Πνευμονική ίνωση σε ασθενείς με χρόνια ΡΑ

Σιμοπούλου Θεοδώρα
Ρευματολόγος
Επιμελήτρια Β'
Κλινική Ρευματολογίας και κλινικής Ανοσολογίας
ΠΓΝΛάρισας

Σύγκρουση συμφερόντων

- Καμία για την παρούσα παρουσίαση

- Εκπαιδευτικές-ερευνητικές-συμβουλευτικές επιχορηγήσεις την τελευταία διετία: Abbvie, Amgen, Boehrigher-Ingelheim, Janssen, Novartis, Vianex

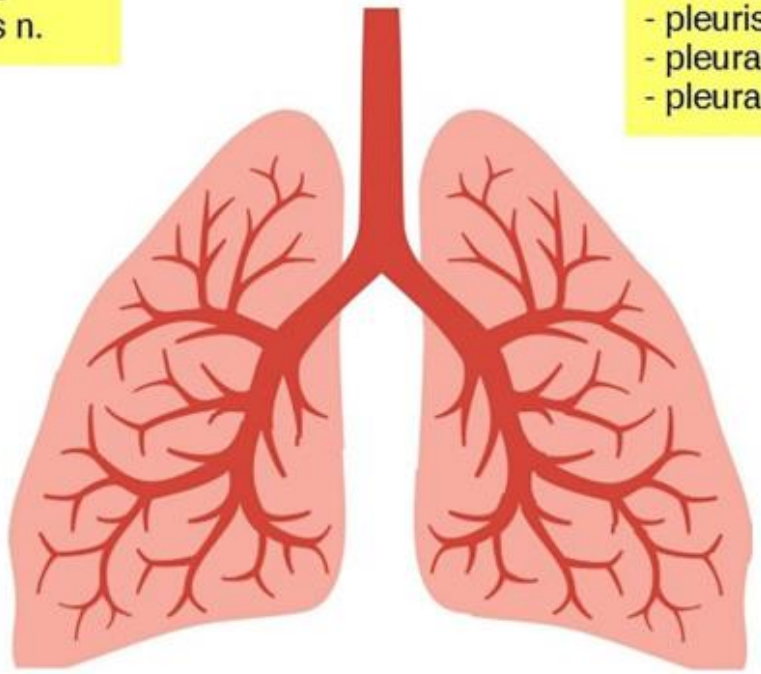
Η προσβολή του αναπνευστικού στην ΡΑ

Upper airways disease:
-cricoarytenoid arthritis
- rheumatoid noduls of vocal cords
- vasculitis of recurrent n. or vagus n.

Lower airways disease:
-follicular bronchiolitis
- Bronchiolitis obliterans
- bronchiectasis

Vascular disease:
- PAH
- pulmonary vasculitis
- diffuse alveolar hemorrhage

Parenchymal disease:
- UIP
- NSIP
- OP
- LIP
- rheumatoid nodules

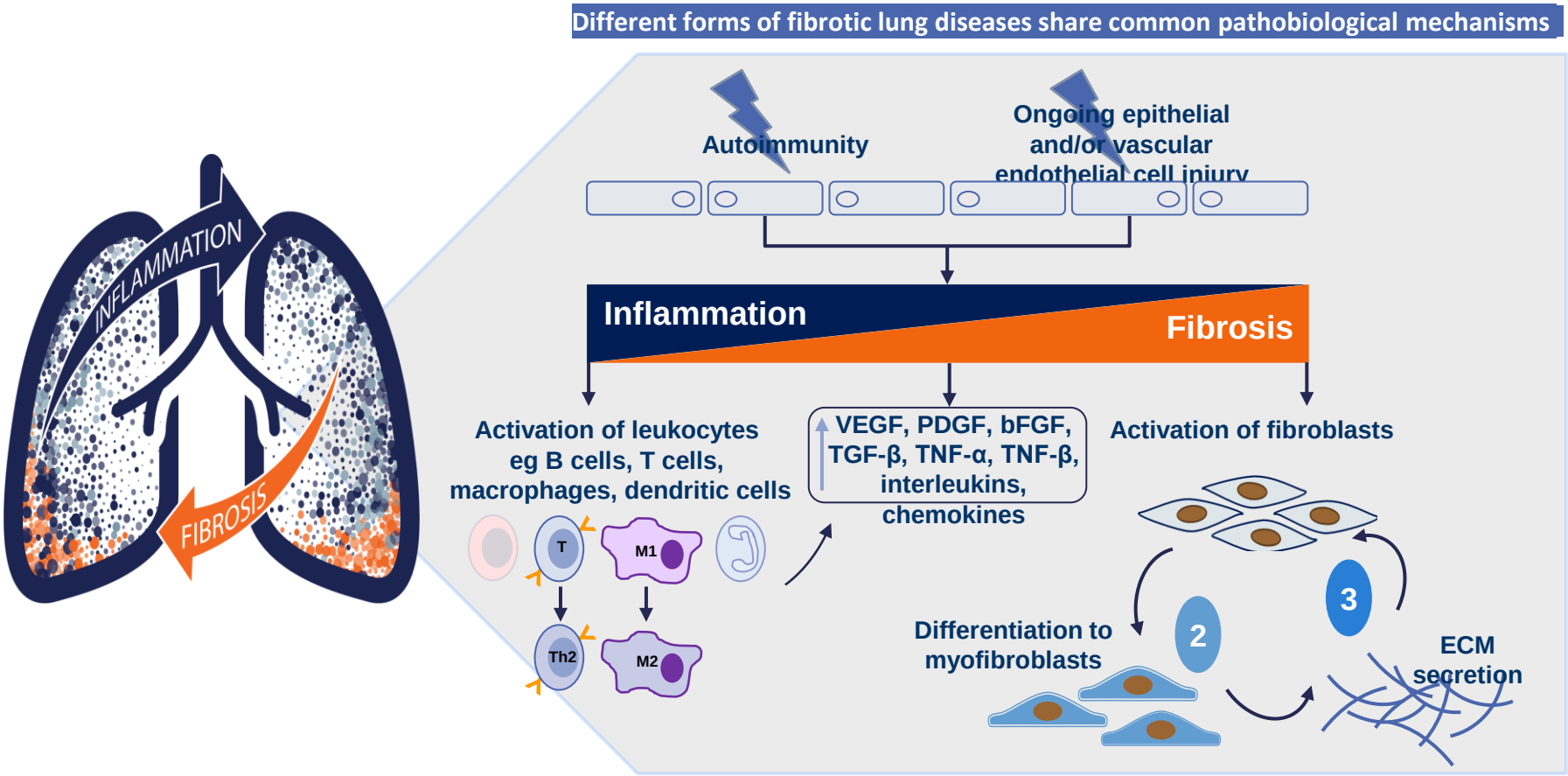


Pleural disease:
- pleurisy
- pleural effusion
- pleural nodules

Comorbidities:
- Caplan's Syndrome
- Amyloidosis.

Drugs toxicity
- LFN, MTX, SSZ and others

Παθογένεια RA-ILD: φλεγμονή + ίνωση



- RA or other immune disorders very likely involve an inflammation that has variable degrees, but that can lead to excessive scarring and fibrosis, as well.
- The most studied ILDs from a mechanistic perspective are IPF and SSc-ILD.
- Παρόλο η παθογένεια των διαφορετικών νοσημάτων του συνδετικού ιστού δεν είναι ίδια, υπάρχουν κοινά παθογενετικά μονοπάτια στην ανάπτυξη της ίνωσης

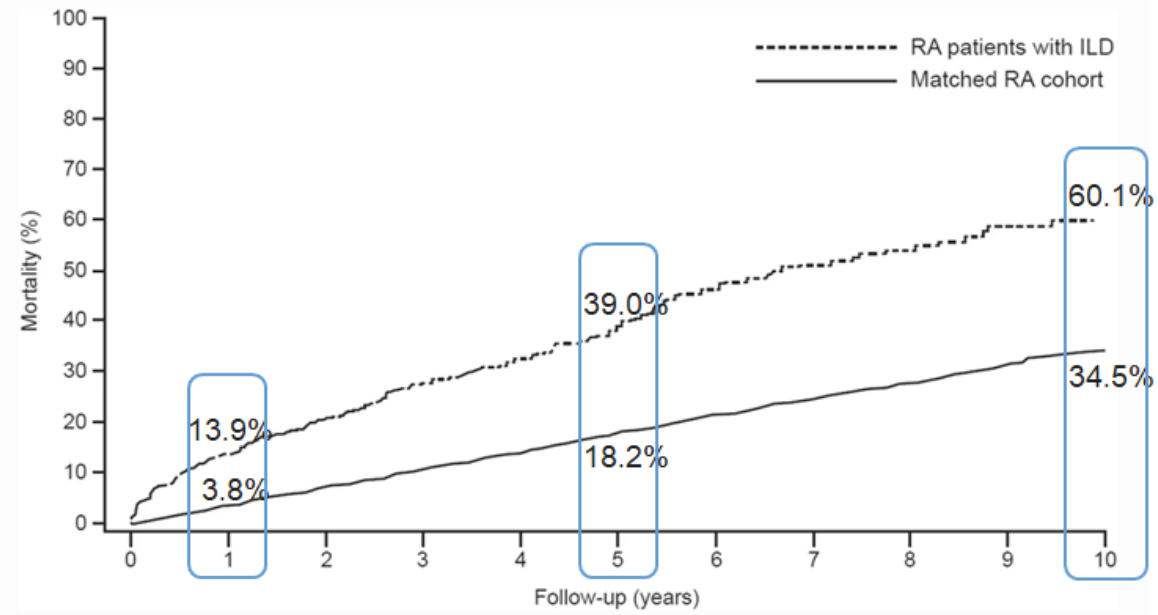
bFGF, basic fibroblast growth factor; CTD-ILD, connective tissue disease-associated interstitial lung disease; CTGF, connective tissue growth factor; M1, classically activated macrophage; M2, alternatively activated macrophage; PDGF, platelet-derived growth factor; TGF, transforming growth factor; Th2, type 2 T helper cell; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor

1. Bagnato G, Harari S. *Eur Respir Rev* 2015;24:102–14; 2. Castelino F, Varga J. *Arthritis Res Ther* 2010;12:213; 3. Dellaripa PF. *Clin Immunol* 2018;186:71–3; 4. Wells A, Denton C. 2014 *Nat Rev Rheumatol* 2014;10:728–39

RA-ILD

Επιδημιολογικά:

- 60% των ασθενών με PA έχουν απεικονιστικά ευρήματα ILD (HRCT)
- Κλινικά σημαντική στο 10% των περιπτώσεων
- Σημαντική αιτία νοσηρότητας και θνητότητας



Kaplan–Meier estimate of mortality

Ann Rheum Dis. 2017 Oct;76(10):1700-1706.

