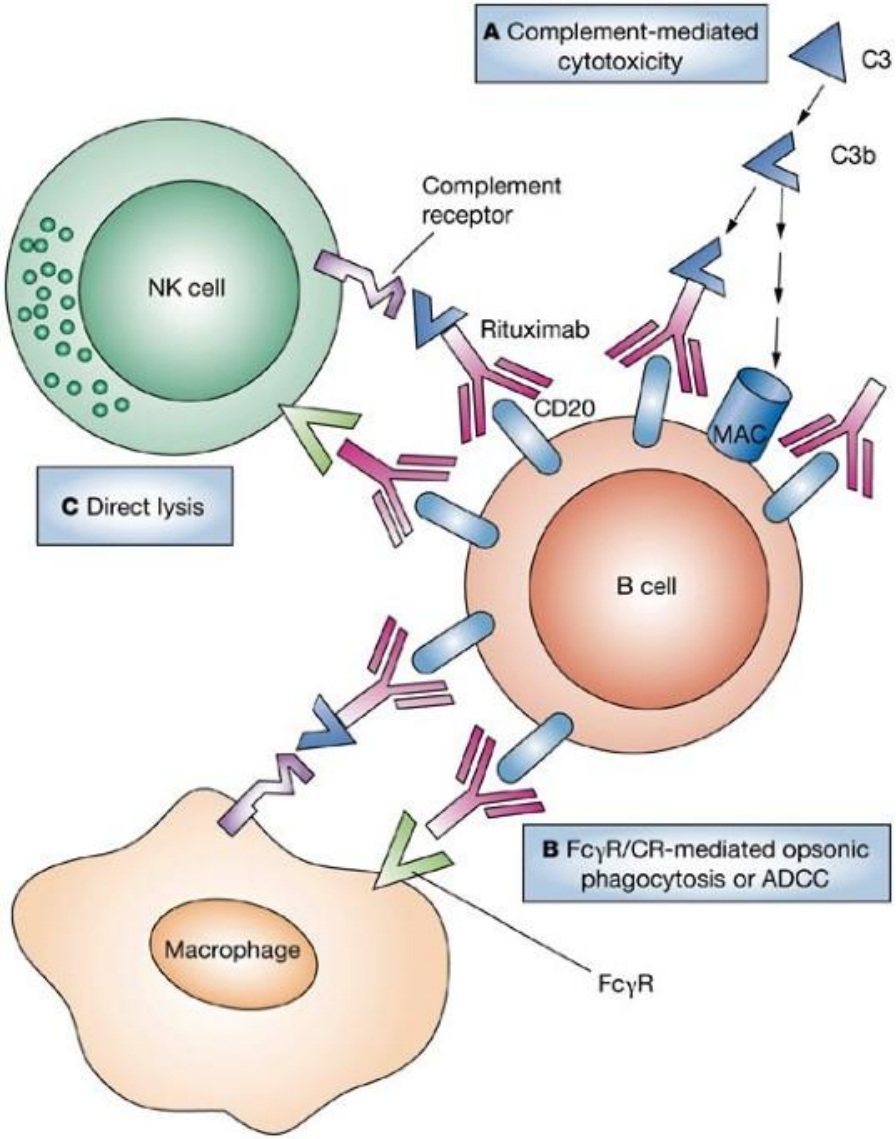
- ✓ TNF-α inhibitors
- ✓ B-cell-targeted therapies
- ✓ T cell costimulatory molecule blockers
- ✓ Immune checkpoint inhibitors

- Beneficial outcomes in a proportion of patients with refractory CTD-ILD
- Rituximab (RTX) and TNF-α inhibitors are the most widely used biological treatments for patients with CTD-ILD

RITUXIMAB

- The chimeric immunoglobulin G1 (IgG1) monoclonal antibody to CD20-positive B cells

- Targets CD20-positive cells (ie, B-cell precursors), leading in most patients to the depletion of B cells in the blood within several weeks of administration



RITUXIMAB

- It is a promising agent for the treatment of both DM and PM.
- It has shown mixed results in case series of connective tissue disease-associated interstitial lung disease (CTD-ILD)

- **Pre-rituximab disease course and treatment**
- **Decision to treat**
- **Rituximab administration**
- **Post-treatment disease course**
- **Adverse effects**

Rheumatology 2016;55:1318–1324
doi:10.1093/rheumatology/kew195
Advance Access publication 8 April 2016

RHEUMATOLOGY

Original article

Rituximab in autoimmune connective tissue disease–associated interstitial lung disease

Charles Sharp[1], Melanie McCabe[2], Nick Dodds[3], Anthony Edey[3], Lloyd Mayers[3], Huzaifa Adamali[3], Ann B. Millar[1] and Harsha Gunawardena[3,4]

Pre-rituximab disease course and treatment

- In case patients had failed to respond adequately to *prior immunosuppressive therapies*

- Induction with pulsed IV CYC (at a dose of 15 mg/kg, capped at 1 g, for six cycles, at 3 week intervals)

- With IV methylprednisolone (500mg~1 g prior to each dose of CYC)

- Mycophenolate Mofetil

Decision to treat

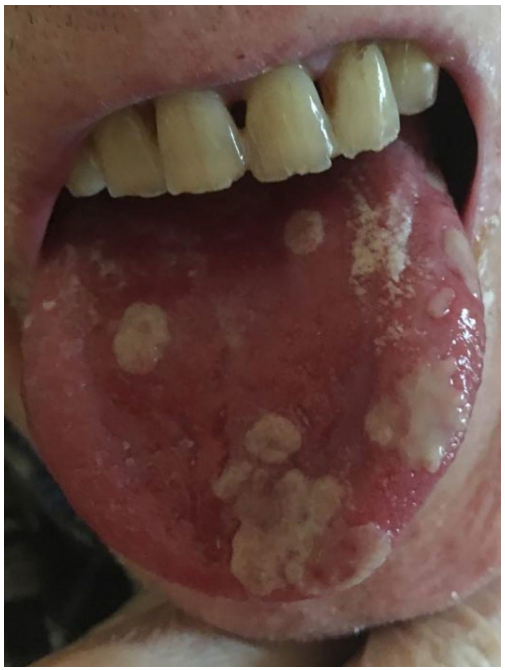
The decision to commence rituximab treatment was based on MDT discussion

- ✓ Clinical features including progression or lack of improvement in rheumatologic features
- ✓ Progressive lung function decline
- ✓ HRCT changes: progressive changes or a failure of disease adjudged as reversible to improve or resolve (e.g. ground glass changes)

