The treatment of rapidly progressing interstitial lung disease in systemic rheumatic diseases

Helder Novais e Bastos

Porto, 2nd July 2026

hnovaisbastos@med.up.pt

Health Research and Innovation
From Lab to Community and back to Lab

Agenda

- How to define rapidly progressing ILD, progressive pulmonar fibrosis and acute exacerbation?
- What are the risk factors for rapidly progressing CTD-ILD?
- What are the evidence for different treatment modalities:
  - Pulse intravenous methylprednisolone
  - Cyclophosphamide
  - Rituximab
  - Intravenous immunoglobulin
  - Calcineurin inhibitors
  - JAK inhibitors
  - Other therapies
- Not talking about oxygen therapy, mechanical ventilation strategies and ECMO

How to define rapidly progressing ILD

Rapidly progressing ILD

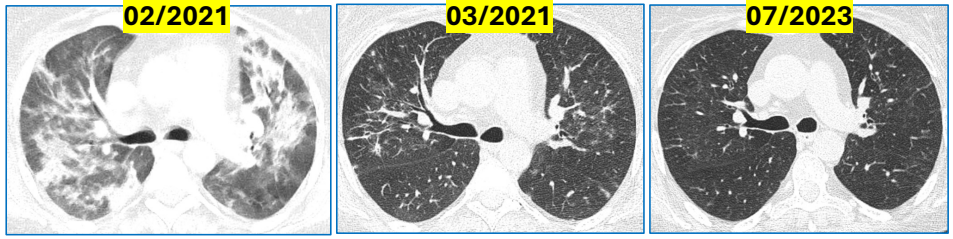
- Rapid progression from breathing room air or a patient's baseline oxygen requirement to a high oxygen requirement or intubation within days to weeks without a documented alternative cause (eg, infection, heart failure).

Johnson et al. Arthritis & Rheumatology 2024

Progressive pulmonary fibrosis

≥2 of the following within 1 year: **(a)** Worsening respiratory symptoms; **(b)** Physiological evidence of disease progression – Absolute decline in (% pred) FVC >5%, or in DLCO >10%; **(c)** Radiological evidence of disease progression.

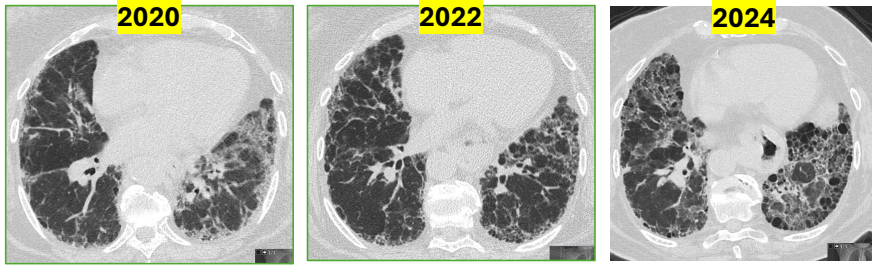
Raghu et al. AJRCCM 2022



Dermatomyositis

HRCT Organizing Pneumonia pattern

Improvement with corticosteroids



Limited cutaneous systemic sclerosis

Familial history of fibrosis (*RTLE1+*, telomeres length percentile <1)

HRCT NSIP-like pattern evolves to UIP

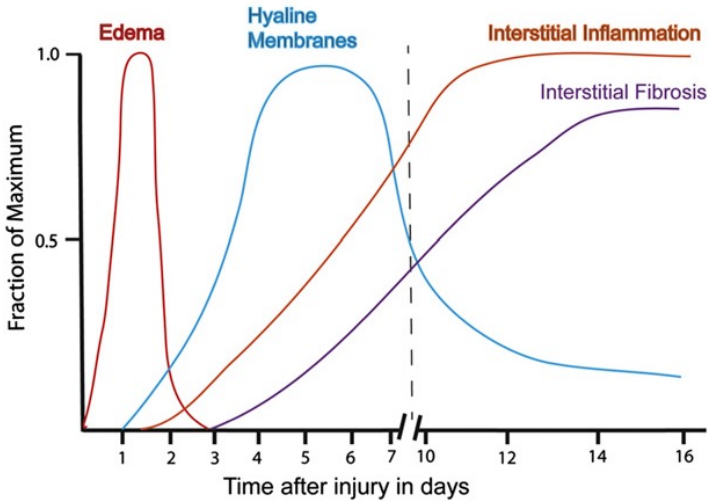
(immunosuppressants toxicity, antifibrotics intolerance)

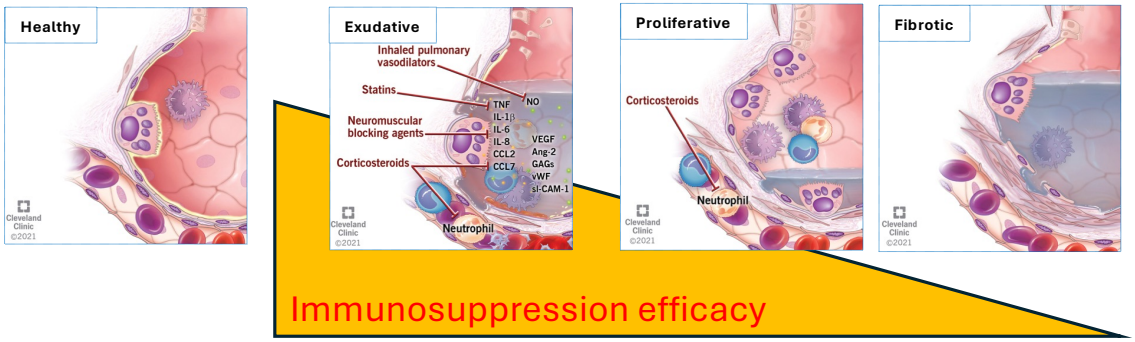
5 years survival

Acute exacerbation (AE-ILD)

New diffuse, bilateral, ground-glass opacification (with or without consolidation) superimposed on a background of chronic fibrotic changes consistent with fibrosing ILDs on HRCT

- Clinical correlation with ARDS
- Histopathological correlation with diffuse alveolar damage (also organising pneumonia)





Potentially reversible causes of worsening ILD

- Pulmonary edema
- Pneumonia
- Aspiration
- Pulmonary hemorrhage
- Pulmonary embolism

AE-ILD potential triggers

- Infection
- Aspiration (GERD)
- Inhalation injury
- Drug toxicity
- Auto-immune flare
- Bronchoscopy ± BAL
- Lung biopsy

Kolb et al. Eur Respir Ver 2018 | Bhargava and Wendt. Translational Research 2012 | Torbic et al. *Journal of Pharmacy Practice* 2024