RA-ILD: Παράγοντες κινδύνου

Δημογραφικοί

- Άνδρες (male-to-female ratio as high as 2:1)
- Κάπνισμα
- Μεγαλύτερη ηλικία

Συνοσηρότητες

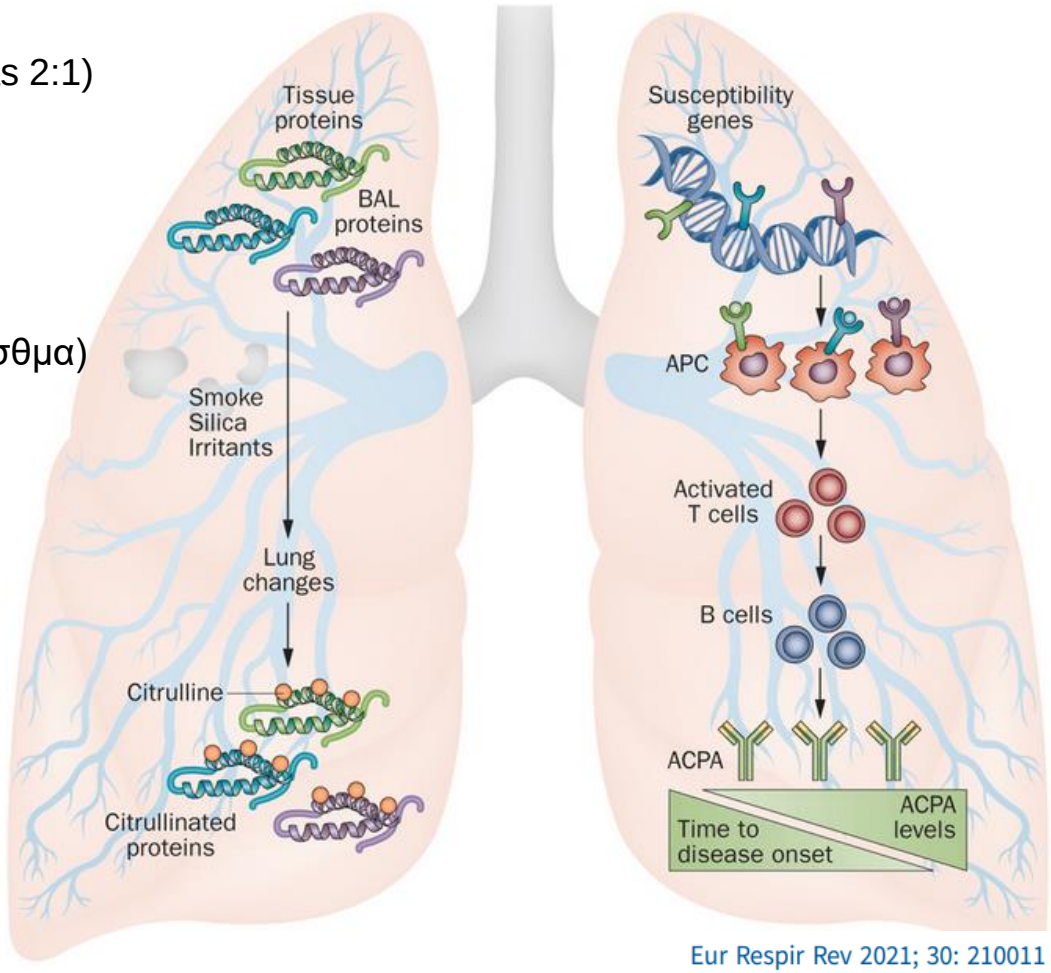
- Παχυσαρκία (+υπνική άπνοια)
- Υποκείμενη πνευμονοπάθεια (ΧΑΠ, άσθμα)

Σχετιζόμενοι με τη PA

- RF+, anti-CCP +
- Υψηλή ενεργότητα νόσου
- Μεγάλη διάρκεια νόσου

Γενετικοί

- MUC5B promoter variant rs35705950
- Mutations in telomerase genes

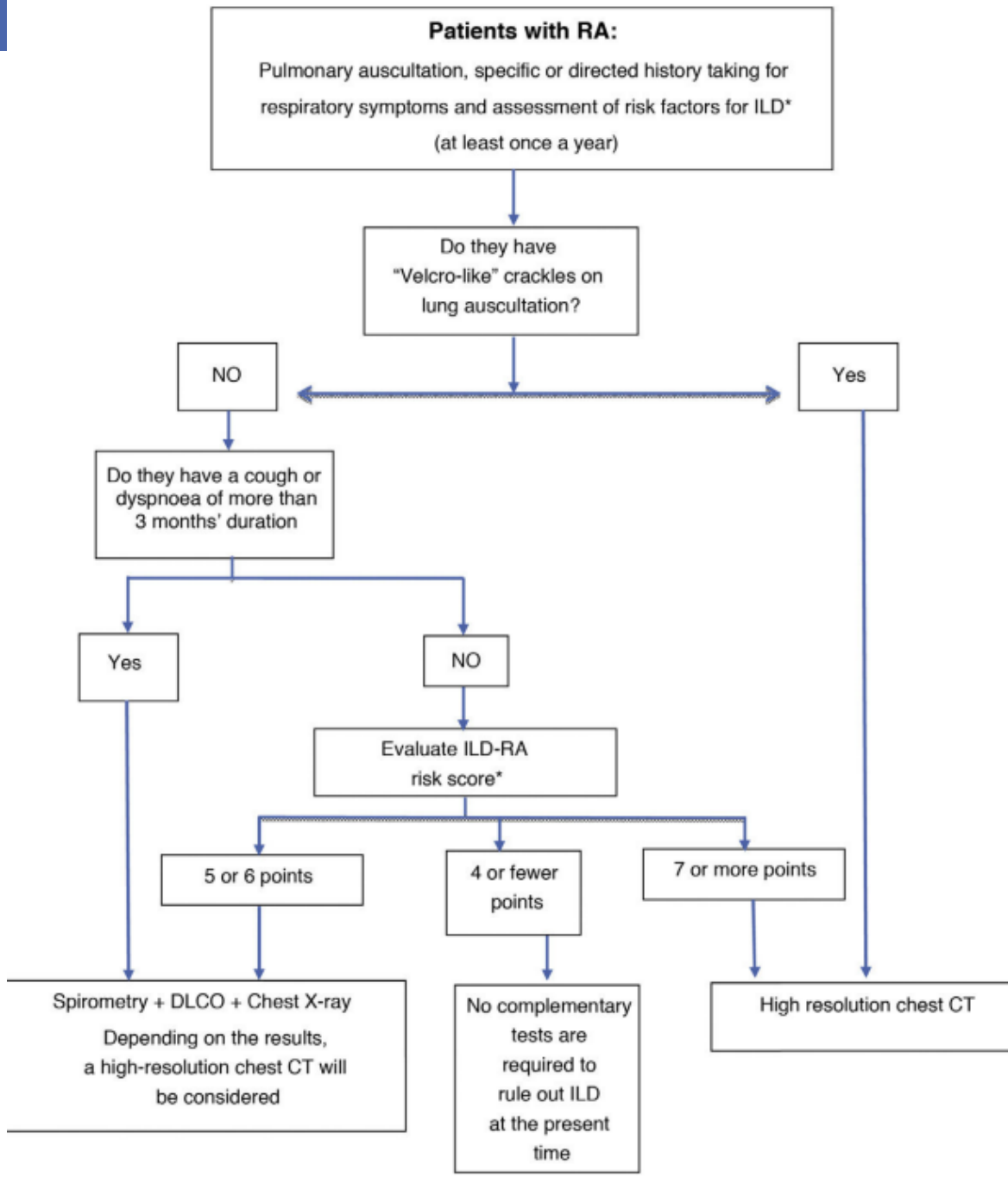


Eur Respir Rev 2021; 30: 210011

Πρωτοδιάγνωση PA → screening για πνευμονική ίνωση

Proposed screening algorithm for ILD screening in patients diagnosed with RA

Set of variables and proposed score for each of the variables for overall calculation	Score
Age ≥ 60 years	2[b]
Male sex	1[b]
History of smoking (active or ex-smoker)	
≤ 20 packs/year: 2 points	2[b]
>20 packs/year: 3 points	3[b]
Disease duration > 5 years	1[c]
Persistent moderate-high disease activity: DAS28-VSG average > 3.2 from diagnosis of the disease in RA onset (time from diagnosis ≤ 12 months) or DAS28-VSG > 3.2 for a minimum of 6 months in established RA	1[c]
Serology (only the criterion with the highest weighting is counted towards the total score)	
RF positive > 3 times above the ULN	1[c]
ACPA positive ≤ 3 times above the ULN	2[c]
ACPA positive > 3 times the ULN	3[c]
Family history of ILD	1[c]