Rituximab administration

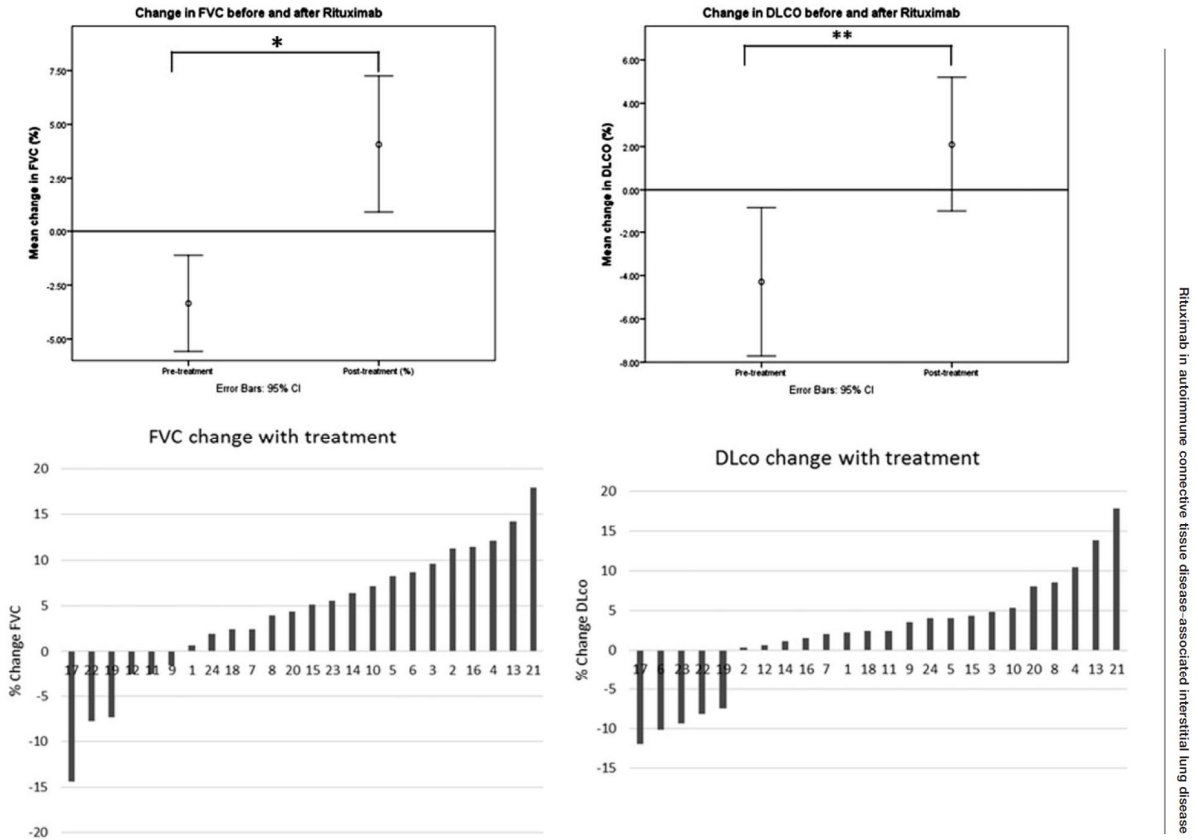
- Rituximab was administered according to rheumatology/CTD protocol, **at a dose of 1 g IV infused on days 0 and 14**.

- Following treatment, oral immunosuppression was continued in all patients.



Post-treatment disease course

Fig. 1 Changes in lung function before and after treatment



(**A**) Mean change in FVC. (**B**) Mean change in DLCO. (**C**) Fountain plot of individual patient changes in FVC. (**D**) Fountain plot of individual patient changes in DLCO. *P = 0.001, **P = 0.02. FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide.

Adverse effects

- Infusion reactions
- Development of antibodies to rituximab
- Viral and fungal infections
- Hypogammaglobulinemia.

Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomised, controlled, phase 2b trial

*Toby M Maher, Veronica A Tudor, Peter Saunders, Michael A Gibbons, Sophie V Fletcher, Christopher P Denton, Rachel K Hoyles, Helen Parfrey, Elisabetta A Renzoni, Maria Kokosi, Athol U Wells, Deborah Ashby, Matyas Szigeti, Philip L Molyneaux, on behalf of the RECITAL Investigators**

- Rituximab was not superior to cyclophosphamide to treat patients with CTD-ILD
- Rituximab was associated with fewer adverse events