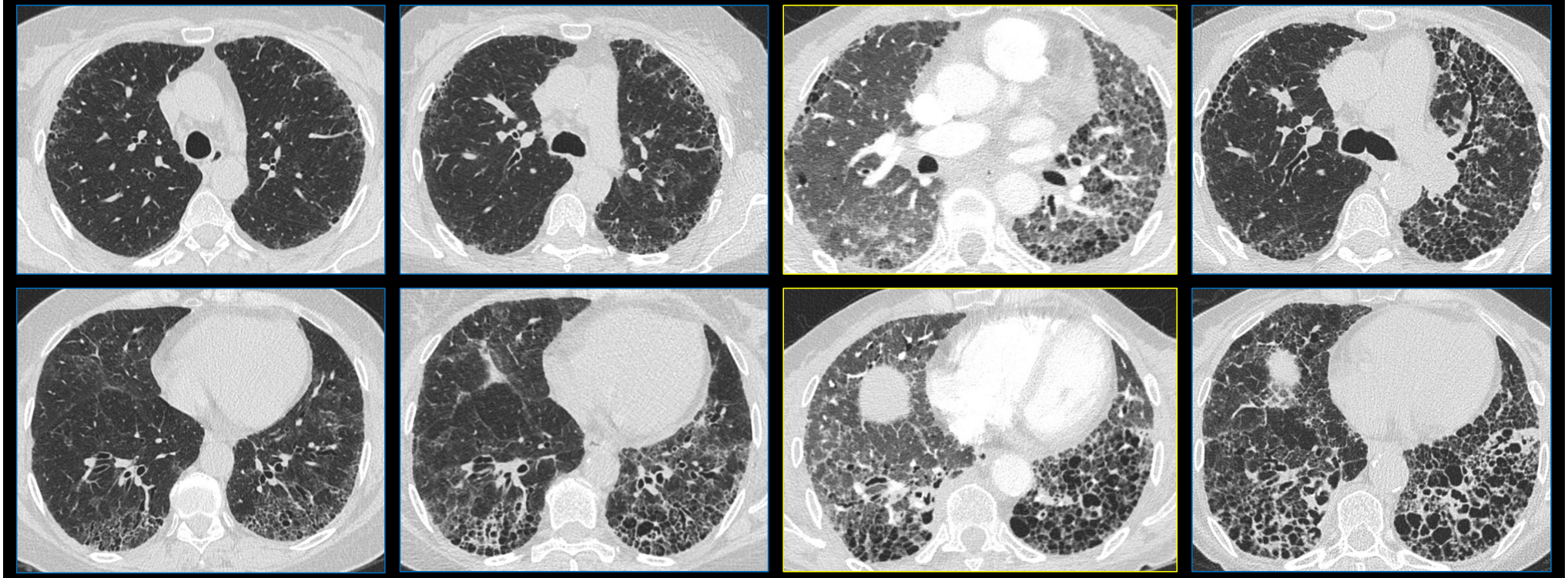
Baseline (2014)	Progressive fibrosis (2019)	Acute exacerbation (2023)	Post-exacerbation (2024)

RA-UIP Methotrexate + steroids → Rituximab → Nintedanib

- FVC 96%, DLCO 53.4%
- 6MWT: 500 m, $SatO_2$ 97 → 92%

- FVC 77.6%, DLCO 29%
- 6MWT: 480 m, $SatO_2$ 96 → 86%

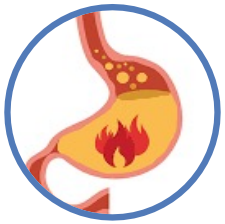
- Steroids, Nintedanib
- Palliation with Oxygen, Morphine
- Stop Rtx (infections, cancer)



Clinical risk factos for progressive ILD

Male gender
Older age

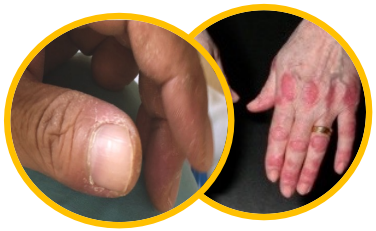
Smoking



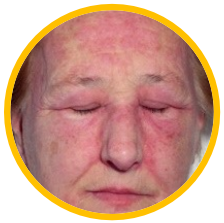
Gastroesophageal reflux disease

Environmental and occupational exposure

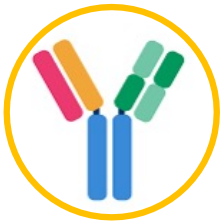
Microbiome



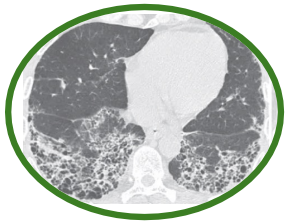
Mechanic's hands & Gottron's papules (IIM)



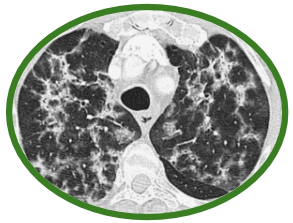
Heliotrope rash (IIM)



Autoimmunity



UIP pattern (RA)

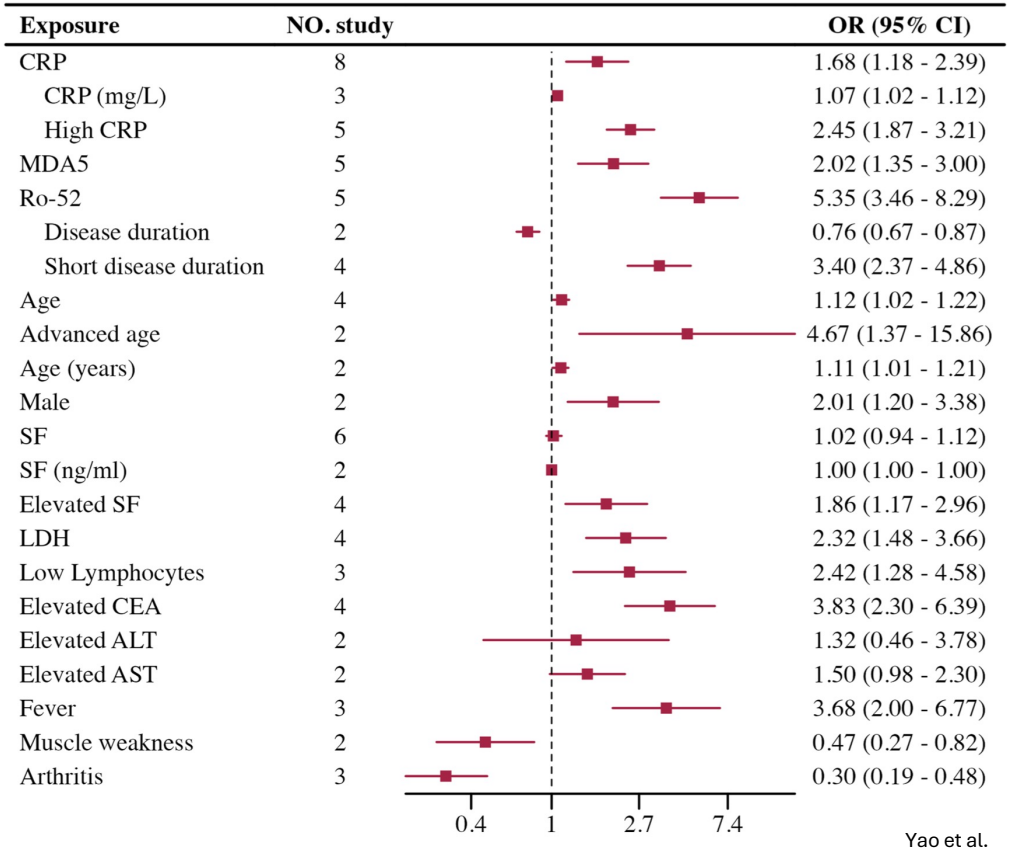


Organizing pneumonia pattern (IIM)

Joy et al. Eur Respir Ver 2023 | Johnson et al. Arthritis & Rheumatology 2024 | Yi et al. Front Immunol 2026

Biomarkers

- Anti-MDA5 (IIM)
- Anti-Ro52
- Anti-Scl-70, IL-6 (SSc)
- Anti-Jo1, anti-PL7, anti-PL12 (antisynthetase syndrome)
- High anti-CCP and RF (RA)
- KL-6, high CRP (CTD-ILD)
- hSP-D
- MMP-7
- CA-125
- etc



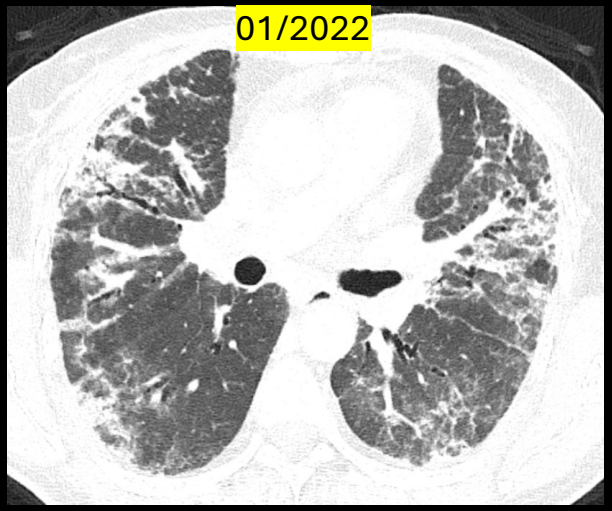
Yao et al.