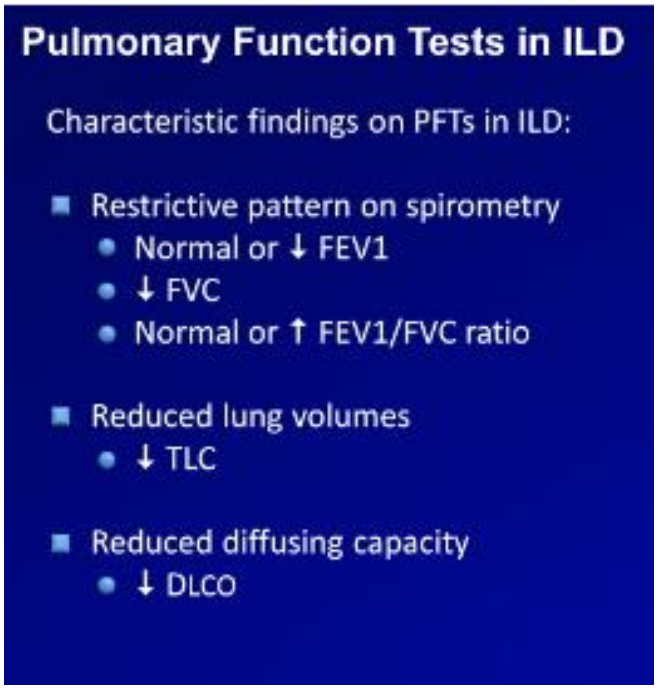


Reumatol Clin (Engl Ed). 2023 Feb;19(2):74-81.

Προσέγγιση ασθενούς με ΡΑ και συμπτώματα από το αναπνευστικό
Δ/δ: αποκλεισμός άλλων αιτιών

Αίτια	
Λοίμωξη	TBC, PCP, chlamydia, fungi, άτυπη πνευμονία
Κακοήθεια	Καρκινωματώδης λεμφαγγειίτιδα από μαστό, πνεύμονα, ΓΕΣ, κ.α.
Φάρμακα	Αντιβιώσεις (INH, νιτροφουραντοίνη) Αντιεπιληπτικά ΧΜΘ Αμιωδαρόνη
Πνευμονίτιδα εξ υπερευαισθησίας	Αγρότες/κτηνοτρόφοι Επαφή με πτηνά Εργάτες σε ξυλεία, συστήματα θέρμανσης/χαμαμ/πισίνες
Ιδιοπαθής	IPF

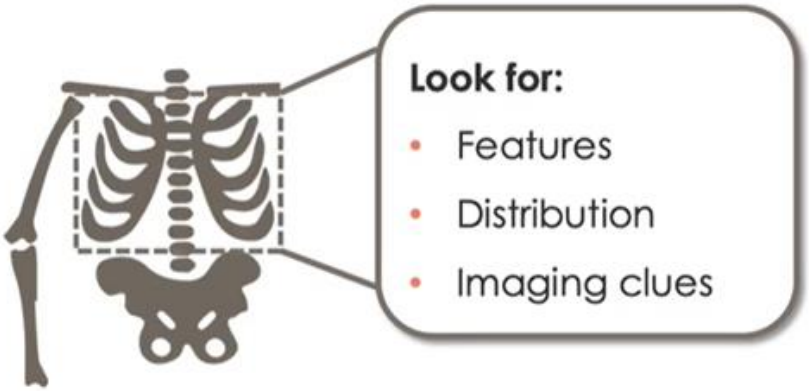
Λειτουργικές αναπνευστικές δοκιμασίες



- Ανίχνευση αναπνευστικής προσβολής (screening tool)
  - Μικρότερη ευαισθησία κ ειδικότητα από την HRCT
- Σταδιοποίηση βαρύτητας
  - DLCO<54%, cut-off for high risk of RA-ILD progression
- Παρακολούθηση

HRCT

- gold standard
- αναγνώριση πνευμονικής προσβολής - διάγνωση
- επιτρέπει τη διάκριση ανάμεσα σε φλεγμονώδεις και ινωτικές αλλοιώσεις



The imaging features and how they are distributed can point to diagnostic patterns

FEATURES	**Indicative of ILD (fibrosis)**
	Honeycombing
	Traction bronchiectasis
	Reticulation
	Other features of ILD
	Ground glass opacity
	Air space consolidation
	Air trapping
	Nodular opacities
DISTRIBUTION	Upper or lower
	Central/peribronchovascular
	Peripheral/subpleural

PA-ILD: ακτινολογικά πρότυπα

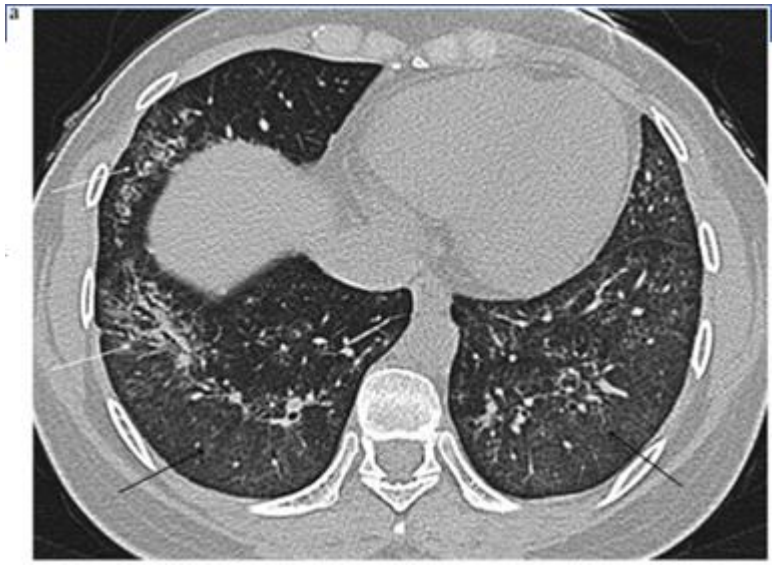
TABLE 1 Prevalence and clinical features of rheumatoid arthritis (RA)-associated lung diseases

Disease phenotype	Clinical features	Prevalence
Parenchymal lung disease		
UIP pattern	Radiographic pattern: subpleural, basal predominant reticular opacities, honeycombing, minimal ground-glass opacity, architectural distortion with traction bronchiectasis Associated with worse outcomes compared to other disease patterns in RA	8–66%
NSIP pattern	Extensive ground-glass opacity, traction bronchiectasis, subpleural sparing Lower risk of disease progression and better treatment response compared with UIP	19–57%
Organising pneumonia	Focal ground-glass opacities, consolidations, reversed halo sign	0–11%
Other (*e.g.* LIP or DIP)	Thin-walled cysts, centrilobular nodules, ground-glass attenuation, peribronchovascular septal thickening, upper-lobe predominant	Rare

	NSIP	UIP	OP	PH	DAD	LIP	Hemorrhage	Airways disease
RA	+	++++	++	+	+	+		++++
SSc	++++	+	+	+++	+			
PM/DM	++++	+	++++		+			
SjS	++	+	+	+	+	++++		+++
MCTD	++	+	+	+	+			
SLE	++	+	+	+	++	+	++	+