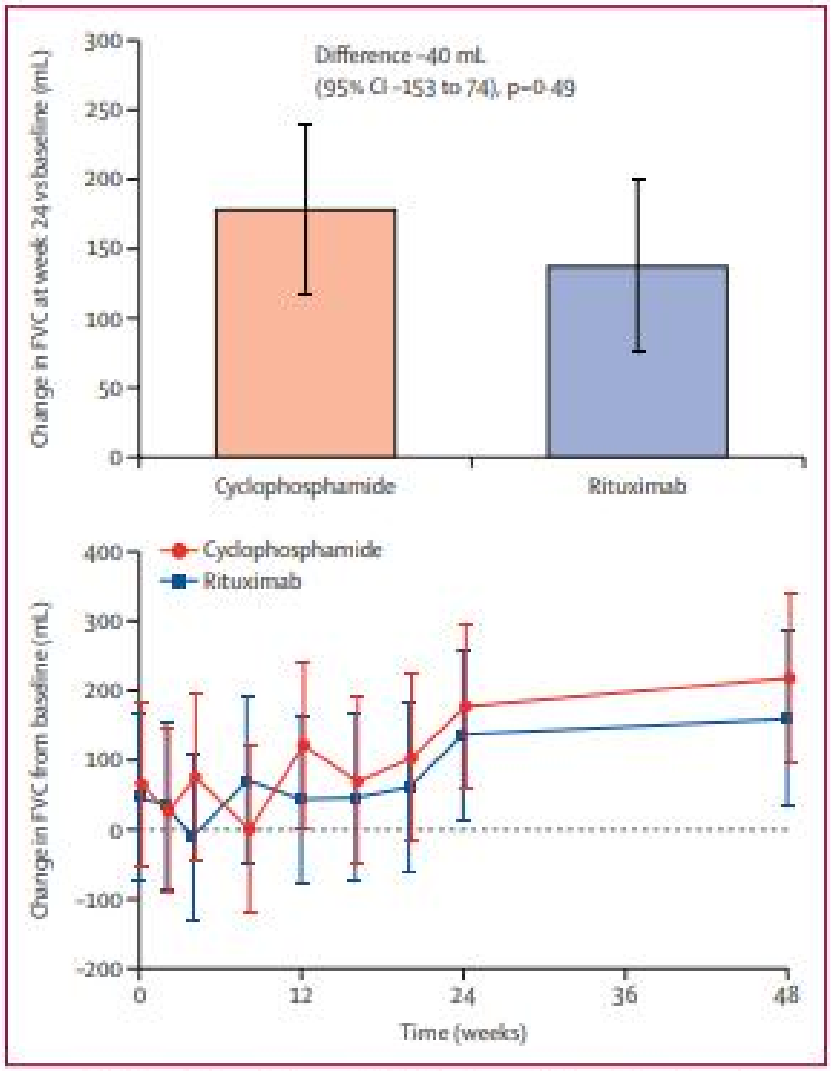


Figure 2: Adjusted rate of change in FVC in the cyclophosphamide and rituximab groups at week 24 (A) and adjusted change in FVC from baseline to week 48 (B)

Error bars in both panels are standard errors for the adjusted rate of change in FVC.

Lancet Respir Med 2023; 11: 45–54

Rituximab should be considered as a therapeutic alternative to cyclophosphamide in individuals with CTD-ILD requiring intravenous therapy.

	Cyclophosphamide group (n=50)	Rituximab group (n=51)
All events	646	445
Blood and lymphatic system disorders	3 (<1%)	0
Cardiac disorders	10 (2%)	6 (1%)
Ear and labyrinth disorders	2 (<1%)	1 (<1%)
Eye disorders	16 (2%)	9 (2%)
Gastrointestinal disorders	170 (26%)	71 (16%)
General disorders and administration site conditions	91 (14%)	52 (12%)
Hepatobiliary disorders	1 (<1%)	1 (<1%)
Immune system disorders	0	2 (<1%)
Infections and infestations	50 (8%)	46 (10%)
Injury, poisoning, and procedural complications	8 (1%)	5 (1%)
Investigations	11 (2%)	8 (2%)
Metabolism and nutrition disorders	5 (1%)	3 (1%)
Musculoskeletal and connective tissue disorders	44 (7%)	40 (9%)
Nervous system disorders	72 (11%)	35 (8%)
Psychiatric disorders	9 (1%)	10 (2%)
Renal and urinary disorders	8 (1%)	1 (<1%)
Reproductive system and breast disorders	5 (1%)	4 (1%)
Respiratory, thoracic, and mediastinal disorders	94 (15%)	101 (23%)
Skin and subcutaneous tissue disorders	38 (6%)	32 (7%)
Surgical and medical procedures	1 (<1%)	0
Vascular disorders	7 (1%)	16 (4%)

Data are number of events (% of total events reported per cohort).

Table 3: Adverse events by system, organ, and class, reported to week 48 for all randomised participants

Lancet Respir Med 2023; 11: 45–54

Rituximab for the treatment of connective tissue disease–associated interstitial lung disease: A systematic review and meta-analysis

Linrui Xu[1,2,3], Faping Wang[1,2,3]* and Fengming Luo[1,2,3]*

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TABLE 1 Baseline clinical characteristics of included studies.

Study	Study design	Country	Population	Patient (*n*)	Sex (F (%)	Mean age (yrs)	Evaluation criteria	Rituximab therapy	Follow-up (months)	Quality score
Sem et al, (2009)	Retrospective study	Norway	AS-ILD	11	63	59 (23–66)	PFT、HRCT	Rituximab (1,000 mg) on D0 and D14 (n = 10) Rituximab (700 mg) on D0 and D14 (n = 1)	6	7
Keir et al, (2014)	Retrospective study	United Kingdom	CTD-ILD	32	33	52.5 ± 10.9	PFT	Rituximab (1,000 mg) on D0 and D14	6–12	7
Allenbach et al, (2015)	Prospective study	French	AS-ILD	10	20	51 (18–57)	PFT、HRCT、SF-36	Rituximab (1,000 mg) on D0, D15 and M6	12	7
Bosello et al, (2015)	Prospective study	Italy	SSC-ILD	14	85	41.4 ± 13.1	PFT、HRCT	Rituximab (1,000 mg) on D0 and D14	12	8
Lepri et al, (2016)	Retrospective study	NA	CTD-ILD	42	75	NA	PFT	NA	12	7
Sharp et al, (2016)	Retrospective study	United Kingdom	CTD-ILD	24	66	51.4 ± 14.9	PFT、HRCT	Rituximab (1,000 mg) on D0 and D14	6–12	7
Yuzaiful (2017)	Retrospective study	United Kingdom	RA-ILD	43	64	64 (59–72)	PFT、HRCT	Rituximab (1,000 mg) on D0 and D14	6–12	7
Sari et al, (2017)	Retrospective study	Turkey	SSC-ILD	14	92	53.2 (46.8–55.5)	PFT	NA	6-?	7
Doyle et al, (2018)	Retrospective study	United States	AS-ILD	22	80	49 ± 12	PFT、HRCT	NA	12–36	8
Sircar et al, (2018)	Prospective study	India	SSC-ILD	30	83	34.67 ± 8.13	PFT、HRCT	Rituximab (1,000 mg) on D0 and D15	6	8
Duarte et al, (2019)	Retrospective study	United Kingdom	RA-ILD	15	66	NA	PFT、HRCT	NA	6–36	7
Javier (2020)	Retrospective study	Spain	SSC-ILD	24	87.5	58.0 ± 14.0	PFT、HRCT	Rituximab (1,000 mg) on D0 and D15	6–24	7
Javier (2020)	Retrospective study	Spain	RA-ILD	31	58	61.0 ± 12.0	PFT、HRCT	Rituximab (1,000 mg) on D0 and D15	6–24	7

Abbreviations: RA-ILD, Rheumatoid Arthritis-Associated Interstitial Lung Disease; AS-ILD: Anti-synthetase Syndrome-Associated Interstitial Lung Disease. CTD-ILD: Connective Tissue Disease-Associated Interstitial Lung Disease; SSC-ILD: Systemic Sclerosis-Associated Interstitial Lung Disease. PFT: pulmonary function test; HRCT: High-Resolution Computed Tomography; SF-36: 36-Item Short-Form Health Survey. N/A: not available.

