ILD Collaborative

Project ECHO

Rheumatoid arthritis-associated ILD: Update on treatment approaches

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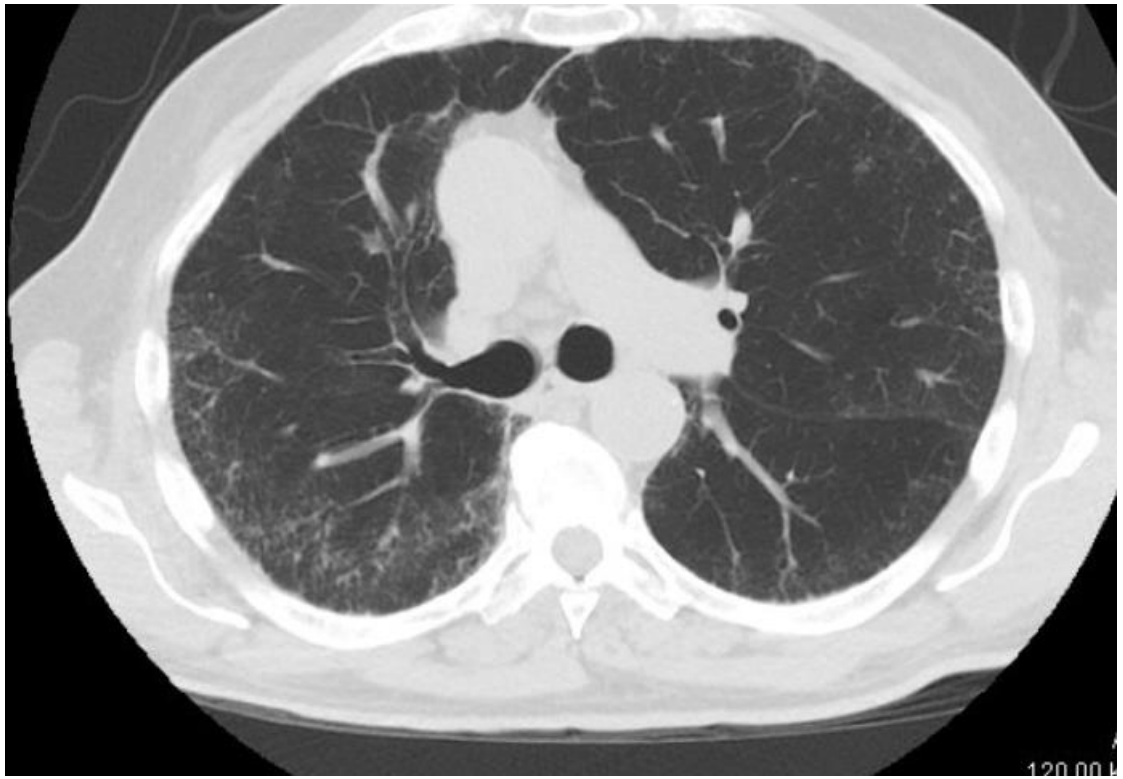
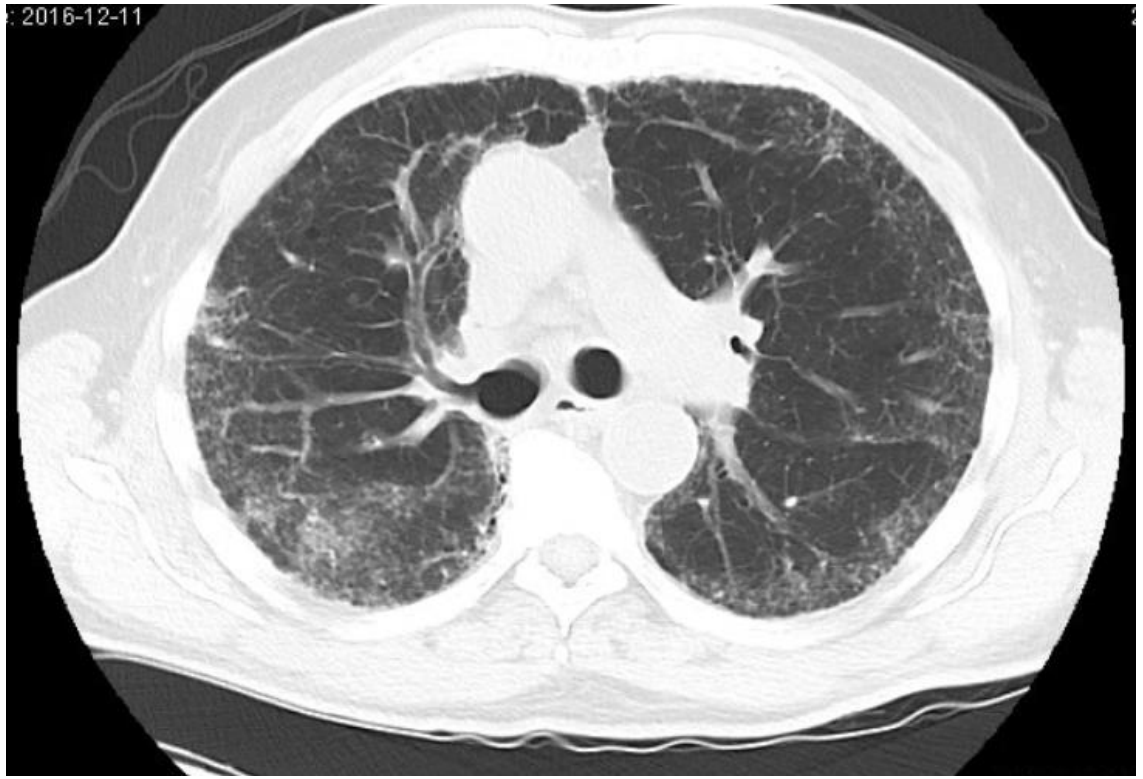
Disclosures