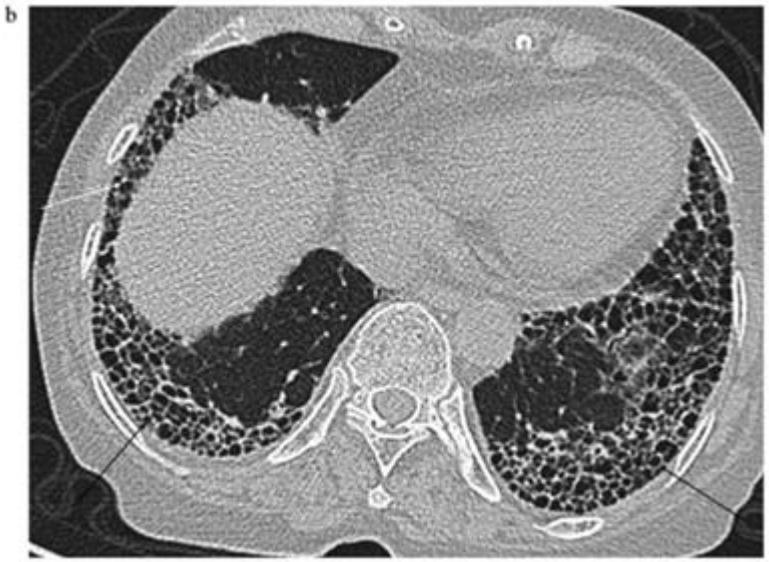
Eur Respir Rev 2021; 30: 210011

PA– ILD: Ακτινολογικό Πρότυπο



NSIP

• Αμφοτερόπλευρη θαμβή ύαλου ± δικτυωτό πρότυπο ± βρογχιεκτασίες
• ±Αναστρέψιμη

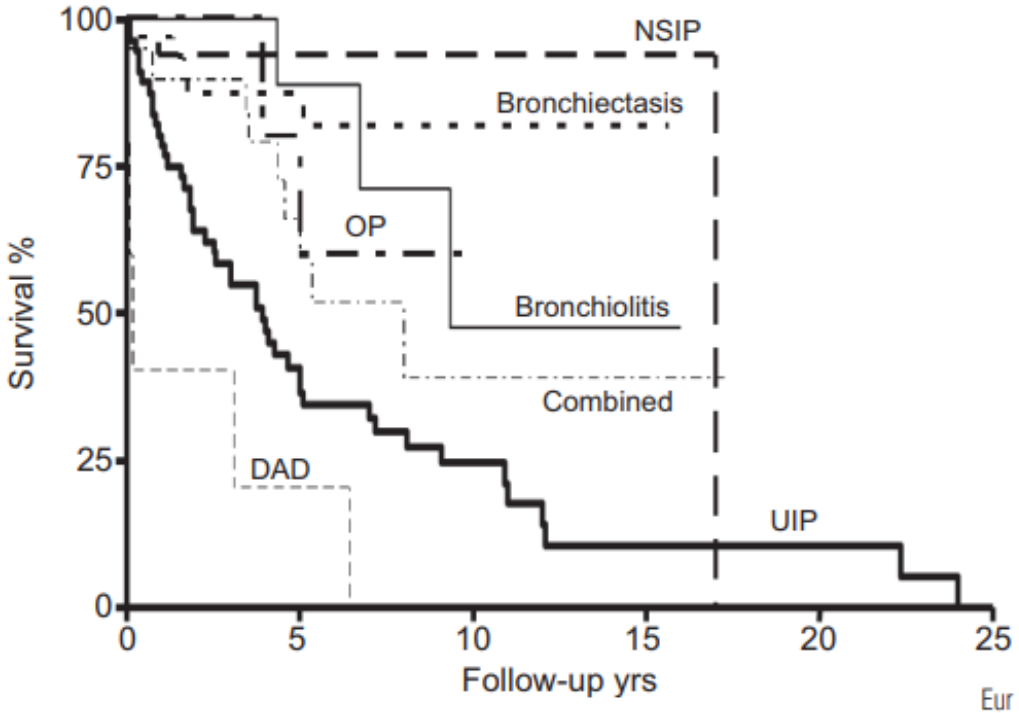


UIP

- Μελισσοκυρήθρα υπουπεζωκοτικά + κάτω λοβούς
- Μη αναστρέψιμη Ίνωση – κακή πρόγνωση

Το ακτινολογικό πρότυπο δίνει πληροφορίες για την πρόγνωση - αναστρεψιμότητα της βλάβης

	UIP	NSIP
Median survival yrs	3.9	17
5-yr survival %	36.6	93.8
10-yr survival %	24.6	93.8



Eur Respir J 2011; 37: 1411–1417

RA – ILD: τεκμηρίωση

- Απαιτείται βρογχοσκόπηση - BAL - βιοψία ?

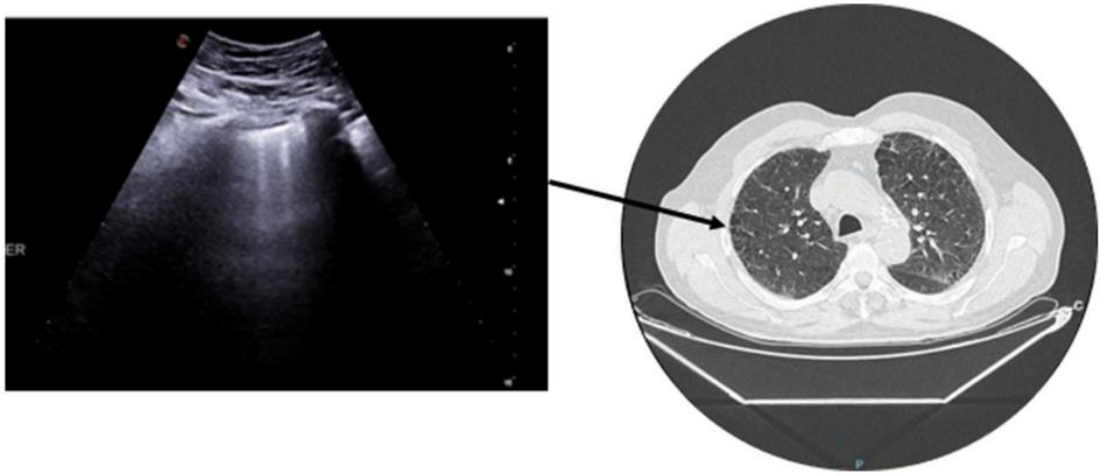
Although bronchoscopy is not necessary for patients with a usual interstitial pneumonia (UIP) pattern on CT scan, bronchoscopy remains necessary for patients with ILD in clinical settings [6]. Bronchoscopy is often required to rule out other conditions, such as respiratory infection. Moreover, factors in bronchoalveolar lavage fluid (BALF) have been used as markers of lower respiratory tract inflammation in many respiratory diseases.

Watase M, et al. PLoS One. 2023. PMID: 36930615

 Συστήνεται για τον αποκλεισμό άλλων καταστάσεων (π.χ. επί υποψίας λοίμωξης ή κακοήθειας)

Υπέρηχος (LUS, Lung UltraSound)

- emerging as a novel diagnostic approach for ILD
- alterations in the pleural line and appearance of vertical artifacts called “B lines.”



High-resolution CT positive for interstitial lung disease and corresponding lung ultrasound patterns

- pleural line becoming irregular and thickened and may appear blurred and fragmented
- B lines are vertical hyperechoic laser beam-like artifacts that arise from the pleural line and extend to the end of the screen without fading, erasing A lines, and moving synchronously with the pleural sliding until defining the “interstitial syndrome”

A preliminary proposal of an algorithm for the use of LUS and KL-6 to screen and follow up early RA-ILD

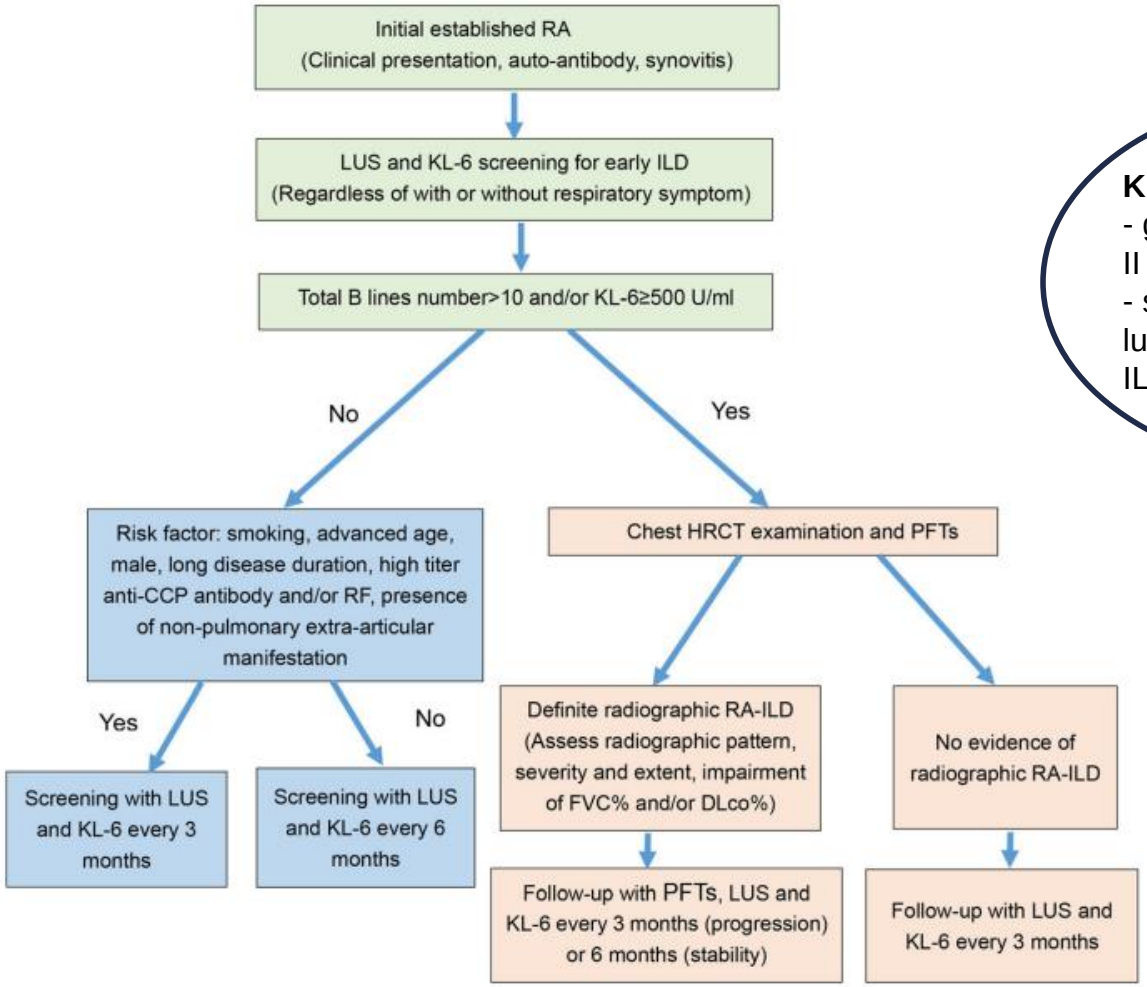


Fig. 1 Preliminary algorithm for screening and follow-up of early RA-ILD. CCP, cyclic citrullinated peptide; DLco, diffusing capacity for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; KL-6, Krebs von den Lungen-6 antigen; LUS, lung ultrasound; PFTs, pulmonary functional tests; RA, rheumatoid arthritis; RA-ILD, rheumatoid arthritis–associated interstitial lung disease; RF, rheumatoid factor