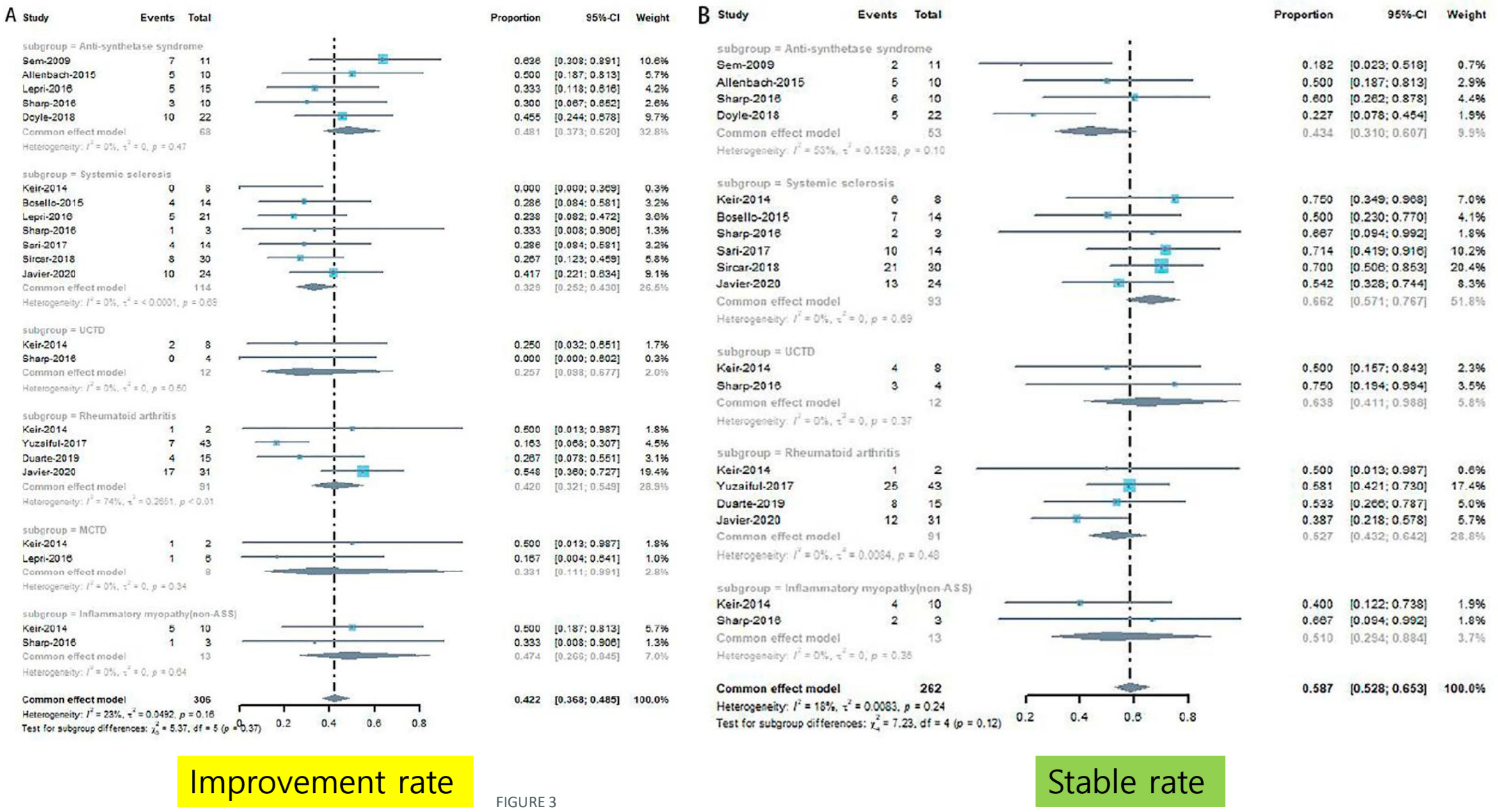


FIGURE 3
Subgroup analyses of improvement rate (A) and stable rate (B) in CTD-ILD studies.

TABLE 3 Adverse events observed after rituximab infusion in CTD-ILD patients.

Study	CTD-ILD patients, *n*	Adverse events, *n*	Adverse events, (*n*)		
			Grade1–2	Grade3-4	Grade5
Sem et al, (2009)	11	8	7	0	1
Keir et al, (2014)	33	3	NA	NA	3
Allenbach et al, (2015)	12	6	6	0	0
Bosello et al, (2015)	14	6	6	0	0
Lepri et al, (2016)	44	12	10	2	0
Sharp et al, (2016)	24	1	0	0	1
Yuzaiful (2017)	56	24	0	15	9
Sari et al, (2017)	14	1	0	1	0
Doyle et al, (2018)	25	13	9	3	1
Sircar et al, (2018)	30	13	11	1	1
Duarte et al, (2019)	26	NA	NA	NA	NA
Javier (2020)	24	9	5	3	1
Javier (2020)	31	10	5	3	2

Abbreviations: CTD-ILD: Connective Tissue Disease-Associated Interstitial Lung Disease; NA: not available. Grade1-2: Mild to moderate. Grade 3: Severe but not immediately life-threatening. Grade 4: Life-threatening consequence. Grade 5: Death.

Journal of
Clinical Medicine

MDPI

Article

Efficacy and Safety of Rituximab in Autoimmune Disease—Associated Interstitial Lung Disease: A Prospective Cohort Study