Lian et al. Chest 2020; Zuo et al. Front Immunol 2022; Gui et al. Rheumatology 2022; Chan et al. BMC Pulm Med 2019; Distler et al. Eur Respir J 2020; Ramahi et al. Rheumatol (Oxford).2023 ; Yao et al. Front Med 2024

RP-ILD is the most serious complication of antisynthetase syndrome

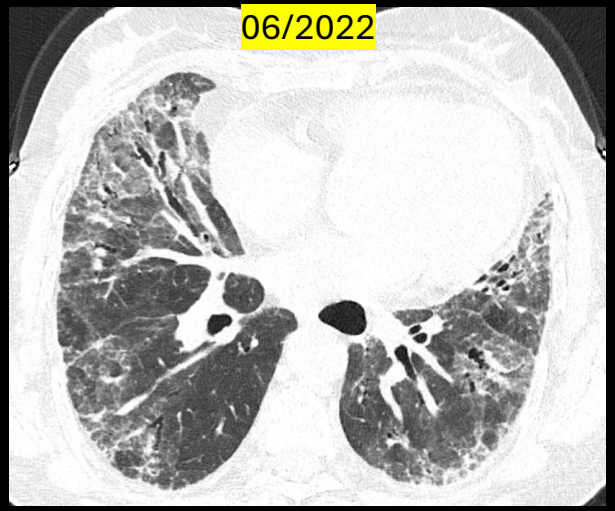
Female patient, 59 years-old
Non-smoker
Fibrosing OP/NSIP pattern, anti-Jo1 antibody

01/2022



- High-dose corticosteroids after pulses
- Cyclophosphamide (4 cycles)
- Rituximab

06/2022



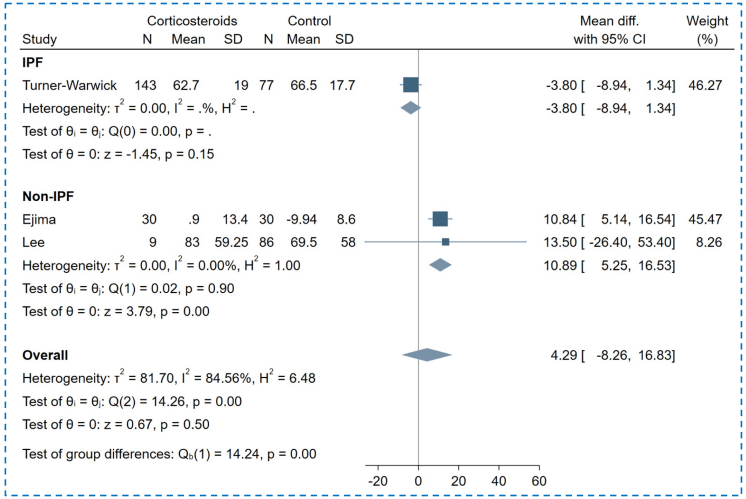
Clinical worsening
Deceased 9 months after diagnosis

Pulse intravenous methylprednisolone

- Rapid onset of action
- No RCTs comparing corticosteroid monotherapy to placebo or standard care
- Oral or IM routes are probably of equivalent efficacy

Pulse corticosteroid therapy provides similar treatment efficacy, earlier reduction in corticosteroid dosage, and a lower incidence of adverse events compared to conventional therapy in patients with anti-ARS ILD.

Kaburaki et al Repir Med 2025



Corticosteroids with **moderate efficacy** measured as change in FVC (% predicted) **in non-IPF fibrotic ILDs**

Pitre T, et al. BMJ Open Respir Res 2023

Protocol

- 500-1000 mg IV MTPDN for 3 days, followed by high-dose oral prednosolone

Monitoring

- Blood pressure
- Serum glucose
- DEXA scan

Prophylaxis

- TMP-SMX
- PPI
- Calcium, vitamin D

Toxicities

- Hyperglycemia, hypertension, mood disturbances, osteoporosis, avascular necrosis
- **Caution in SSc**

Cyclophosphamide

- FVC improvement in SSc (SLS-I, SLS-II, RECITAL)[1-3]
- CYC did not show a survival benefit in patients with acute exacerbation of RA-ILD[4]
- Preferred intravenous over oral administration[5]
  - Less leucopenia, haemorrhagic cystitis and alopecia

Table IV. Specific adverse events of oral and intravenous CYC at end of treatment and end of follow-up evaluations.

	EoT *vs.* BL			FU *vs.* EoT		
	PO CYC (149 pts)	IV CYC (153 pts)	PO *vs.* IV *p*	PO CYC (149 pts)	IV CYC (153 pts)	PO *vs.* IV *p*
Platelet <100000/ul, n (%)	5 (3.4)	0 (0)	0.065	1 (0.7)	0 (0)	0.966
Haemoglobin <8,0 g/dl, n (%)	2 (1.4)	1 (0.7)	0.972	1 (0.7)	1 (0.7)	>0.999
Leukocytes <2500/mm^3, n (%)	32 (22.1)	2 (1.3)	**<0.001**	0 (0)	2 (1.3)	0.515
Gastrointestinal bleeding, n (%)	4 (2.8)	2 (1.3)	0.649	2 (1.5)	1 (0.7)	0.936
Haemorrhagic cystitis, n (%)	8 (5.5)	0 (0)	**0.011**	1 (0.7)	0 (0)	0.989
Cancer new diagnosis, n (%)	2 (1.4)	2 (1.3)	>0.999	6 (4.4)	4 (2.7)	0.647
Oxygen supplementation needed, n (%)	4 (2.7)	12 (8)	0.079	3 (2)	11 (7,2)	**0.049**
Total parenteral nutrition, n (%)	2 (1.4)	0 (0)	0.469	3 (2)	1 (0.7)	0.566
Cardiomyopathy new diagnosis, n (%)	8 (5.4)	15 (9,8)	0.194	3 (2)	5 (3,3)	0.084
Amenorrhoea, n (%)	6 (4)	6 (3.9)	>0.999	0 (0)	0 (0)	N.A.
Alopecia, n (%)	29 (19.5)	2 (1.3)	**<0.001**	1 (0.7)	0 (0)	0.488

BL: baseline visit; CYC: cyclophosphamide; EoT: end of treatment visit; FU: follow-up visit; IV: intravenous; PO: oral.

[1] Taskin et al. NEJM 2006 (SLS-I); [2] Taskin et al. Lancet Respir Med 2016 (SLS-II); [3] Maher et al. Lancet Respir Med 2023; [4] Nakamura et al. Semin Arthritis Rheum 2021; [5] Bruni et al. Clin Exp Rheumatol 2020

Protocol

- 500-750 mg/m^2 IV every 4 weeks for 6 months

Monitoring/Screen

- Screen for HBV, HCV and latent TB infection
- In females, pregnancy test and cervical cancer screening (HPV)
- Complete blood cell counts, liver and kidney blood tests
- Urinalysis