Wang *et al. Arthritis Research & Therapy* (2021) 23:212

KL-6 (Krebs von den Lungen 6)
- glycoprotein expressed by type II alveolar cells
- serum levels correlate with lung damage in patients with ILD

Συζήτηση περιστατικών

ΠΑΡΟΥΣΙΑΣΗ ΠΕΡΙΣΤΑΤΙΚΟΥ #1

Παρουσίαση περιστατικού #1

Άνδρας 65 ετών, πρώην καπνιστής

PA από 4ετίας

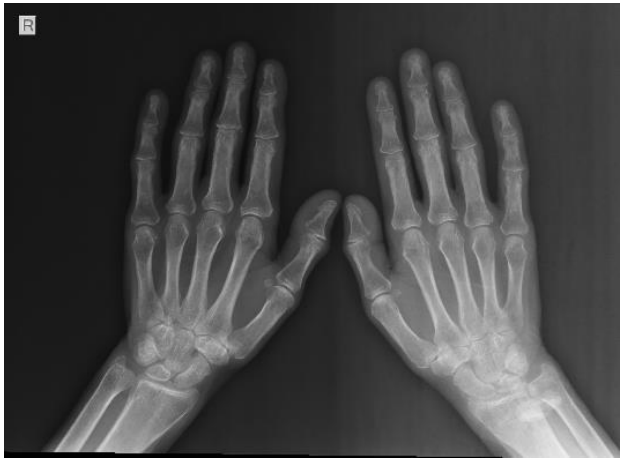
- Συμμετρική πολυαρθρίτιδα άκρων χειρών

- RF+++, aCCP-

- MTX 15mg/w
- a-TNF

- Βήχας ξηρός από 9μήνου

- Velcro βάσεων άμφω

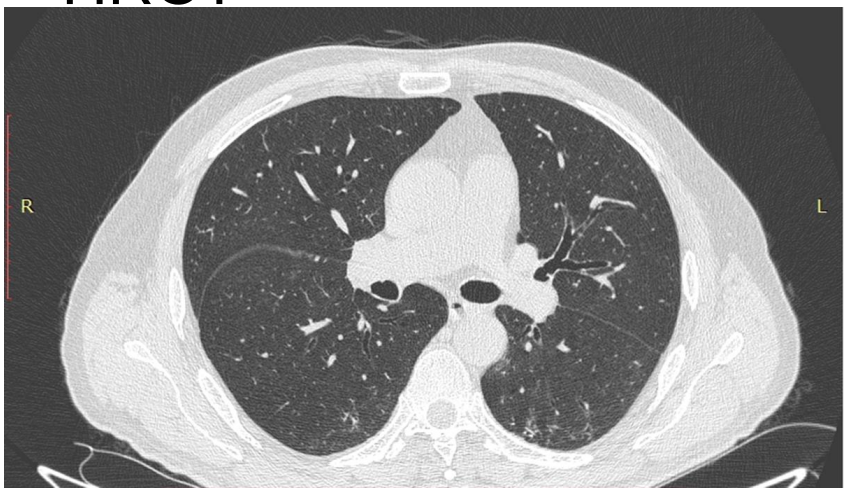


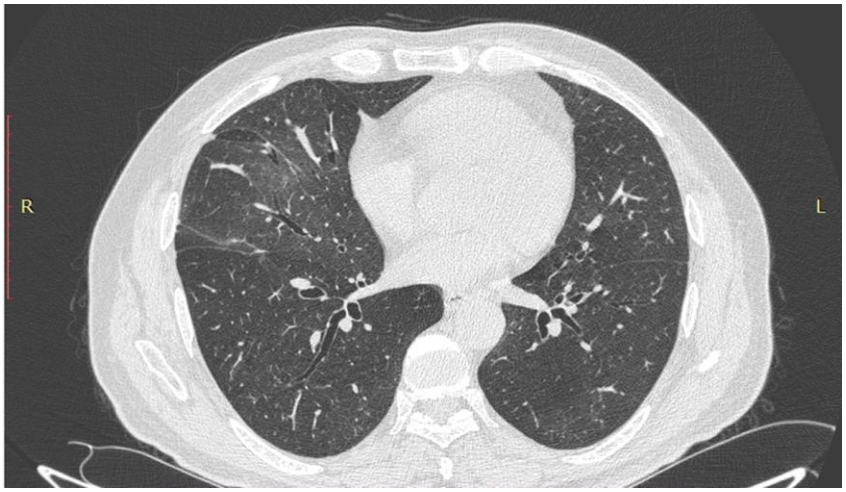
		Pred	ПРО B/Δ	%Pred
VC IN	[L]	4.97	4.10	82.47
VC EX	[L]	4.97	3.89	78.22
VC MAX	[L]	4.97	4.10	82.47
IC	[L]	3.66		
ERV	[L]	1.31		
FVC	[L]	4.77	3.89	81.54
FEV 1	[L]	3.78	3.16	83.49
FEV 1 % VC MAX	[%]	77.31	77.03	99.64
FEV 1 % FVC	[%]		81.21	
PEF	[L/s]	9.02	9.04	100.18
MEF 75	[L/s]	7.93	9.02	113.73
MEF 50	[L/s]	4.88	4.14	84.73
MEF 25	[L/s]	2.01	0.84	41.87
MMEF 75/25	[L/s]	3.89	2.65	68.32
FEV 0.5	[L]			
FEV6	[L]			
FVC IN	[L]			
FIV1	[L]			
FIF 50	[L/s]			
FEF50 % FIF50	[%]			

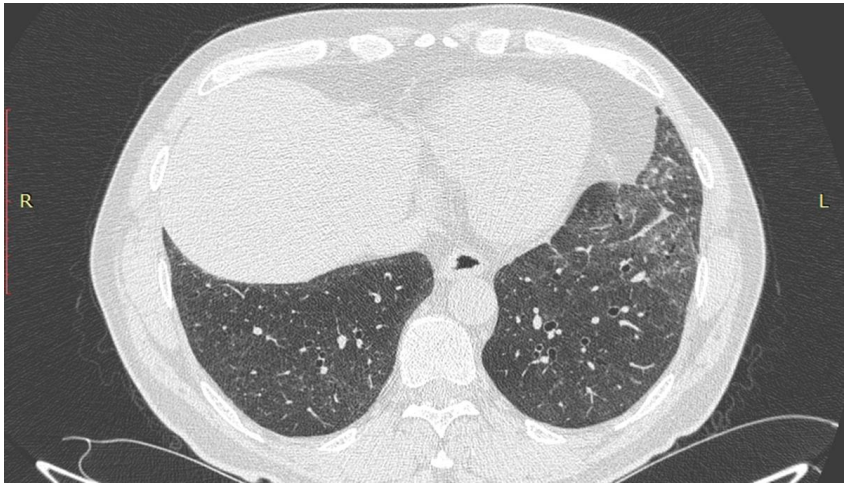
		Pred	A1	%(A1/P)
SR eff	[kPa*s]	1.18	1.79	152.2
R eff	[kPa*s/L]	0.30	0.38	128.0
ITGV	[L]	3.68	3.95	107.4
RV	[L]	2.36	2.27	96.5
TLC	[L]	7.54	7.11	94.2
VC IN	[L]	5.00	4.84	96.7
FVC	[L]	4.80	4.61	96.1
FEV 1	[L]	3.81	4.18	109.6
FEV 1 % VC MAX	[%]	77.49	86.41	111.5
FEV 1 % FVC	[%]		90.68	
FEF 25	[L/s]	7.96	10.08	126.7
FEF 50	[L/s]	4.91	7.62	155.2
FEF 75	[L/s]	2.03	2.03	99.9
MMEF 75/25	[L/s]	3.93	5.44	138.5
PEF	[L/s]	9.06	10.19	112.4
PIF	[L/s]		6.01	
FEV1 % FIV1	[%]		91.64	
VT	[L]	0.69	1.42	205.6
BF	[1/min]	20.00	27.93	139.7
VC IN	[L]	5.00	4.84	96.7
VC MAX	[L]	5.00	4.84	96.7
ERV	[L]	1.32	1.68	127.0