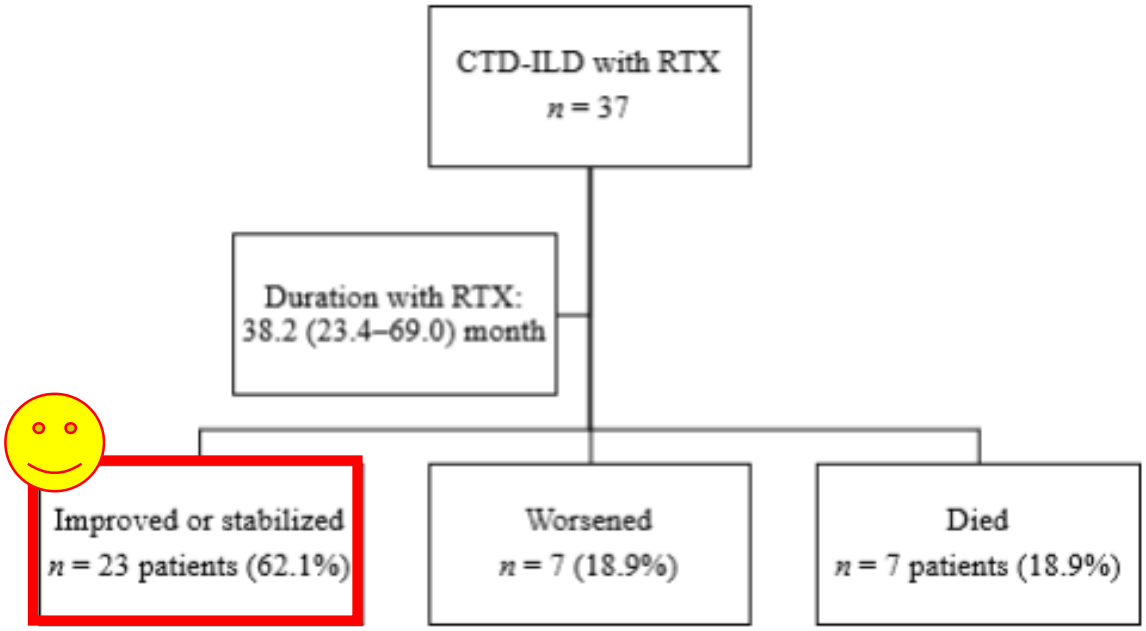
Natalia Mena-Vázquez [1,2,3,*], Rocío Redondo-Rodríguez [1,2], Marta Rojas-Gimenez [4,5], Carmen María Romero-Barco [1,6], Sara Manrique-Arija [1,2,3], Rafaela Ortega-Castro [4,5], Ana Hidalgo Conde [7], Rocío Arnedo Díez de los Ríos [7], Eva Cabrera César [8], Francisco Espildora [9], María Carmen Aguilar-Hurtado [10], Isabel Añón-Oñate [11], Lorena Pérez-Albaladejo [12], Manuel Abarca-Costalago [7], Inmaculada Ureña-Garnica [1,2], Maria Luisa Velloso-Feijoo [13], Maria Victoria Irigoyen-Oyarzábal [1,2] and Antonio Fernández-Nebro [1,2,3]

J. Clin. Med. **2022**, 11, 927.

Protocol

- Rituximab was administered in 2 intravenous infusions of 1000 mg on days 1 and 15 every 6 months or more, depending on pulmonary or joint symptoms and serum immunoglobulin levels.

- All patients were premedicated at each infusion with 100 mg of methylprednisolone, antihistamines, and antipyretic agents



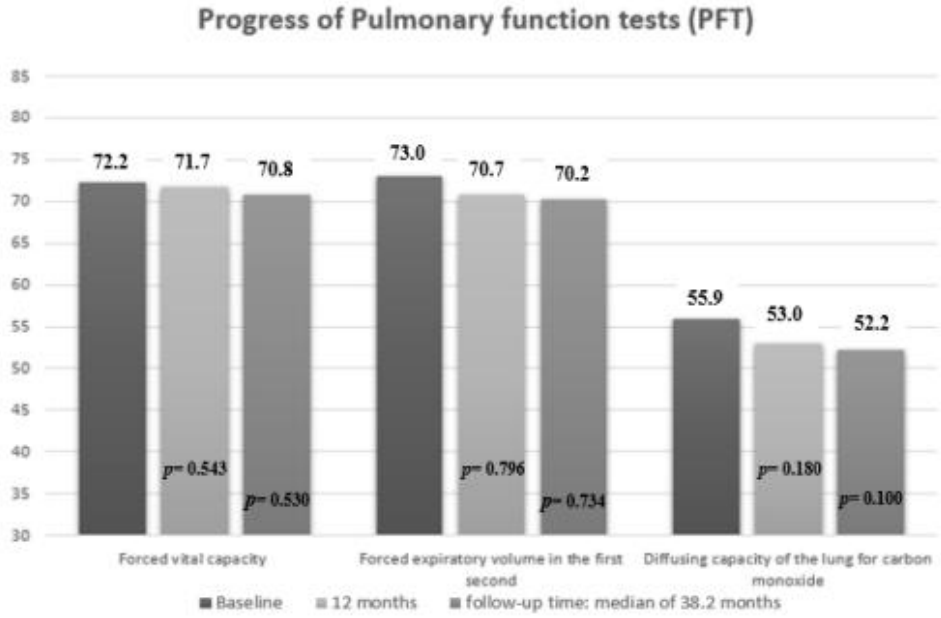


Figure 3. Pulmonary function results at 12 months and at the end of follow-up in patients with CTD-ILD receiving rituximab. P = *p* value for comparison between 12 months with baseline, and end of follow-up with baseline.

Effect size of rituximab on pulmonary function in the treatment of connective-tissue disease-related interstitial lung disease: a systematic review and meta-analysis

Yuanchen Zhao[1,4], Yang Gao[1,4], Tananchai Petnak[2,4], Wisit Cheungpasitporn[3], Charat Thongprayoon[3], Xing Zhang[1] and Teng Moua[4*]

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Total	Relative weight
Statistics for each study									
Dacousis et al 2012	9.170	4.168	17.372	1.001	17.339	2.200	0.028	8	5.64
Keir et al 2012	2.500	10.766	115.907	-18.601	23.601	0.232	0.816	6	0.85
Fitzgerald et al 2015	6.460	10.527	110.818	-14.173	27.093	0.614	0.539	10	0.89
Chen et al 2016	1.700	8.546	73.031	-15.049	18.449	0.199	0.842	10	1.34
Lepri et al (1) 2016	-3.500	4.879	23.807	-13.063	6.063	-0.717	0.473	5	4.12
Lepri et al (2) 2016	10.050	17.194	295.647	-23.650	43.750	0.584	0.559	6	0.33
Lepri et al (3) 2016	-6.500	15.488	239.869	-36.855	23.855	-0.420	0.675	10	0.41
Sharp et al 2016	4.100	3.043	9.263	-1.865	10.065	1.347	0.178	24	10.58
Dacousis et al 2017	6.080	6.084	37.013	-5.834	18.014	1.001	0.317	33	2.65
Md Yusof et al 2017	4.200	3.972	15.777	-3.585	11.985	1.057	0.290	55	6.21
Sari et al 2017	4.210	5.551	30.809	-6.669	15.089	0.758	0.448	14	3.18
Doyle et al 2018	8.000	9.453	89.350	-10.527	26.527	0.846	0.397	12	1.10
Sircar et al 2018	6.220	3.806	14.485	-1.240	13.680	1.634	0.102	30	6.76
Duarte et al 2019	4.300	1.360	1.848	1.635	6.965	3.163	0.002	49	53.02
Ebata et al 2019	20.600	10.333	106.769	0.348	40.852	1.994	0.046	9	0.92
Fu et al 2019	5.900	6.970	48.595	-7.761	19.561	0.846	0.397	14	2.02
	4.567	0.990	0.980	2.627	6.507	4.614	0.000		