Prophylaxis

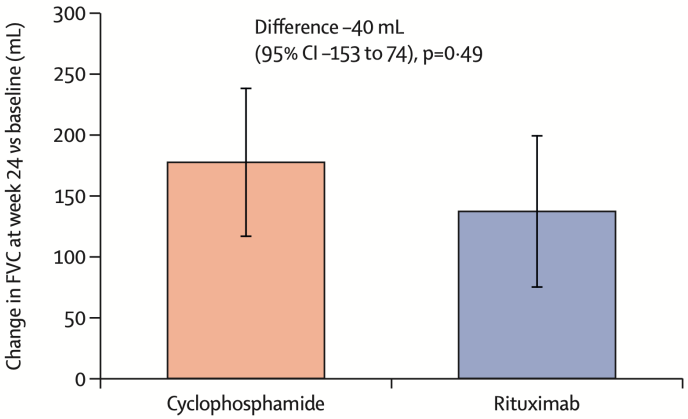
- Contraception
- TMP-SMX

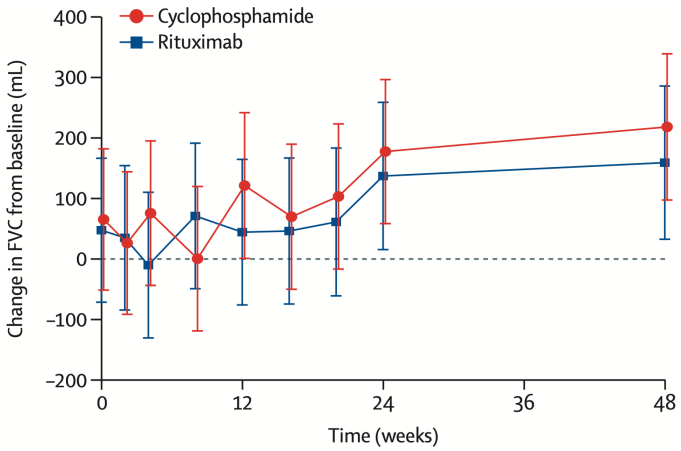
Toxicities

- Cytopenias
- Opportunistic infections
- Gonadal dysfunction
- Teratogenicity
- Hemorrhagic cystitis
- Bladder cancer

Rituximab

- **RECITAL trial** (included 44 IIM, 37 SSc and 16 MCTD)
  - FVC and KBILD QoL scores improvement at 24 weeks (RTX ~ CYC)
  - Lower corticosteroid exposure over 48 weeks of follow-up in RTX group
  - Fewer adverse events were reported by participants receiving RTX





Maher et al. Lancet Respir Med 2023

Protocol

- 500-750 mg/m^2 IV every 4 weeks for 6 months

Monitoring/Screen

- Screen for HBV, HCV and latent TB infection
- Complete blood cell counts
- Urinalysis

Prophylaxis

- Premedication with antihistamines, paracetamol, methylprednisolone
- TMP-SMX (limited data)

Toxicities

- Infusion reactions
- Cytopenias
- Opportunistic infections
- Hypogammaglobulinemia
- Progressive multifocal leukoencephalopathy

Rituximab

RHEUMATOLOGY

Rheumatology 2018;57:2106–2113
doi:10.1093/rheumatology/key213
Advance Access publication 26 July 2018

Original article

Intravenous cyclophosphamide *vs* rituximab for the treatment of early diffuse scleroderma lung disease: open label, randomized, controlled trial

Geetabali Sircar[1], Rudra Prosad Goswami[1], Dipankar Sircar[2], Alakendu Ghosh[1] and Parasar Ghosh[1]

N=60 SSc
RCT 1:1

CYC 500 mg/m2 monthly
RTX 1000 mg 2 doses at 0, 15 days

Adverse event	Rituximab group (30 patients)	CYC group (30 patients)
Upper respiratory tract infections	2 (6.67)	2 (6.67)
Pneumonia	1 (3.34)	4 (13.4)
Urinary tract infections	1 (3.3)	2 (6.67)
Herpes zoster	1 (3.3)	3 (10)
Cholecystitis (requiring cholecystectomy)	1 (3.3)	0
Premature ovarian failure	0	2 (6.67)
Gangrene	0	1 (3.34)
Malignancy	0	1 (3.34)
Leukopenia	0	2 (6.67)
Vomiting	0	4 (13.4)
Transfusion reactions	3 (10)	0

Parameter	Rituximab ($n=30$)			CYC ($n=30$)			Difference at 6 months	
	Baseline, mean (S.D.)	6 months, mean (S.D.)	*P*-value	Baseline, mean (S.D.)	6 months, mean (S.D.)	*P*-value	Mean (95% CI)	*P*-value
Forced vital capacity, %	61.30 (11.28)	67.52 (13.59)	0.002[a]	59.25 (12.96)	58.06 (11.23)	0.496[a]	9.46 (3.01 to 15.90)*	0.003[b]
Forced vital capacity, l	1.51 (0.45)	1.65 (0.47)	<0.001	1.42 (0.49)	1.42 (0.46)	0.356	0.23 (−0.013 to 0.47)**	0.091[b]
Modified Rodnan skin score at baseline	21.77 (9.86)	12.10 (10.14)	<0.001	23.83 (9.28)	18.33 (7.69)	<0.001	−6.23 (−10.88, −1.58)***	0.001[b]
Medsgers severity scale	8.33 (3.04)	4.67 (2.35)	<0.001	9.60 (2.44)	5.96 (2.81)	<0.001	−1.30 (−2.64, 0.04)[#]	0.036[b]
6-min walking test, m	359.63 (65.95)	409.60 (69.29)	<0.001	335.90 (89.30)	349.14 (99.75)	0.428	60.46 (16.07, 104.84)**** [##]	0.001[b]
Pulmonary hypertension present (%)	4 (13)	5 (16)		5 (16)	5 (16)			

Protocol

- 500-750 mg/m^2 IV every 4 weeks for 6 months

Monitoring/Screen

- Screen for HBV, HCV and latent TB infection
- Complete blood cell counts
- Urinalysis

Prophylaxis

- Premedication with antihistamines, paracetamol, methylprednisolone
- TMP-SMX (limited data)

Toxicities

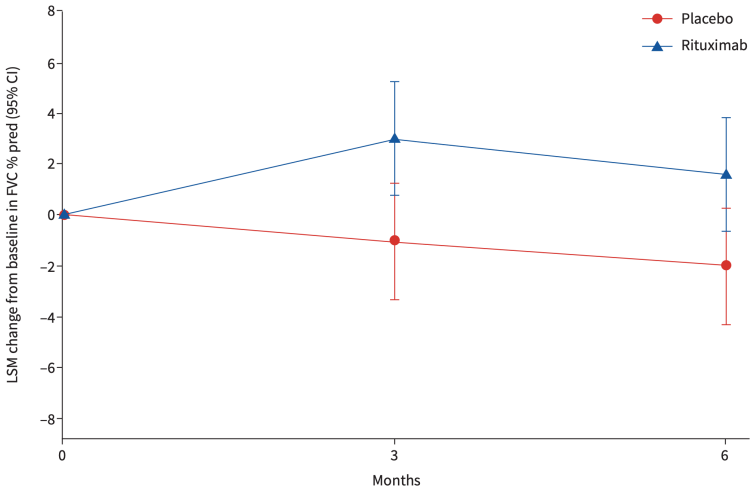
- Infusion reactions
- Cytopenias
- Opportunistic infections
- Hypogammaglobulinemia
- Progressive multifocal leukoencephalopathy

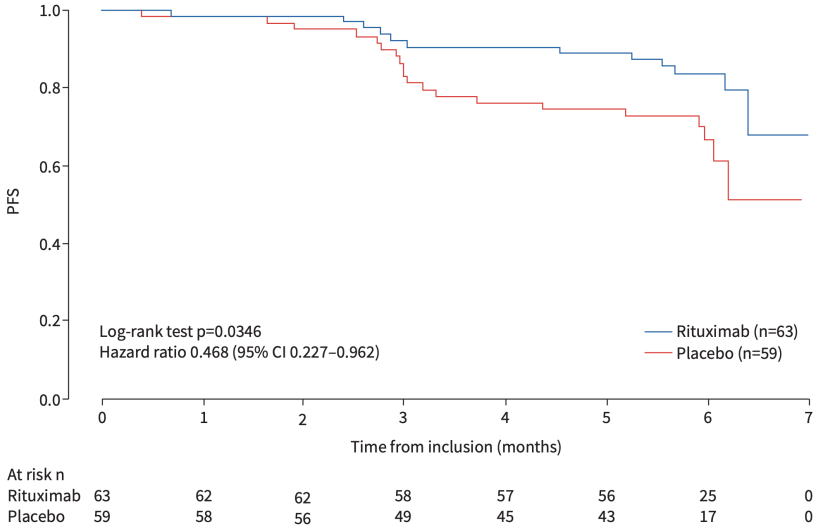
Rituximab and mycophenolate mofetil combination in patients with interstitial lung disease (EVER-ILD): a double-blind, randomised, placebo-controlled trial