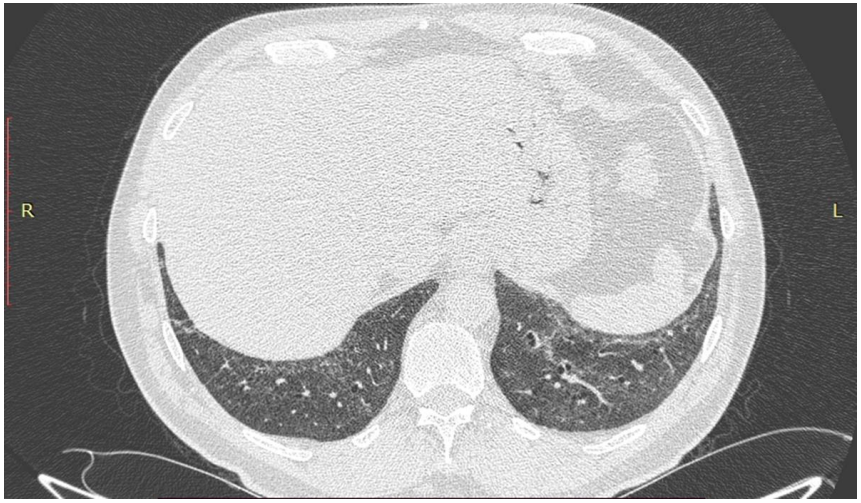
Παρουσίαση περιστατικού #1

- HRCT





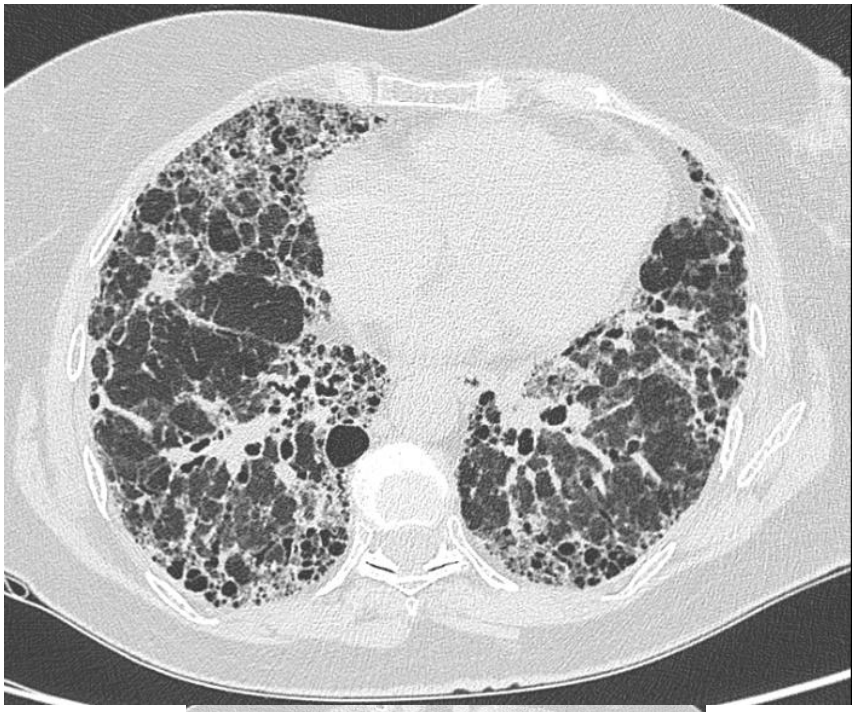


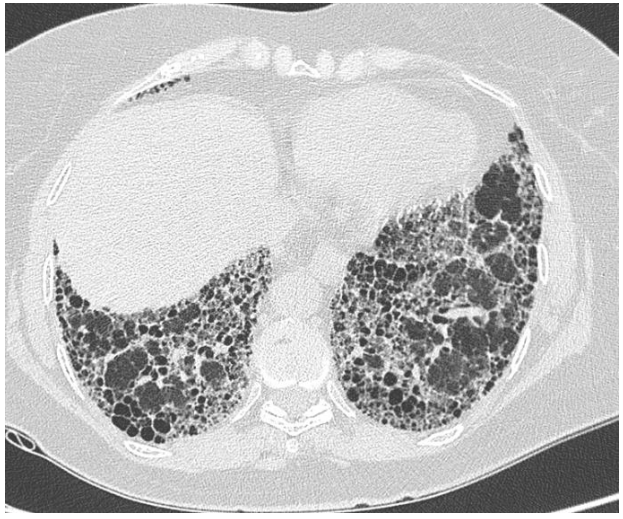


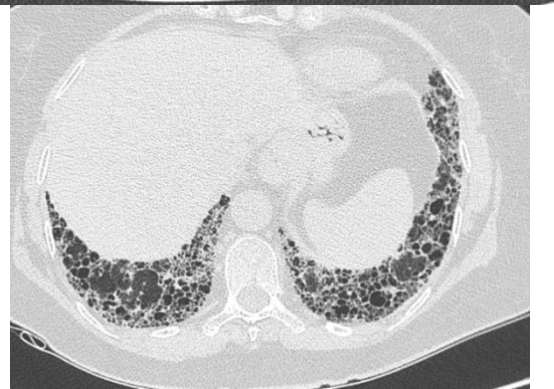
ΠΑΡΟΥΣΙΑΣΗ ΠΕΡΙΣΤΑΤΙΚΟΥ #2

Παρουσίαση περιστατικού #2

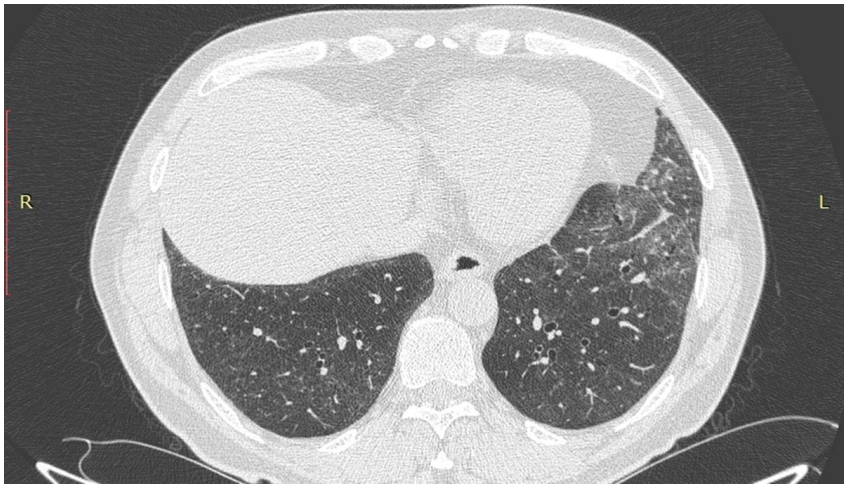
- Γυναίκα 75ετών, μη καπνίστρια
- Οροθετική ΡΑ από το 1998
- Πνευμονική ίνωση από το 2007
- Φ.Α.: Στο παρελθόν είχε λάβει λεφλουνομίδη, υδροξυχλωροκίνη, μεθοτρεξάτη, mabthera
- prezolon 5mg και κατ'οίκον O_2
- Δύσπνοια στην ελάχιστη κόπωση, βήχα και επεισόδια αποκορεσμού (από έτους χειρότερα)