$I^2 = 0\%$, $P = 0.94$

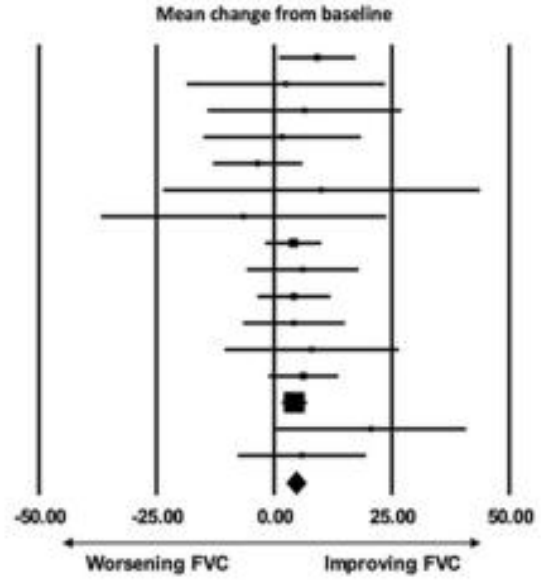


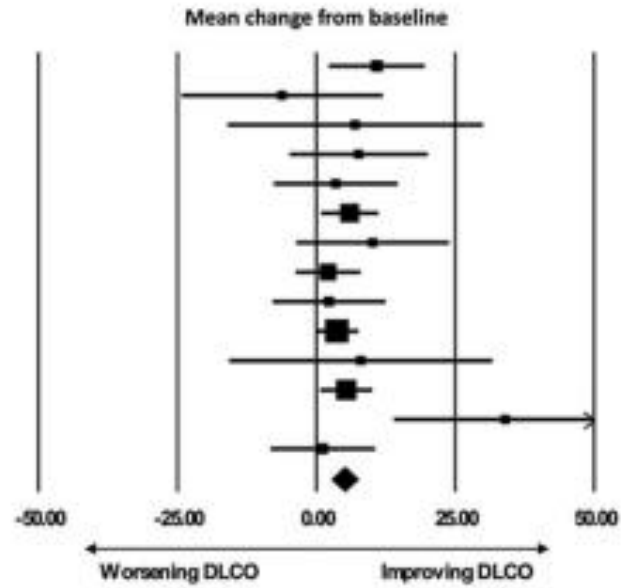
Fig. 2 FVC% meta-analysis forest plot, random-effects analysis

Zhao et al. Respiratory Research (2022) 23:164

Effect size of rituximab on pulmonary function in the treatment of connective-tissue disease-related interstitial lung disease: a systematic review and meta-analysis

Yuanchen Zhao[1,4], Yang Gao[1,4], Tananchai Petnak[2,4], Wisit Cheungpasitporn[3], Charat Thongprayoon[3], Xing Zhang[1] and Teng Moua[4*]

Studyname	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Total	Relative weight
	Statistics for each study								
Daoussis et al 2012	10.880	4.429	19.613	2.200	19.560	2.457	0.014	8	6.36
Keir et al 2012	-6.170	9.269	85.920	-24.337	11.997	-0.666	0.506	6	1.56
Fitzgerald et al 2015	6.990	11.744	137.917	-16.027	30.007	0.595	0.552	10	0.98
Chen et al 2016	7.600	6.353	40.363	-4.852	20.052	1.196	0.232	10	3.24
Lepri et al (1) 2016	3.500	5.712	32.632	-7.696	14.696	0.613	0.540	8	3.96
Lepri et al (2) 2016	6.000	2.638	6.959	0.830	11.170	2.274	0.023	5	15.42
Lepri et al (3) 2016	10.150	7.042	49.588	-3.652	23.952	1.441	0.149	5	2.66
Sharp et al 2016	2.100	2.997	8.982	-3.774	7.974	0.701	0.483	24	12.56
Daoussis et al 2017	2.290	5.207	27.114	-7.916	12.496	0.440	0.660	33	4.72
Md Yusof et al 2017	3.700	1.995	3.979	-0.210	7.610	1.855	0.064	56	23.21
Doyle et al 2018	8.000	12.104	146.511	-15.724	31.724	0.661	0.509	9	0.92
Duarte et al 2019	5.400	2.412	5.818	0.672	10.128	2.239	0.025	49	17.69
Ebata et al 2019	34.000	10.266	105.388	13.879	54.121	3.312	0.001	9	1.28
Fu et al 2019	1.140	4.819	23.227	-8.306	10.586	0.237	0.813	14	5.45
	5.000	1.170	1.370	2.706	7.294	4.272	0.000		



I^2 = 10%, P = 0.34

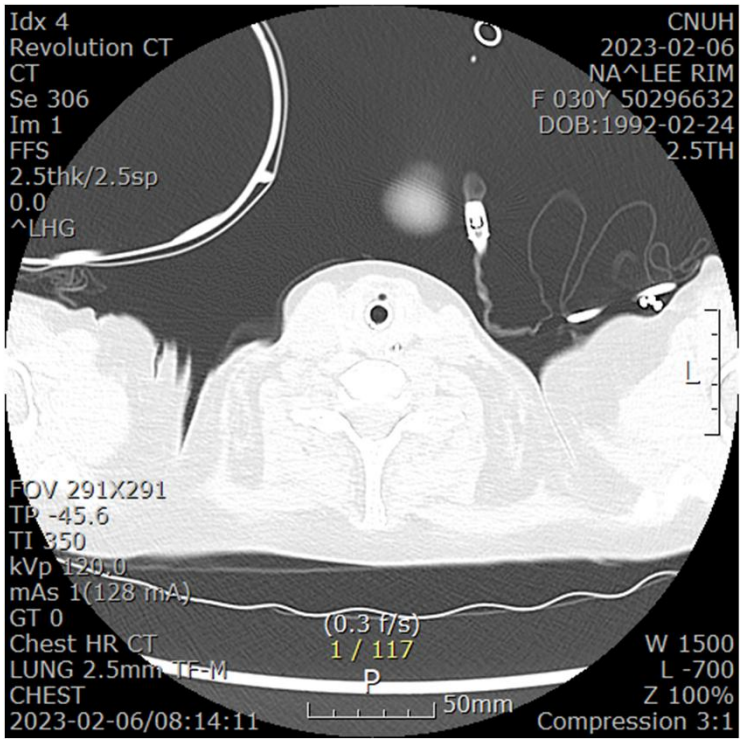
Fig. 3 DLCO% meta-analysis forest plot, random effects analysis