Mankikian et al. Eur Respir J 2023

N=122 patients with CTD-ILD or idiopathic NSIP

- PFS was better in the RTX + MMF group (vs placebo + MMF)
- Similar rate of adverse events (41% vs 39%)
- The infections observed with the RTX+ MMF were mainly nonserious viral infections





Intravenous immunoglobulin (IVIG)

- Limited data
- Lower infection risk
- Improved survival in MDA5+ DM with rapidly progressive ILD
- But, limited supply and costly

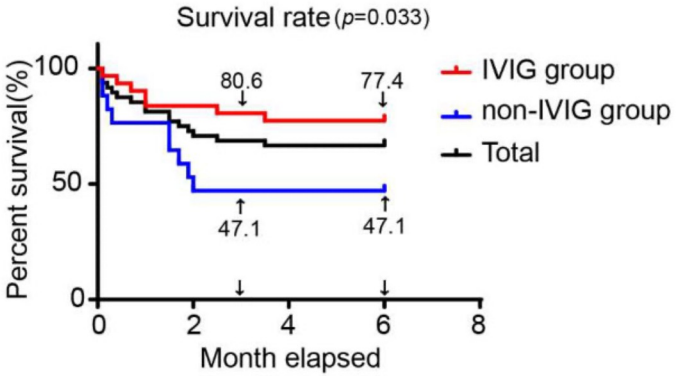
RHEUMATOLOGY
Rheumatology 2022;61:3704–3710
https://doi.org/10.1093/rheumatology/keab928
Advance Access publication 23 December 2021

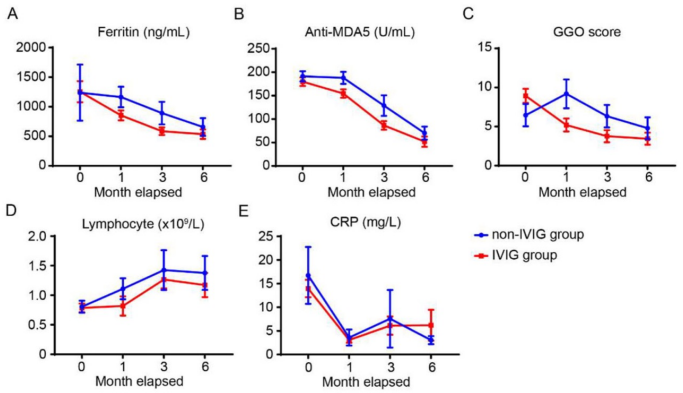
Original article

Intravenous immunoglobulin for interstitial lung diseases of anti-melanoma differentiation-associated gene 5-positive dermatomyositis

Li-Mei Wang [1], Qi-Hua Yang, Lei Zhang [1], Sheng-Yun Liu[1], Pan-Pan Zhang [1], Xin Zhang[1], Xiao-Jun Liu[1], Li-Shuai Han[1] and Tian-Fang Li[1]

- All patients were treated with high-dose GC and immunosuppressants initially within one week after diagnosis
- In the IVIG group, the treatment started within one week of diagnosis with a dose of **IVIG at 400 mg/kg/day for 5 consecutive days** in the first course, and additional courses were applied **2–4 weeks later**





Protocol

- 2 g/kg IV divided over 2-5 days, repeat 4 weeks

Monitoring/Screen

- IgA
- Renal function
- Anaphylaxis during infusion (IgA-deficient)
- Thromboembolic events

Prophylaxis

- Prehydration
- Sometimes premedication needed (paracetamol, NSAIDs, corticosteroids)

Toxicities

- Aseptic meningitis
- Venous thromboembolism
- Renal insufficiency
- Hemolytic anemia

Calcineurin inhibitors (CNI)

Protocol

- Cyclosporine 3mg/kg/day PO (target trough levels 100-150 ng/mL)

Protocol

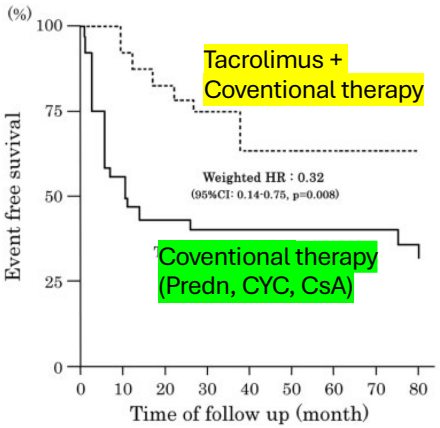
- Tacrolimus 0.075mg/kg/day PO (target trough levels 5-10 ng/mL)

- Observational studies suggest improved survival in IIM-ILD (no-RP-ILD)
- Lower evidence compared to RTX, CYC or MMF
- Tacrolimus may be better tolerated and more effective than cyclosporine

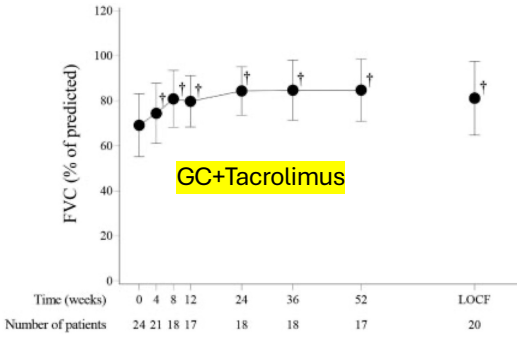
Monitoring/Screen

- Blood pressure
- Complete blood cell counts, renal function, uric acid, magnesium, potassium, lipid profile

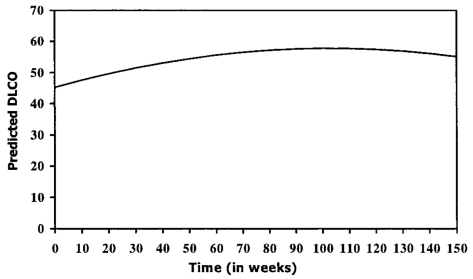
Addition of tacrolimus improved the prognosis, FVC and DLCO in IIM-related ILD