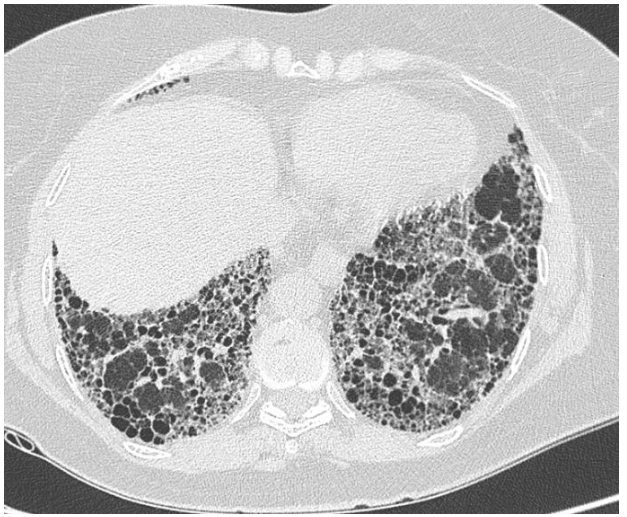




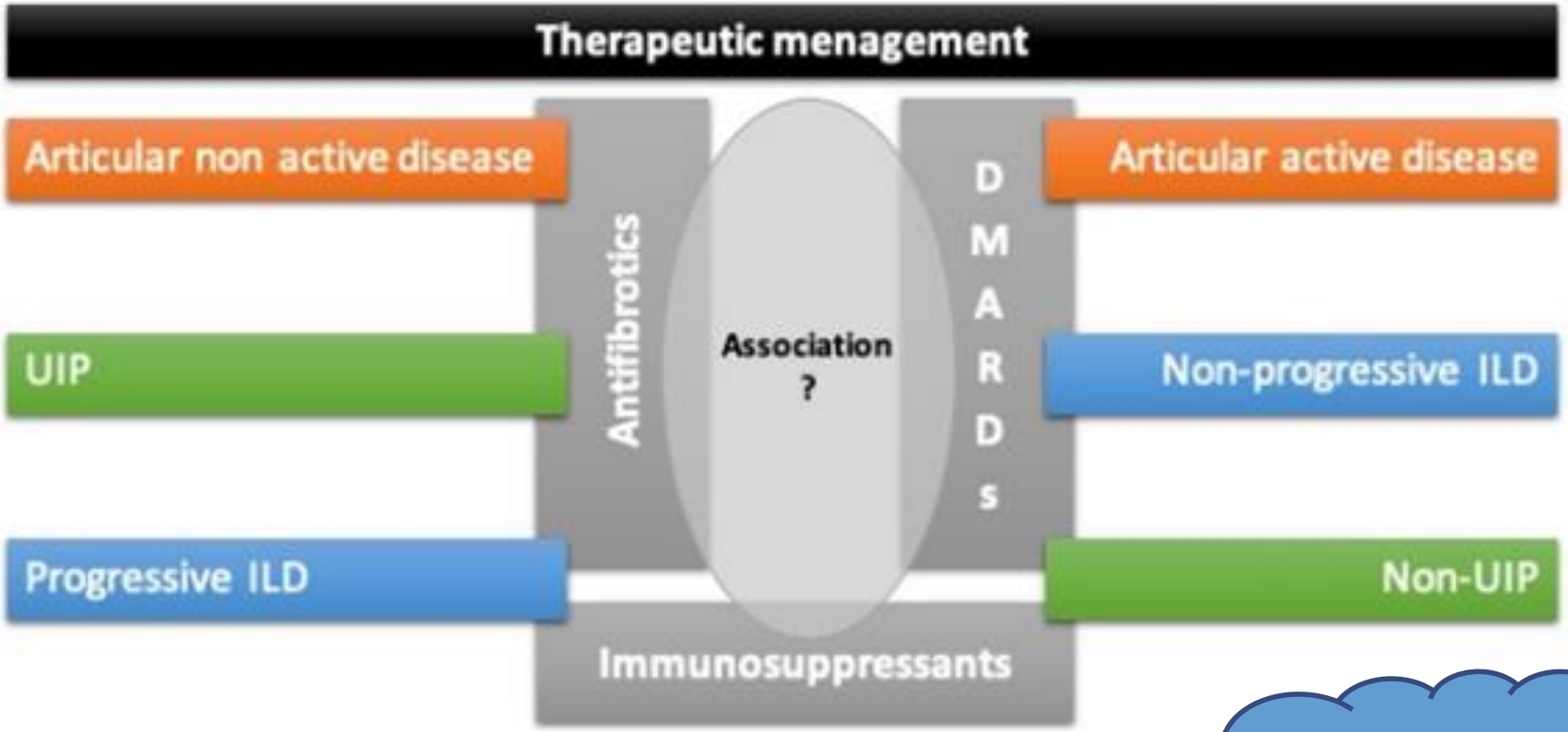


PA-ILD: Θεραπεία
Ποιος (?) πρέπει να λάβει ποια (?) θεραπεία ?





Proposed framework for the management and treatment of RA-ILD patients.



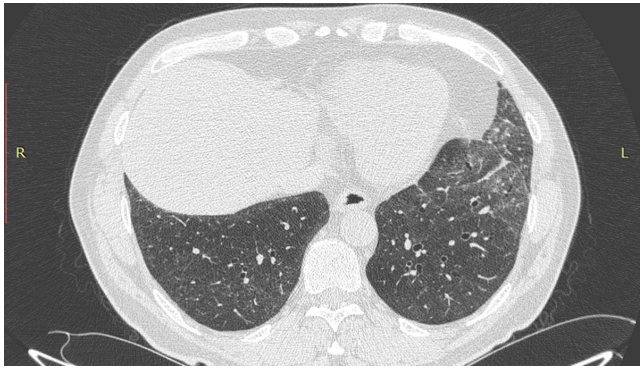
Επιδείνωση συμπτωμάτων?

Συνεργασία Ρευματολόγου & Πνευμονολόγου

J. Clin. Med. **2020**, *9*, 1082

Παρουσίαση περιστατικού #1

Άνδρας 65 ετών, πρώην καπνιστής



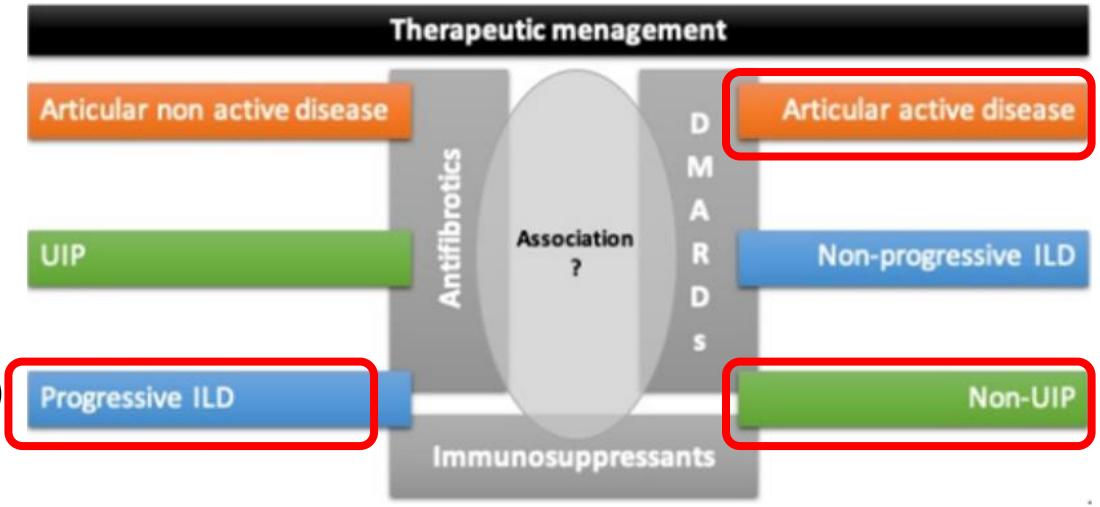
PA από 4ετίας
- Συμμετρική πολυαρθρίτιδα άκρων χειρών

- RF+++, aCCP-

- MTX 15mg/w
- a-TNF

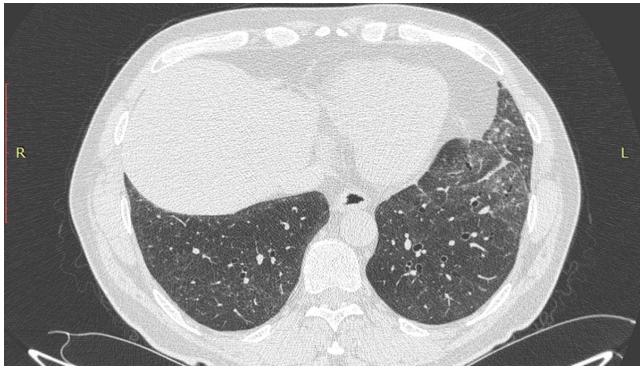
- Βήχας ξηρός από 9μήνου

- Velcro βάσεων άμφω
- FVC 82% (96% προ 2ετίας)



Παρουσίαση περιστατικού #1

Άνδρας 65 ετών, πρώην καπνιστής



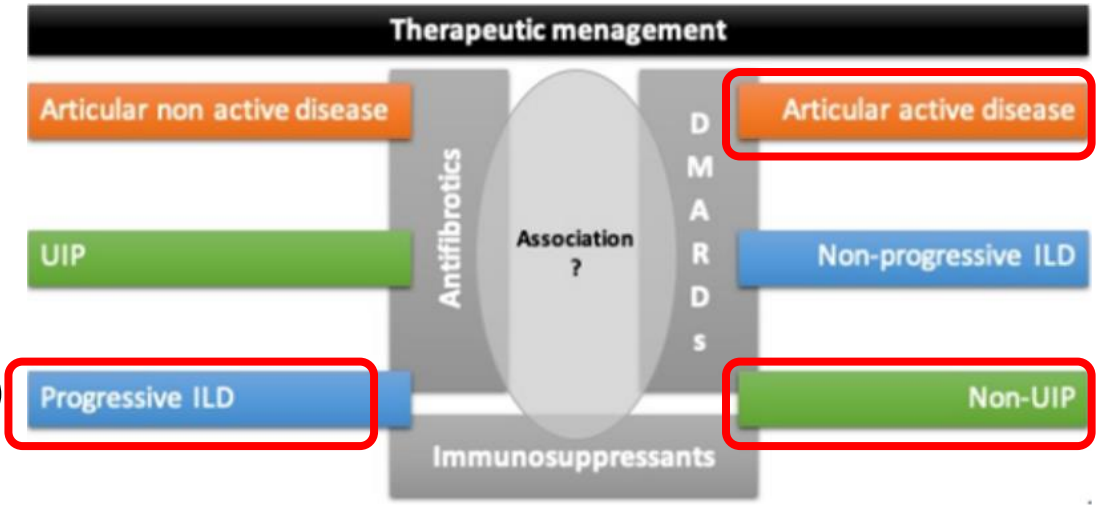
PA από 4ετίας
- Συμμετρική πολυαρθρίτιδα άκρων χειρών

- RF+++, aCCP-

- **MTX 15mg/w**
- **a-TNF**

- Βήχας ξηρός από 9μήνου

- Velcro βάσεων άμφω
- FVC 82% (96% προ 2ετίας)



Πνευμονίτιδα από μεθοτρεξάτη

- >120 αναφορές στη βιβλιογραφία
- Συνήθως υποξεία εμφάνιση σε διάστημα εβδομάδων (οξεία εκδήλωση εντός ημερών ή χρόνια σε διάστημα μηνών έχουν επίσης περιγραφεί)

Table 3. – Clinical features of methotrexate pneumonitis: literature review

	Total	Histological study
Subjects n	123	49
Age yrs	49.3	52.1
Sex M/F	47/76	24/25
Shortness of breath/Dyspnoea	101 (82.1)	38 (77.6)
Cough	100 (81.3)	38 (77.6)
Fever	94 (76.4)	38 (77.6)
Chest pain	12 (9.8)	5 (10.2)
Tachypnoea	52 (42.3)	28 (57.1)
Crackles	64 (52.0)	32 (65.3)

- Περιφερική ηωσινοφιλία (20.3%)
- X-ray: διάμεσο ή μεικτό διάμεσο και κυψελιδικό πρότυπο

Eur Respir J 2000; 15: 373–381

Front Med (Lausanne). 2019 Oct 23;6:238.