Zhao et al. Respiratory Research (2022) 23:164

Return to case

Weekly SLE Lab f/u)

- Anti-dsDNA 2.5 [0~7 IU/ml]
- Ig G 1141.0 [700~1600 mg/dl]
- C3 68.3 62.7 [90~180mg/dl]
- C4 11.6 11.4 [17.1~46.5mg/dl]
- CH50 32.0 [31.7~51.6 U/mL]



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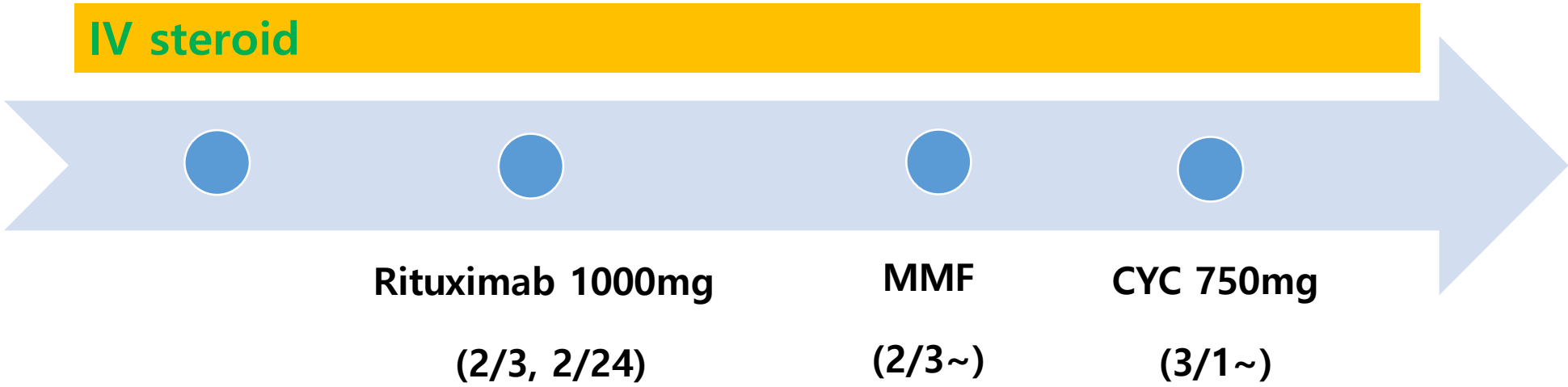

AE ILD에서 initial Tx.로 가능할까??

AE IPF에서는??

Biologic Treatments in Interstitial Lung Diseases

Theodoros Karampitsakos[1], Argyro Vraka[2], Demosthenes Bouros[2], Stamatis-Nick Liossis[3] and Argyris Tzouvelekis[2]*

[1] 5th Department of Pneumonology, General Hospital for Thoracic Diseases Sotiria, Athens, Greece, [2] First Academic Department of Pneumonology, Hospital for Thoracic Diseases, Sotiria Medical School, National and Kapodistrian University of Athens, Athens, Greece, [3] Division of Rheumatology, Department of Internal Medicine, Patras University Hospital, University of Patras Medical School, Patras, Greece

Interstitial lung diseases (ILD) represent a group of heterogeneous parenchymal lung disorders with complex pathophysiology, characterized by different clinical and radiological patterns, ultimately leading to pulmonary fibrosis. A considerable proportion of these disease entities present with no effective treatment, as current therapeutic regimens only slow down disease progression, thus leaving patients, at best case, with considerable functional disability. Biologic therapies have emerged and are being investigated in patients with different forms of ILD. Unfortunately, their safety profile has raised many concerns, as evidence shows that they might cause or exacerbate ILD status in a subgroup of patients. This review article aims to summarize the current state of knowledge on their role in patients with ILD and highlight future perspectives.

Keywords: interstitial lung diseases, biologic treatments, pulmonary fibrosis, treatment, safety

Front. Med. 6:41.

TABLE 2 | Biologic treatments in pulmonary sarcoidosis.

Study	Biologic agent	Mechanism of action	Number of patients/Outcome	References
Baughman et al.	Infliximab	Chimeric monoclonal antibody against TNF	148 patients Improvement of 2.5% in FVC over 24 weeks	(46)
Rossman et al.	Infliximab	Chimeric monoclonal antibody against TNF	19 patients No significant improvement over 6 and 14 weeks	(47)
Vorselaars et al.	Infliximab	Chimeric monoclonal antibody against TNF	56 patients Improvement of 6.6% in FVC Uptake value on ^{18}F-FDG-PET predictive of response	(48)
Vorselaars et al.	Infliximab	Chimeric monoclonal antibody against TNF	47 patients Relapse 62% Increased SUV, IL-2r predictors	(49)
Sweiss et al.	Adalimumab	Humanized monoclonal antibody against TNF	11 patients Improvement in FVC (4), stabilization in FVC (7), improvement in 6MWD (5), improvement in Borg (9) over 24/52 weeks	(50)
Utz et al.	Etanercept	Receptor antagonist of TNF	17 patients Excessive treatment failure	(51)
Judson et al.	Ustekinumab/ golimumab	Humanized monoclonal antibody against IL12,IL23/and against TNF, respectively	173 patients (pulmonary or cutaneous) No significant improvement over 28 weeks	(52)
Sweiss et al.	Rituximab	Humanized monoclonal antibody against CD20	10 patients >5% improvement in FVC (5) improvement by >30 m in 6MWD (5) over 24/52 weeks	(53)
NCT02888080	Canakinumab	Human monoclonal antibody against IL-1 b	Change in PFTs from baseline to week 24/Recruiting	(54)

CD, Cluster of Differentiation; IL, interleukin; ^{18}F-FDG-PET, Fludeoxyglucose (^{18}F) Positron Emission Tomography; FVC, Forced Vital Capacity; PFTs, Pulmonary Function Tests; SUV, Standardized Uptake Value; TNF, Tumor Necrosis Factor; 6MWD, 6 Minute Walk Distance.