Kurita et al. Rheumatology 2015



Takada et al. Rheumatology 2020

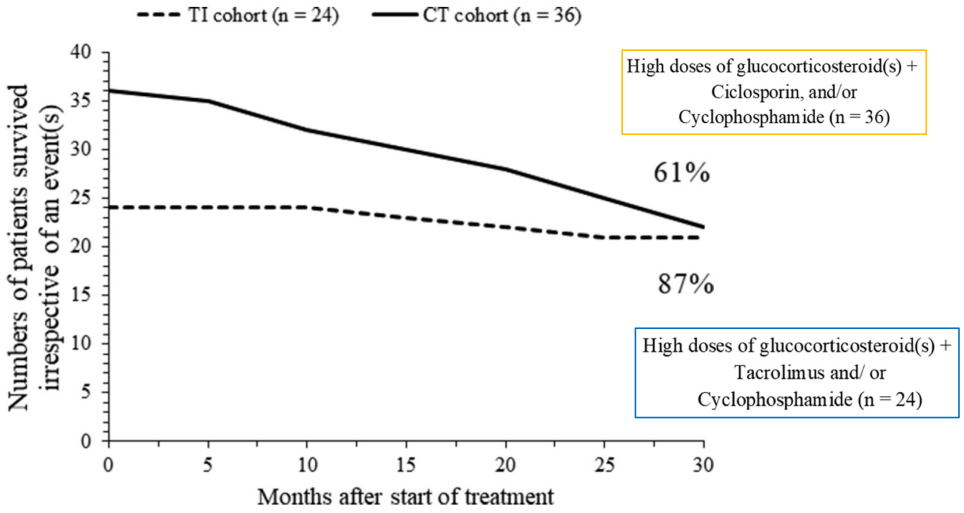


Wilkes et al. Arthritis Rheum 2005

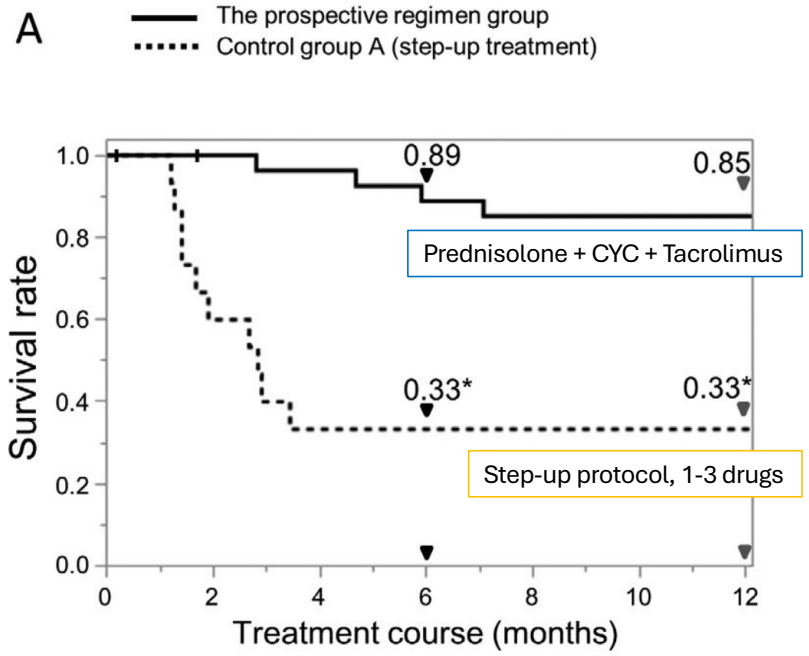
Toxicities

- Infection
- Hypertension
- Nephrotoxicity, hyperkalemia
- Hepatotoxicity
- Neurotoxicity
- Gingival hyperplasia, hirsutism
- Thrombotic microangiopathy
- Malignancy

The combination of Tacrolimus to high doses GC with CYC had good results in treatment for severe DM-ILD



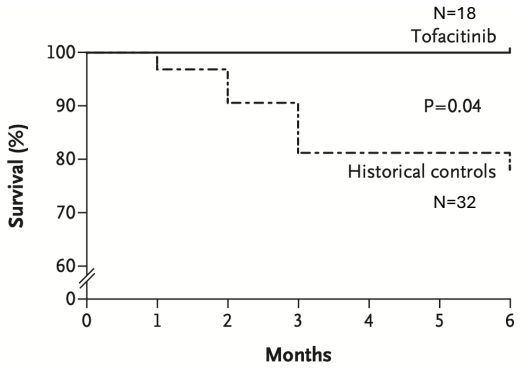
Li et al. Medicine 2022



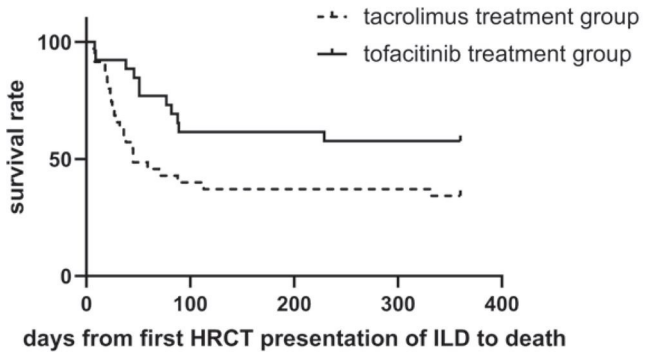
Tsuji et al. Arthritis & Rheum 2020

JAK inhibitors (JAKi)

- Observational studies suggest effectivenesse in MDA5-ILD
- Lower evidence compared to RTX, CYC or MMF
- Metanalysis reports reduced risk all-cause mortality (Wang et al. Ther Adv Respir Dis 2024)
  - RR 0.61, n=148 tofacitinib vs n=90 controls)
- Potential rescue option after failure of conventional treatment (Kurasawa et al. Rheumatology 2018)



Chen et al. NEJM 2019



Fan et al. J Rheumatol 2022

Protocol

- Tofacitinib 5 mg PO bid, or 11 mg extended-release PO id

Monitoring/Screen

- Screen for HBV, HCV and latent TB infection
- Complete blood cell counts, renal, liver and lipid profile

Prophylaxis

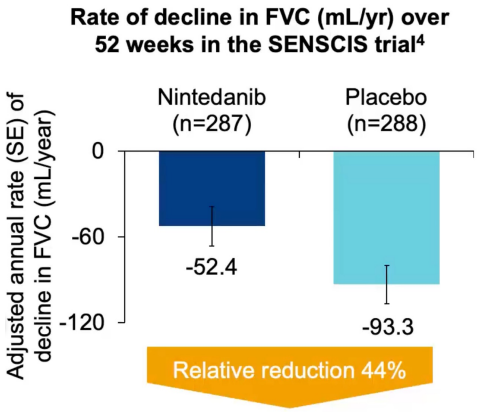
- HZV vaccine
- Contraception

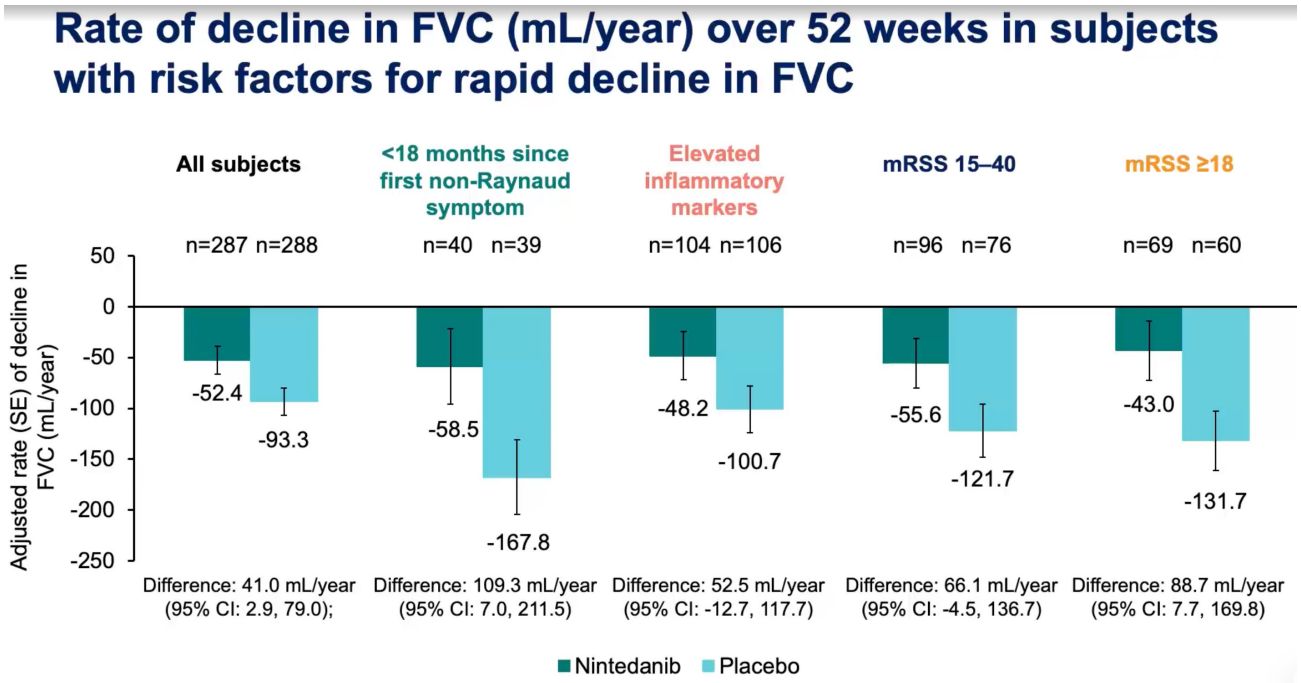
Toxicities

- Leukopenia
- Herpes zoster
- Gastrointestinal perforation
- Major adverse cardiovascular events
- Malignancy