- Speaking and consulting fees from Boehringer Ingelheim
- Research trials with Boehringer, Genentech, Galapagos, Hoffmann-La Roche, Nitto Denko, Vicore
- Authorship fees from UpToDate, Dynamed

73 M with long-standing seropositive RA





Joint pain minimal on prednisone 5 daily, hydroxychloroquine

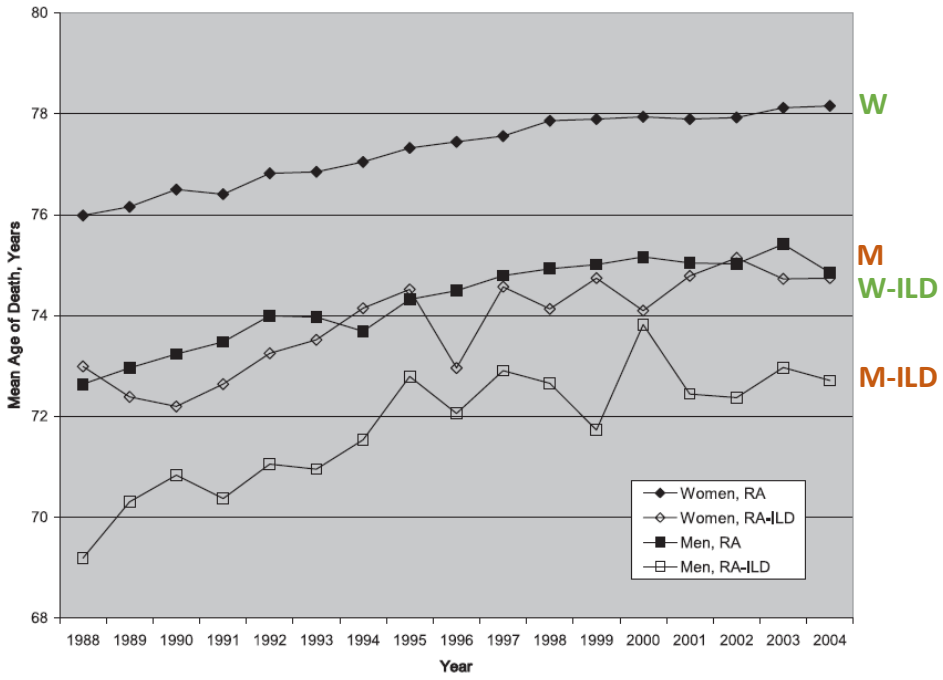
ILD is common in patients with RA

- Reported prevalence of clinically significant RA ranges from 2-15%
- Incidentally found in up to 50% of autopsy cases
- ILD precedes the diagnosis of RA in at least 14% of patients
- ILD develops within the first year of RA diagnosis in 33% of patients

Koduri et al. *Rheumatology (Oxford).* 2010;49(8):1483-9.
Bongartz et al. *Arthritis Rheum.* 2010;62(6):1583-91.
Hyldgaard et al. *Ann Rheum Dis*. 2017;76(10):1700-6.
Raimundo et al. *J Rheumatol.* 2019;46(4):360-9.

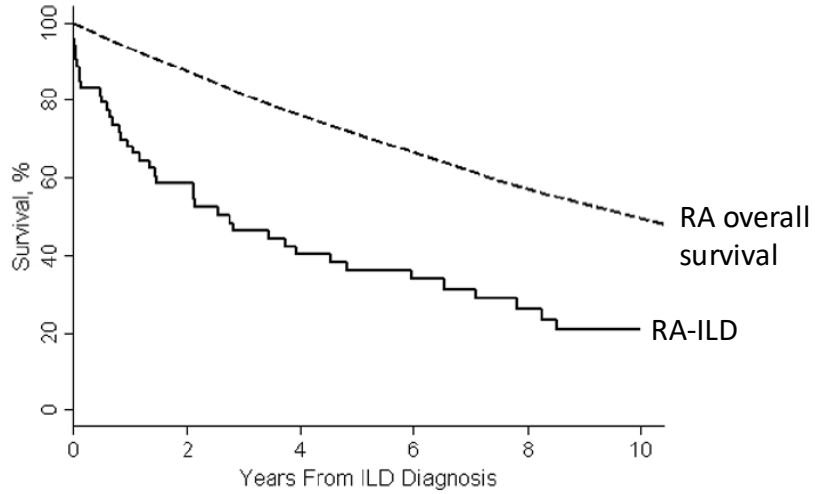
ILD is associated with death in RA

- Natl Ctr Health Stats 1988-2004
- ILD was the leading cause of death (35.3%)
- "RA complications" second leading cause (35%)



Olson et al. *Am J Respir Crit Care.* Med Vol 183. pp 372–378, 2011

- 582 pts with RA, 603 pts without RA followed a mean of 16.4 /19.3 yrs
- 7.7% developed ILD, with a lower median survival than expected (2.6 vs 9.9 yrs)
- ILD HR for death 2.86



Bongartz et al. *Arthritis Rheum.* 2010 June ; 62(6): 1583–1591.