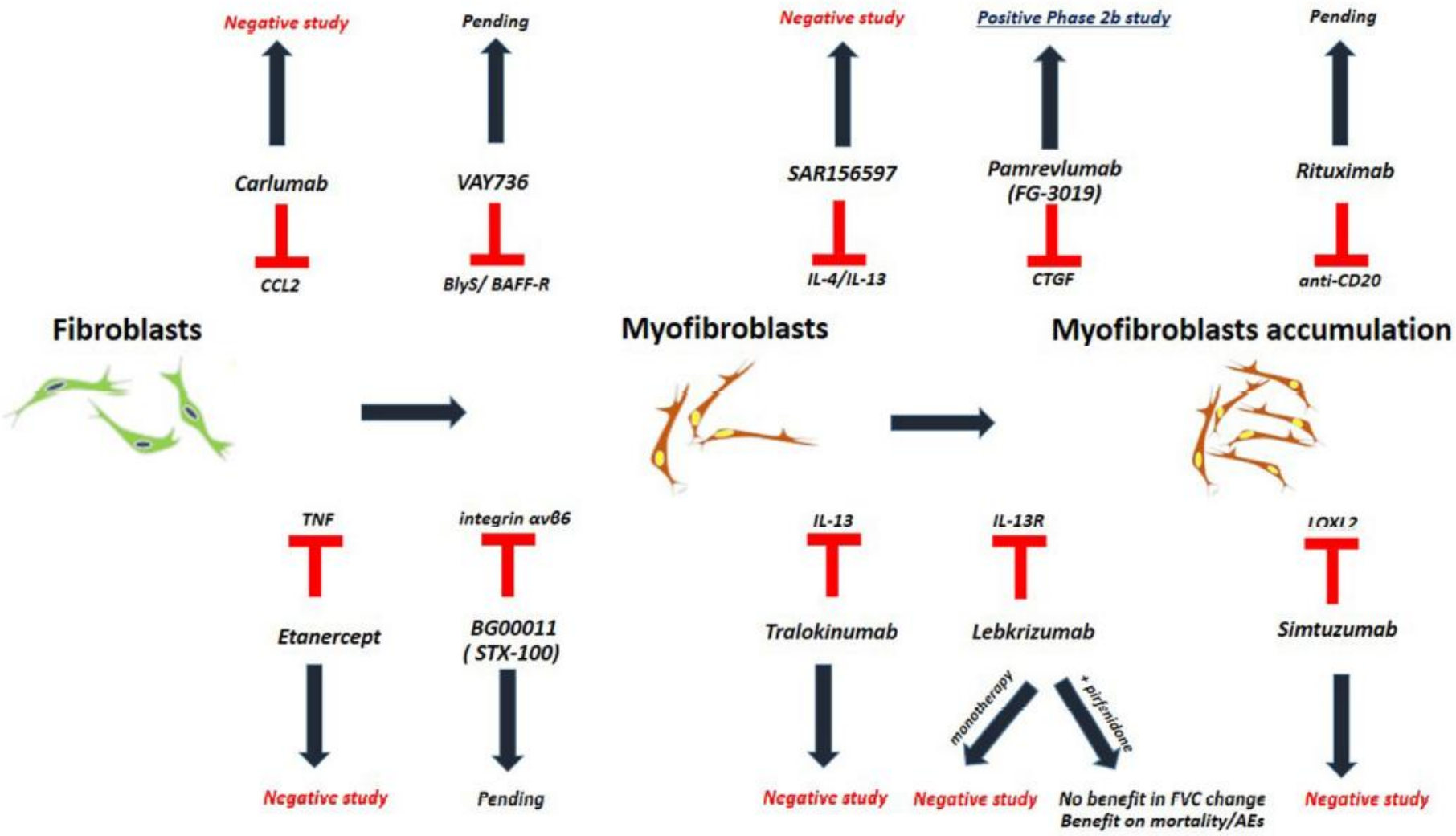

FIGURE 1 | Studies investigating biologic treatments in patients with IPF.

TABLE 3 | Phase 2 clinical trials for biologic treatments in patients with IPF.

Biologic agent	Mechanism of action	Outcome	References
Carlumab	CCL2 inhibitor	Negative study	NCT00786201 (62)
Etanercept	Receptor antagonist of TNF	Negative study	NCT00063869 (63)
Imatinib	Tyrosine kinase inhibitor	Negative study	NCT00131274 (64)
Lebrikizumab	anti- IL13	Monotherapy: Negative study Combination with pirfenidone: Trend for benefit on AE/mortality	NCT01872689 (65–67)
Pamrevlumab (FG-3019)	Monoclonal antibody against CTGF	Positive phase 2 open label trial	NCT01262001 (68)
simtuzumab	Anti-LOXL2	Negative study	NCT01769196 (69)
Tralokinumab	Anti-IL13	Negative study	NCT01629667 (70)
BG00011 (STX-100)	Humanized monoclonal antibody against integrin αvβ6	Pending	NCT01371305 (66)
VAY736	Monoclonal antibody against BlyS/ BAFF-R	Pending	NCT03287414 (71)
SAR156597	Bispecific monoclonal antibody against IL-4 and IL-13	Negative study	NCT02921971 (72)
Rituximab	anti-CD20	Pending	NCT01969409 NCT03286556 (73, 74)

BAFF-R, B cell activating factor; CCL2, chemokine (C-C motif) ligand 2; CTGF, Connective Tissue Growth Factor; IL, interleukin; LOXL2, Lysyl oxidase homolog 2; RCT, Randomized Controlled Trial; TNF, Tumor Necrosis Factor.

Summary

- ILD는 흔한 폐 질환이지만 원인 및 임상경과, 분류가 다양하고 그에 따라 불량한 예후 및 높은 사망률을 보임.
- 특히 ILD AE 혹은 refractory ILD의 경우, mortality가 높지만 스테로이드 치료 이외에 TOC로 선택할 만한 옵션이 많지 않음.
- 최근 CTD-ILD를 포함하여 ILD 치료에 있어 rituximab (RTX)과 같은 Immunomodulatory Tx.의 효용성에 대한 연구들이 진행되고 있음.
- 앞으로 CTD-ILD 뿐만 아니라 넓은 범위의 ILD 급성 악화에서도 이러한 치료가 대안이 될 가능성이 있음.

이에 대한 더 많은 연구와 관심이 필요


박수 한 번 주세요
펭펭!!
발표 들어주셔서
감사합펭!!
펭펭!!
펭펭!!
YullA_PPT