Antifibrotic Nintedanib reduce incidence of RP-ILD

in Systemic sclerosis

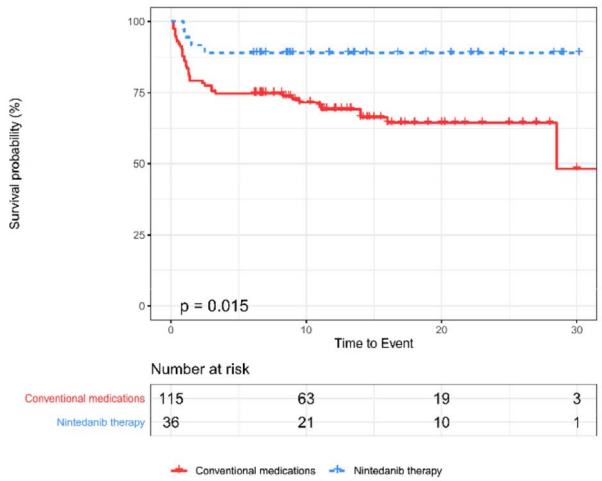




Khanna et al. RMD Open. 2023

Antifibrotic Nintedanib reduce incidence of RP-ILD

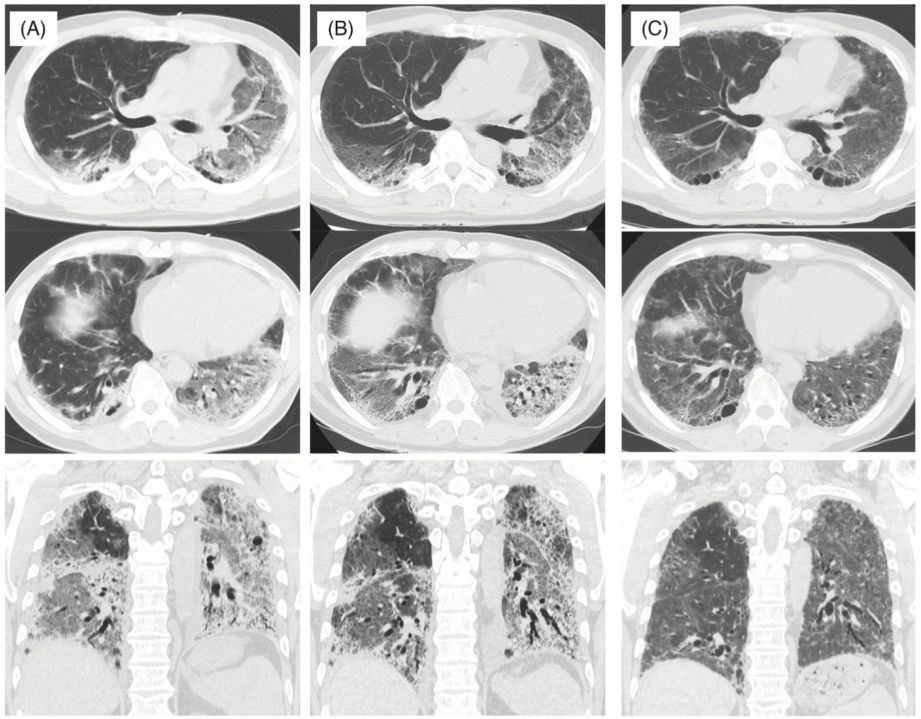
in Idiopathic Inflammatory Myopathy

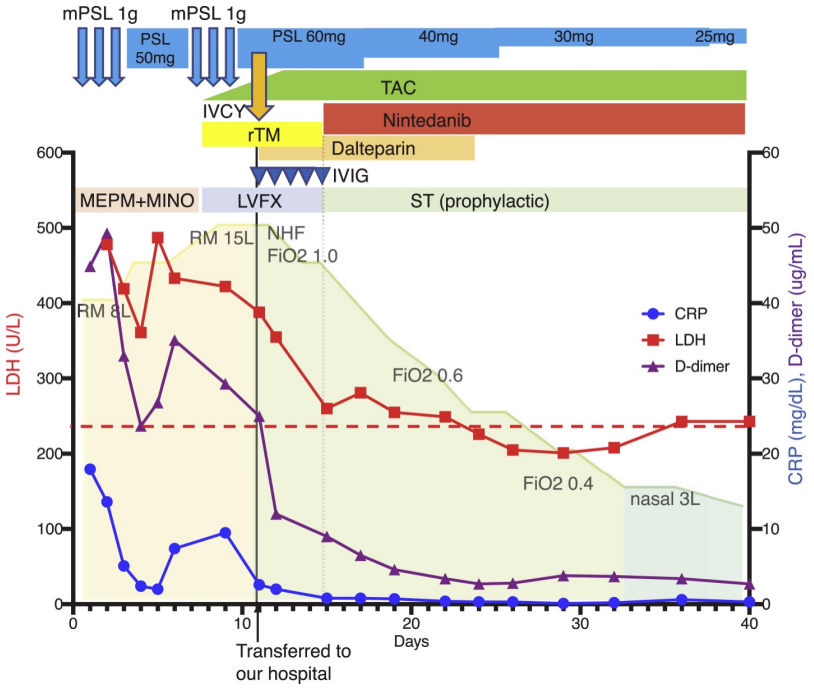


Factors	Before propensity score matching			After propensity score matching		
	P-value	OR value	95%CI	*P*-value	OR value	95% CI
Therapies						
Steroid monotherapy	0.411	1.001	0.999~1.004	0.555	1.001	0.998~1.003
Steroid + DMARDs	0.167	0.561	0.247~1.274	0.026	0.345	0.135~0.882
Steroid + IVIG	0.015	3.492	1.273~9.579	0.002	5.625	1.845~17.153
Steroid + DMARDs + IVIG	0.961	0.967	0.257~3.644	0.783	0.800	0.163~3.917
Maximum dosage of steroid[a]	0.363	1.001	0.998~1.005	0.527	1.001	0.998~1.004
Nintedanib	0.030	0.192	0.043~0.851	0.025	0.179	0.040~0.808