Risk Factors for developing ILD and ILD *progression* in RA

- Advanced age
- Male sex
- RA duration
- Smoking history
- Disease severity
- HLA allele variants
- Elevated antibody titers: RF, CCP

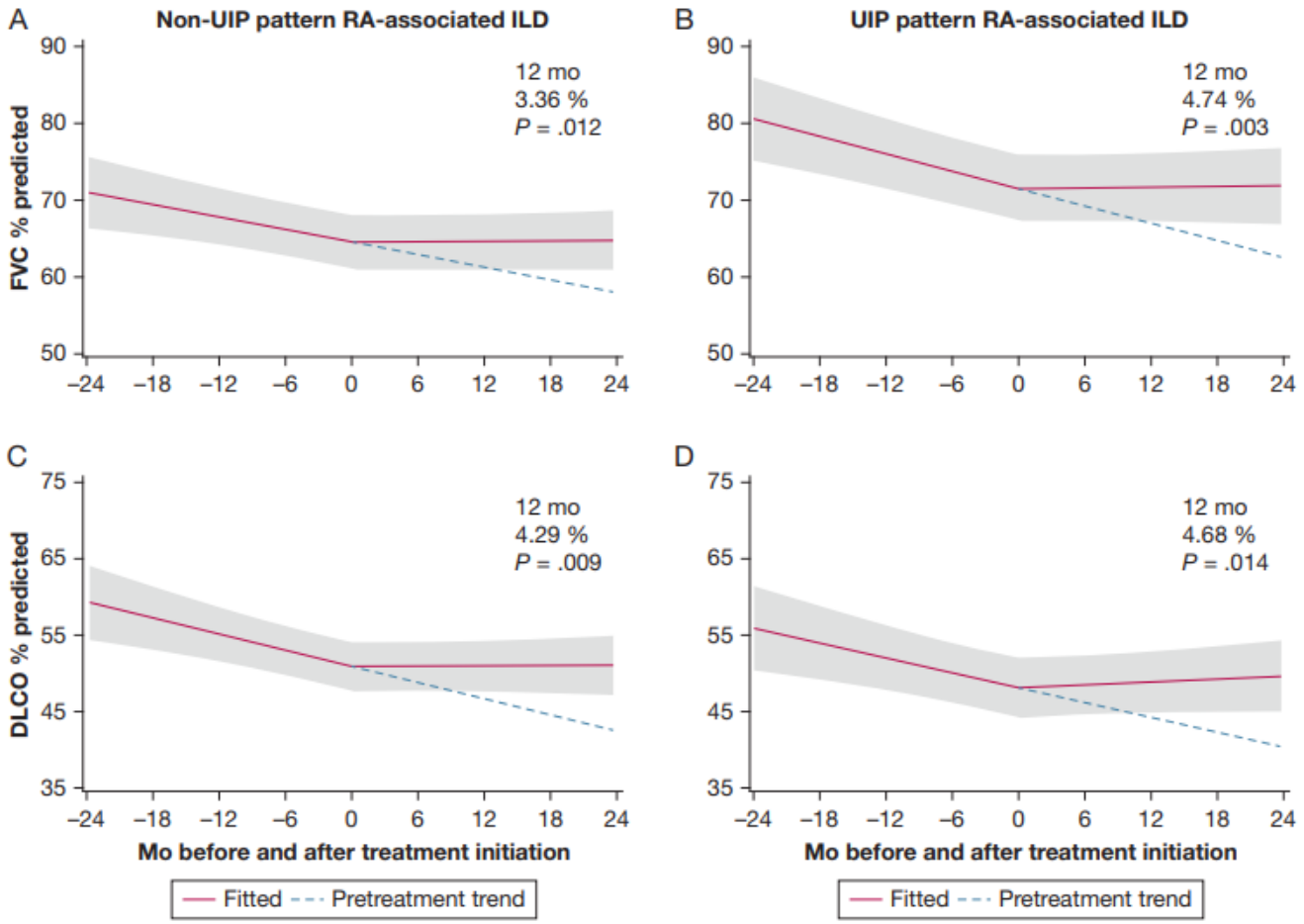
Kur-Zalewska et al. *PLOS ONE* April 16, 2021.
Hallowell and Horton. *Drugs* (2014) 74:443–450.