Liang et al. Front. Med. 2021

Case of fulminant onset RP-ILD with anti-PL-7 antibodies treated with Nintedanib

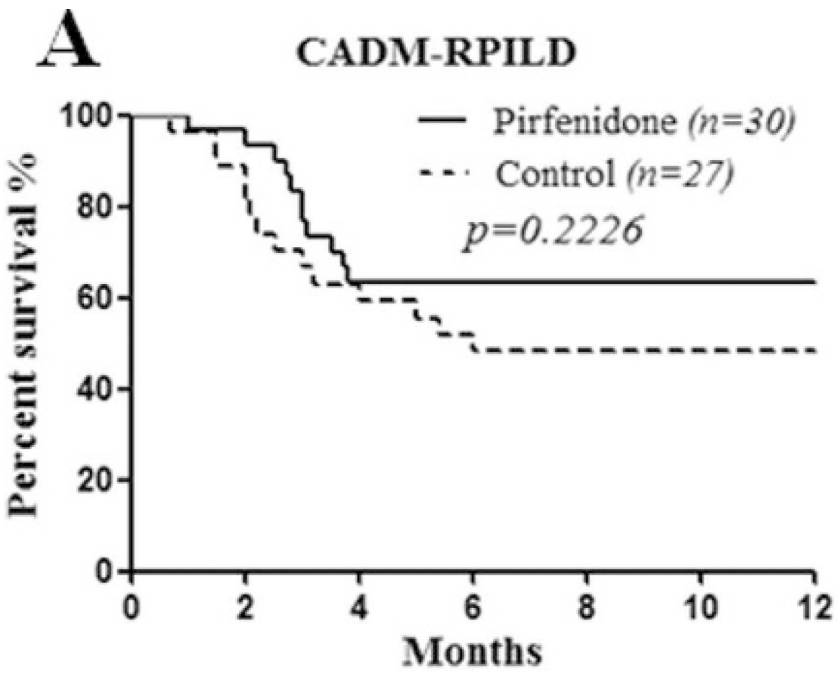


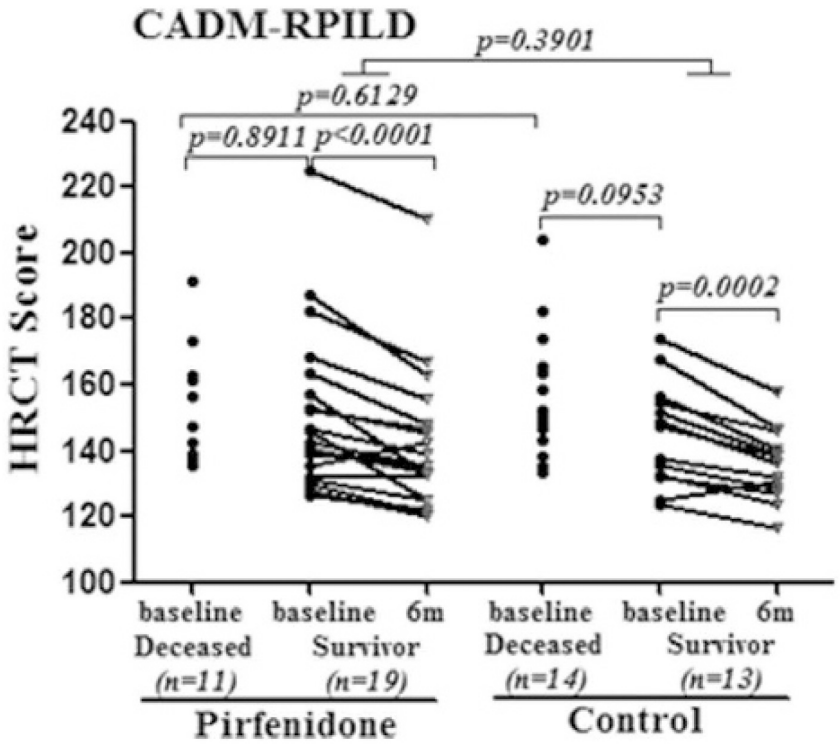


mPSL: methylprednisolone, PSL: prednisolone, IVCY: intravenous cyclophosphamide, TAC: tacrolimus, rTM: recombinant thrombomodulin, IVIG: intravenous immunoglobulin
MEPM: meropenem, MINO: minocycline, LVFX: levofloxacin, ST: sulfamethoxazole-trimethoprim

Yanagihara et al. Respiratory Medicine Case Reports 2020

RP-ILD associated with clinically amyopathic dermatomyositis
with Pirfenidone add-on over CS+IS





Li et al. Scientific Reports 2016

Special situations

- **Mycophenolate** (when concerns about cyclophosphamide toxicity) [1-4]
- **Plasma-exchange** (salvage therapy; avoid combination with RTX or IVIG) [5]
- **Stem cell transplantation** (may have a role in select cases of SSc-ILD) [6]
- **Lung transplantation** (referral criteria[7]):
  - UIP pattern
  - FVC <80% or DLCO <40% and PPF criteria
  - Resting or exertional oxygen requirement

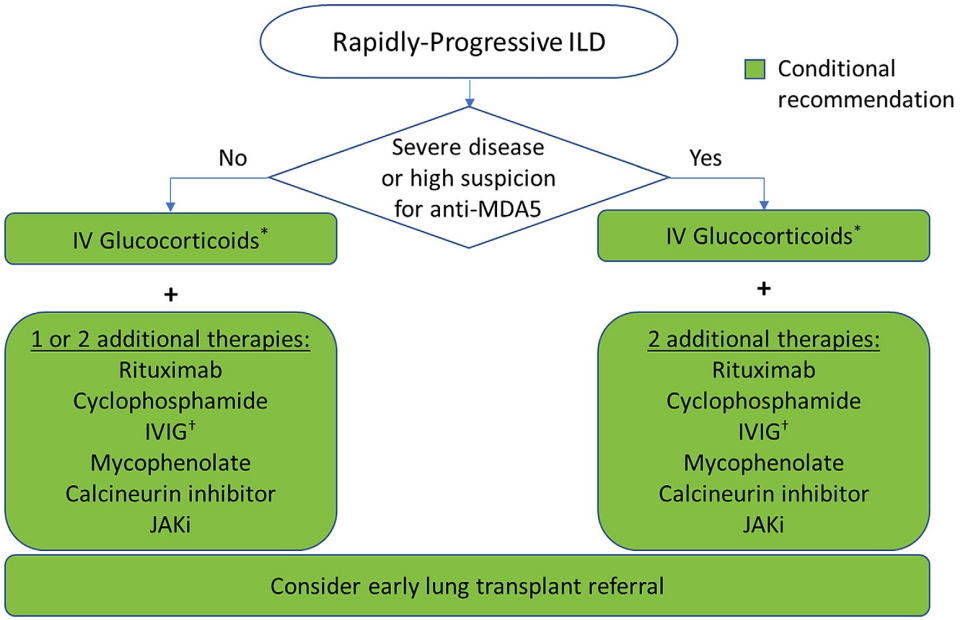
[1] Papoulos et al. Lung 2013; [2] Shenoy et al. Arthritis Res Ther 2016; [3] Tashkin et al. Chest 2017; [4] Volkmann et al. Ann Rheum Dis 2019; [5] Abe et al. Rheumatology (Oxford) 2020; [6] Sullivan et al. NEJM 2018

Summary of recommendations

- GC are a pillar due to rapid onset action
- Avoid long-term use of high-dose CS
- Combination therapy is better than monotherapy
- If anti-MDA5 suspected (see risk factors), triple treatment is usual preferred, for example:
  - GC + CYC + tacrolimus
  - GC + RTX + IVIG (±MMF)
- Promising data for Tofacitinib add-on and for antifibrotics (Nintedanib > Pirfenidone)
- Limited/conflicting data for plasma-exchange or stem cell transplantation (salvage therapy)

2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) Guideline for the Treatment of Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Diseases

Johnson et al. Arthritis & Rheumatology 2024



FIBRALUNG

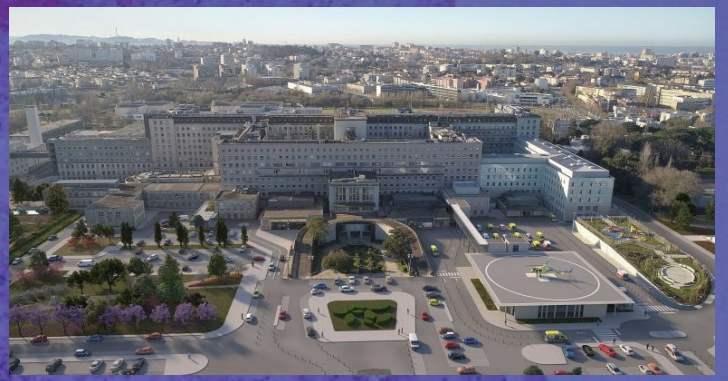
FIBROSING **INTERSTITIAL LUNG DISEASES**

<u>Clinical team</u>

António Morais (CHUSJ)
Patrícia Mota (CHUSJ)
Filipa Aguiar (CHTS)
Catarina Cardoso (CHUSJ)
David Coelho (CHUSJ)
André Terras (CHUSJ)
Natália Melo (CHUSJ)
Inês Neves (ULSM)
Susana Guimarães (CHUSJ)
Conceição Souto Moura (CHUSJ)
André Carvalho (CHUSJ)
Pedro Fernandes (CHUSJ)

<u>Lab team</u>

Andreia Coelho (i3S)
Rita F. Santos (i3S)
Mariana Resende (i3S)
Margarida Saraiva (i3S)
Oksana Sokhatska (FMUP)
Marília Beltrão (FMUP)
Luís Delgado (FMUP)
Melany Gonçalves (i3S)



Funding

FCT Fundação para a Ciência e a Tecnologia
MINISTÉRIO DA CIÊNCIA, TECNOLOGIA E ENSINO SUPERIOR

FUNDAÇÃO AMÉLIA DE MELLO desde 1964
JOSÉ DE MELLO SAÚDE
BOLSA D. MANUEL DE MELLO

SPP SOCIEDADE PORTUGUESA DE PNEUMOLOGIA

SÃO JOÃO HOSPITAL

FACULDADE DE MEDICINA DO PORTO 1825

FIBRALUNG.PT