Immunosuppression can be useful in RA-ILD, regardless of the radiographic pattern

- Retrospective study of 212 patients
- 92 AZA; 77 MMF; 43 RTX
- No difference between treatment groups

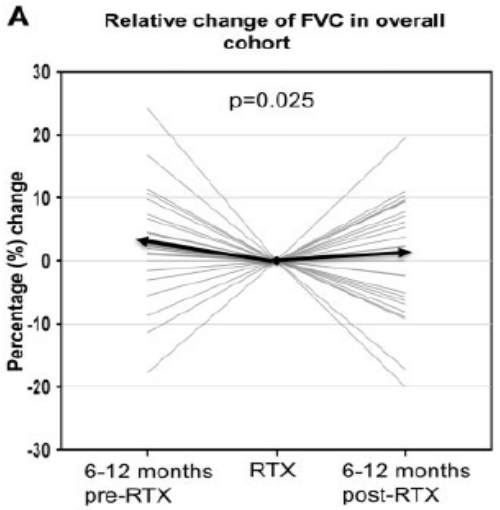
Concurrent therapy

Prednisone	67.9%
HCQ	26.4%
Leflunomide	13.7%
Methotrexate	11.8%
Infliximab	7.1%
Sulfasalazine	6.1%
Etanercept	5.7%
Abatacept	4.7%
Adalimumab	3.8%
Tofacitinib	1.9%

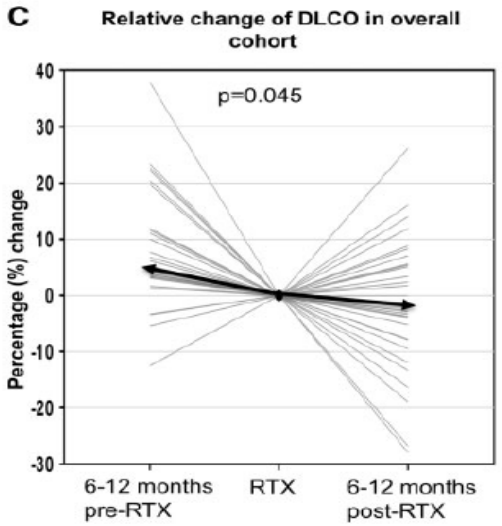


Matson et al. *Chest*. 2023; 163(4):861-869

Rituximab for RA-ILD



Impact on FVC
-2.4% vs +1.2%
(P = 0.025)



Impact on DLCO
-4.4% vs -1.3%
(P = 0.045

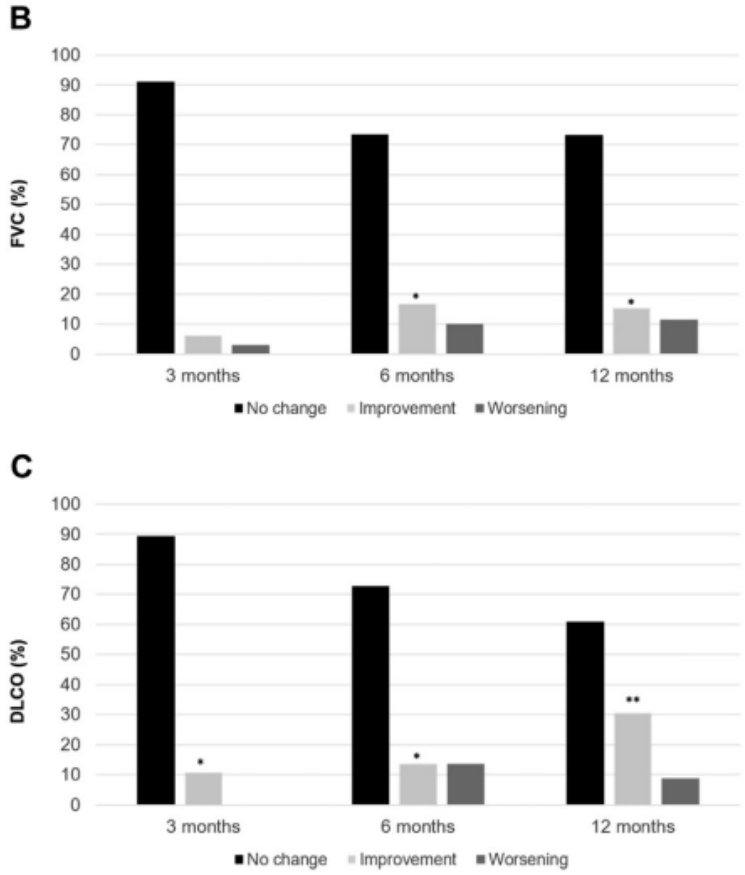
52% stabilized; 16% improved

- Retrospective study, 44 RA-ILD pts
  60% NSIP; 36% UIP
- Prior treatments
  TNFα-i 29%
  CyC 18%
- Concurrent treatment
  MTX 78%
  AZA 14%
  LEF 5%
  MMF 3%

Yusof et al. *Rheumatology* 2017;56:13481357

Abatacept for RA-ILD

- Open-label registry study
- 63 RA-ILD patients receiving ABA



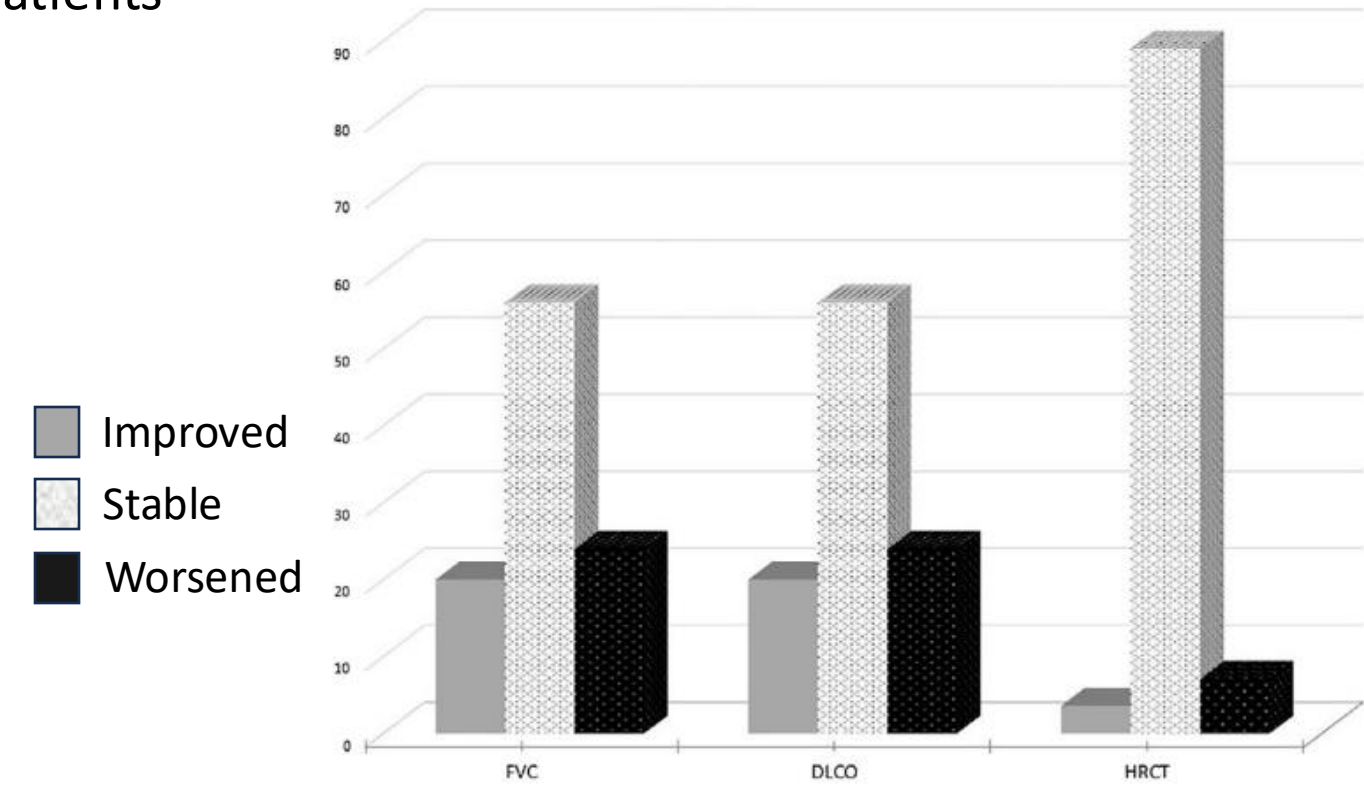
- Prospective observational study
- 57 RA-ILD patients who received ABA

Variable	Baseline	12 Months	End of Follow-Up
Overall progress of lung disease **			
Improvement, n (%)	3 (5.3) *	7 (13.7)	6 (10.5)
Stabilization, n (%)	28 (48.4) *	34 (66.6)	35 (61.4)
Worsening, n (%)	26 (45.6) *	10 (17.5)	13 (22.8)
Death, n (%)	-	-	3 (5.3)

Fernandez-diaz et al. *Sem in Arthr and Rheum* Volume 48, Issue 1, August 2018, Pages 22-27

Tocilizumab for RA-ILD

- Multi-center, retrospective study of RA-ILD patients
- 28 received at least one dose of Toci
- Mean f/u was 30 months



Manfredi et al. *Internal Medicine Journal* 50 (2020) 1085–1090

IVIG as adjunct therapy for RA-ILD

- Prospective pilot study of RA-ILD patients over 52 wks
- 40 received standard care
  (prednisone 40 mg/d with taper to 10 mg + MTX)
- 40 received standard care + IVIG
- Propensity score matching in a 1:1 ratio:
  (age, sex, FVC, severity of ILD, ESR)

Characteristic	Control group ($n=30$)	Immunoglobulin group ($n=30$)	p
CAT score (mean ± SD)			
Pre-	22.7 ± 2.6	21.8 ± 3.0	.43
Post-	19.1 ± 3.3	17.7 ± 3.4	.03
p	.01	<.001	
Distance of 6MWD (mean ± SD)			
Pre-	265.6 ± 42.4	266.5 ± 46.7	.93
Post-	332.3 ± 55.1	364.4 ± 54.3	.04
p	.02	<.001	
FVC (mean ± SD)			
Pre-	58.7 ± 11.5	57.3 ± 13.1	.85
Post-	66.6 ± 11.2	78.8 ± 12.6	.05
p	.05	.01	
HRCT score (mean ± SD)			
Pre-	9.2 ± 2.5	9.5 ± 1.9	.56
Post-	7.6 ± 1.6	6.0 ± 1.5	.04
p	.04	.01	
ESR (mean ± SD)			
Pre-	39.2 ± 14.6	38.4 ± 13.8	.85
Post-	14.1 ± 6.2	7.4 ± 3.3	.045
p	.01	<.001	

Pirfenidone for (RA-ILD) TRAIL1

- Phase 2 RCT at 34 centers
- Failed to meet its recruitment goal due to COVID
- 123 patients randomized (goal 270)
- Primary composite endpoint
  (10% FVC decline or death) not met

- Pirfenidone associated with slower estimated annual rate of FVC decline (–66 *vs* –146; p=0·0082)

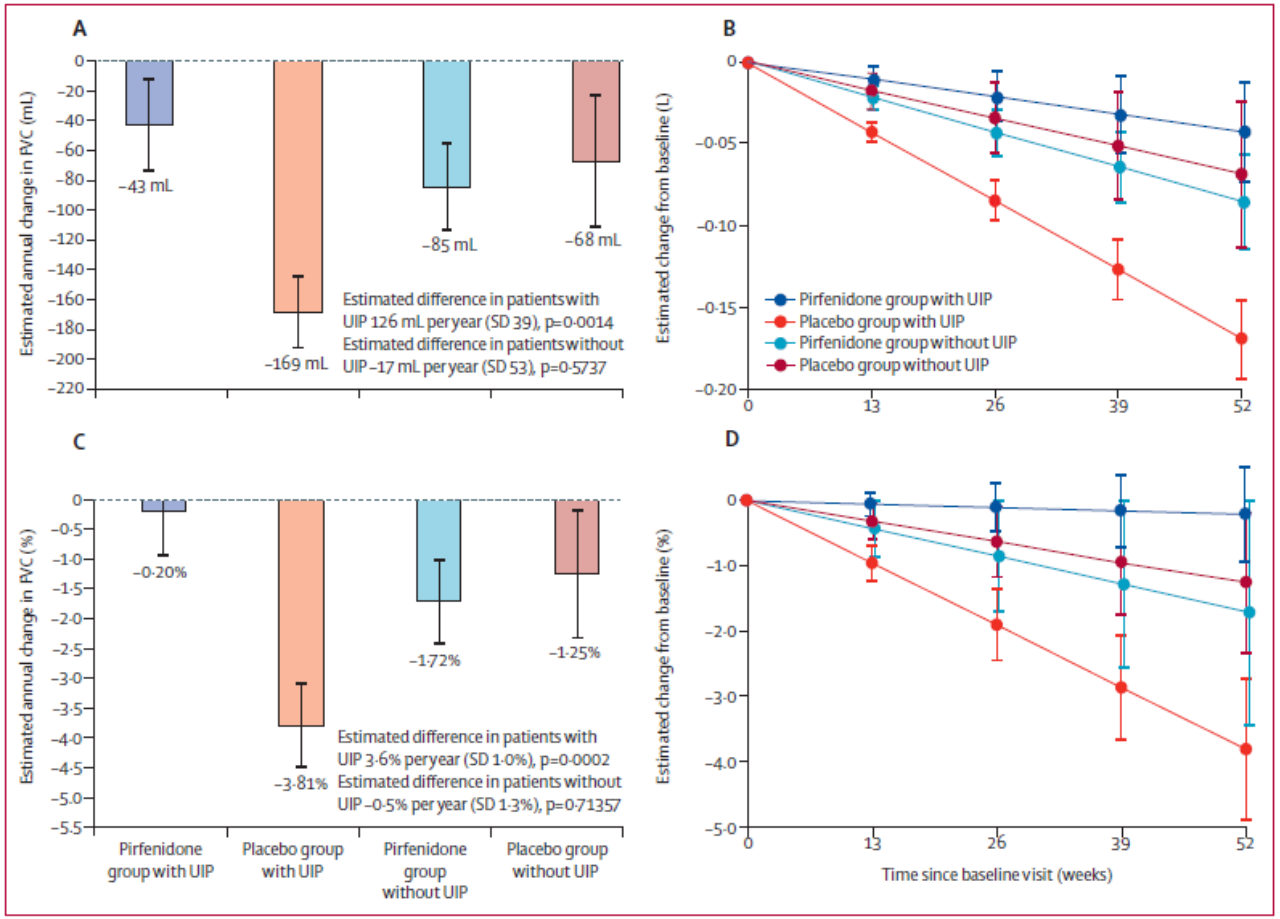
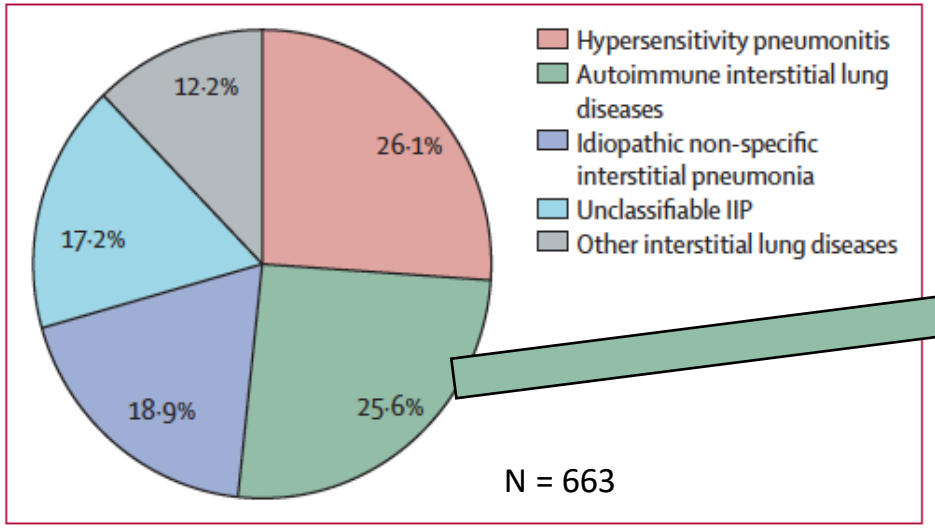
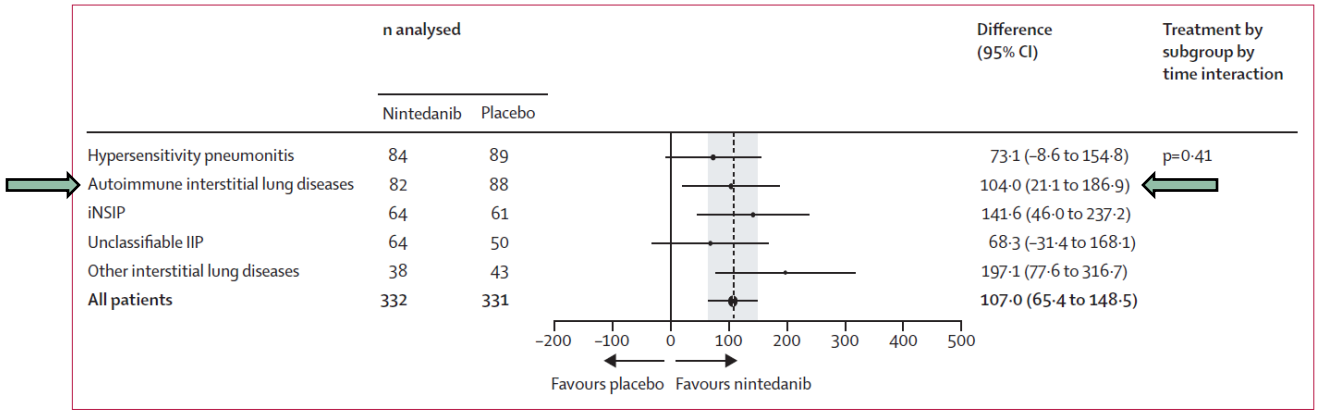


***Figure 3*: Estimated change in FVC and percent predicted FVC by high-resolution CT pattern**
(A) Estimated annual change in FVC (mL). (B) Estimated change in FVC (L) from baseline. (C) Estimated annual change in percent predicted FVC (%). (D) Estimated annual change in percent predicted FVC (%) from baseline. Error bars are SE. FVC=forced vital capacity. UIP=usual interstitial pneumonia.

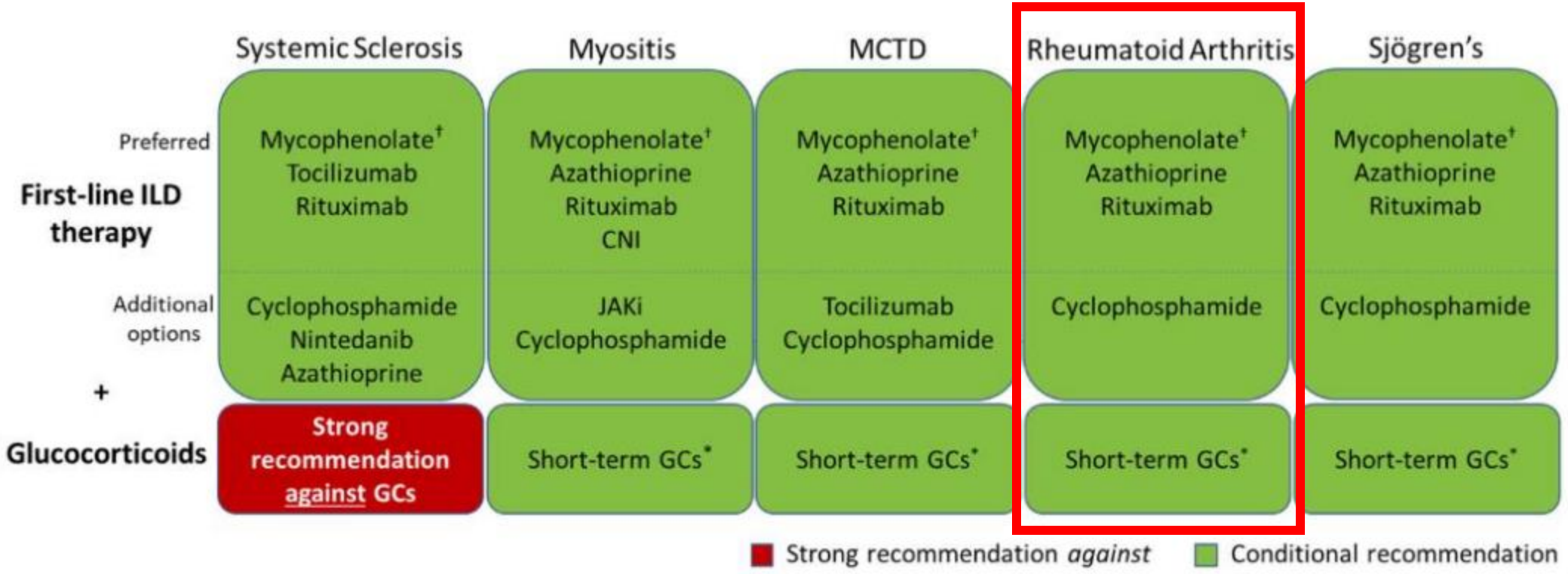
The INBUILD trial (Nintedanib) included patients with RA-ILD



Subgroup analysis of 25.6% (170) autoimmune patients:
--13.4% of patients had RA-ILD
--Difference in FVC decline vs placebo: 104 mL/year

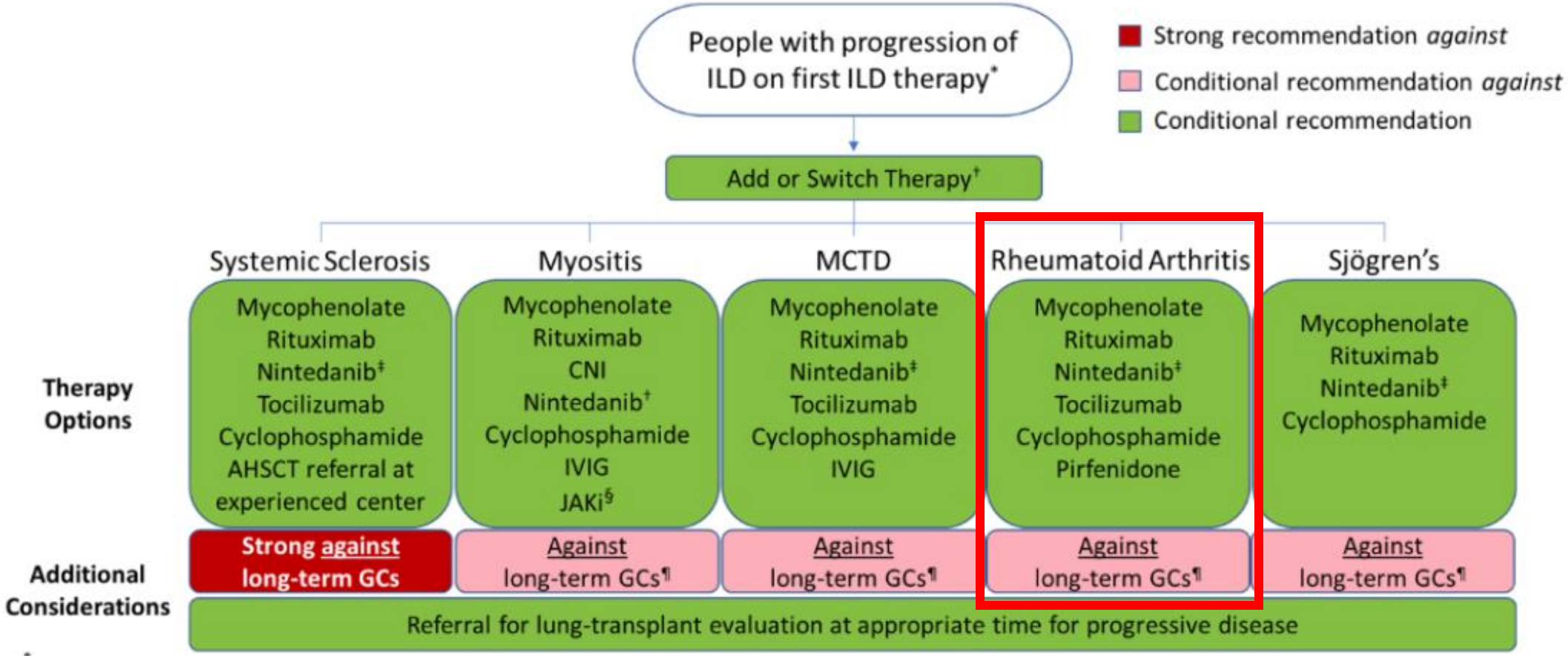


First-line therapy for SARD-ILD (ACR)



- "For people with SARD-ILD, we conditionally recommend against leflunomide, methotrexate, TNFi, and abatacept as first-line ILD treatment options."

Therapy for progressive SARD-ILD (ACR)



Summary

- ILD is common in RA and associated with morbidity and mortality
- Patients with RA-ILD may benefit from immunosuppression that targets the lungs
- Data supporting the use of a particular immunosuppressant agent is lacking