Review > Semin Arthritis Rheum. 2022 Aug;55:152031. doi: 10.1016/j.semarthrit.2022.152031. Epub 2022 May 30.

Methotrexate use reduces mortality risk in rheumatoid arthritis: A systematic review and meta-analysis of cohort studies

Jianbin Xu [1], Lianbo Xiao [2], Jie Zhu [3], Qiu Qin [3], Yuedie Fang [3], Jin-An Zhang [4]

Affiliations + expand

PMID: 35671648 DOI: 10.1016/j.semarthrit.2022.152031

Abstract

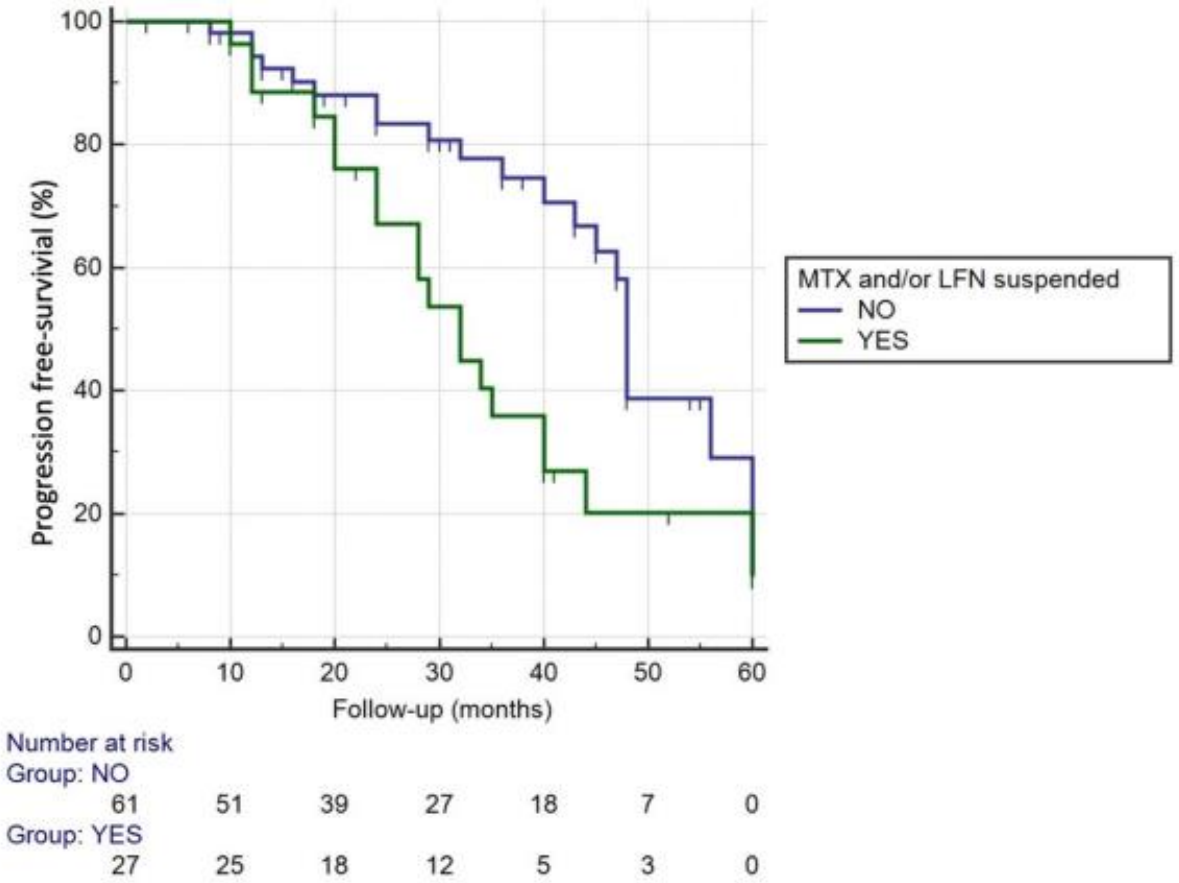
Background: Rheumatoid arthritis(RA) sufferers have a higher mortality risk than the healthy population, and methotrexate (MTX) as a base drug for RA treatment is believed to affect patients mortality. Systematic analyses of MTX and RA mortality are lacking and it is still confused about the role of MTX on the long-term prognosis of RA.

Methods: We performed a systematic review and meta-analysis to identify any influence of MTX on mortality among RA patients. Hazard ratio(HR) for all-cause mortality were pooled in a meta-analysis, and HR for mortality from RA with cardiovascular diseases (RA-CVD) and mortality from RA associated interstitial lung diseases (RA-ILD) were also pooled and analyzed.

Results: Fifteen studies were eventually included. Meta-analysis of data from 15 studies on overall mortality showed that MTX significantly reduced mortality in patients with RA (HR = 0.59, 95%CI 0.50-0.71, P < 0.001), MTX was independently associated with decreased RA-CVD-induced mortality (HR = 0.72, 95%CI 0.53-0.97, P = 0.031). In the meanwhile, MTX was also significantly reduced mortality in RA-ILD (HR = 0.44, 95%CI 0.20-0.95, P = 0.037).

Conclusion: MTX can significantly decrease the overall mortality for RA patients, specifically, RA-CVD- and RA-ILD-induced mortality were reduced.

Διακοπή της MTX και/ή της λεφλουνομίδης και επιδείνωση ILD



Kaplan–Meier curve for disease progression in RA-ILD during 5 years period, grouped by discontinuing or not MTX and/or LFN at the moment of ILD diagnosis (Log Rank Test: p=0.0139).

Sci Rep. 2021 Apr 28;11(1):9184.

Guidelines?

- EULAR 2022 – καμία σύσταση για PA-ILD

- ACR 2021 –
- Methotrexate is conditionally recommended over alternative DMARDs for the treatment of inflammatory arthritis for patients with clinically diagnosed mild and stable airway or parenchymal lung disease, or incidental disease detected on imaging, who have moderate-to-high disease activity

Arthritis & Rheumatology
Vol. 73, No. 7, July 2021, pp 1108–1123

- Taiwan Society of Rheumatology
- Spanish Society of Rheumatology (SER), Pneumology and Thoracic Surgery (SEPAR)
  - Against the use of MTX and LEF
  - In favor of RTX and ABA

Rituximab & RA-ILD

Treating Autoimmune-Related Interstitial Lung Disease With B Cell Depletion

Stamatis-Nick C. Liossis [1,2] and Constantina A. Bounia [1]*

TABLE 4 | Trials of RTX use in RA/AS/SS/SLE-ILD.

References	No of patients	Disease	RTX scheme	Follow up	Outcomes	Safety of RTX
Fui et al. (33)	14 RTX vs. 14 non-RTX	RA	RA scheme	12 m	Stable PFTs and HRCT score vs. reduced PFTs in control	No serious AE
Md Yusof et al. (34)	56	RA	RA scheme	12 m	Increased PFTs/HRCT score	33/56 serious AEs/infections 12/56 deaths
Narvaez et al. (35)	31	RA	RA scheme	12 m	Improved PFTs improved/stable HRCT	Few serious AE 10/31 2/31 deaths
Mattesson et al. (36)	10	RA	RA scheme	12 m	Stable PFTs/stable HRCT	3/7 AEs 2/7 death
Vadillo et al. (37)	31 RTX/37 non-RTX	RA	RA scheme	6 m	Stable PFTs vs. non-stable PFTs in control group	A few AEs

Front Med (Lausanne). 2022 Jun 30;9:937561.

Abatacept in RA-ILD

- 263 RA-ILD ασθενείς, 12 μήνες follow-up
  Δεν υπήρξε επιδείνωση:
  - δύσπνοια (MMRC) (91.9%)
  - FVC (87.7%)
  - DLCO (90.6%)
  - HRCT (76.6%)

Rheumatology (Oxford). 2020 Dec 1;59(12):3906-3916.

- 44 ασθενείς
  - 5 (11.4%) showed RA-ILD progression
  - 32 (72.6%) were considered stable
  - 7 (16.0%) showed an RA-ILD improvement

Clin Rheumatol. 2021 Dec;40(12):4861-4867.

- 57 ασθενείς
  - lung disease had improved or stabilized in 41 patients (71.9%)
  - worsened in 13 (22.8%)
  - 3 died

Biomedicines. 2022 Jun 22;10(7):1480.

JAKis in RA-ILD

A retrospective study of the efficacy of JAK inhibitors or abatacept on rheumatoid arthritis-interstitial lung disease

- 75 patients with RA-ILD receiving JAKis (31) or ABA (44) were retrospectively evaluated at baseline and after 18 months of treatment.
- In the JAKis group, five patients (16.1%) showed RA-ILD progression, 20 patients (64.5%) were considered stable, and six patients (19.4%) demonstrated RA-ILD improvement.
- In the ABA group, five patients (11.3%) showed RA-ILD progression, 32 patients (72.7%) were stable, and seven patients (16.0%) demonstrated RA-ILD improvement.
- **Treatment with JAKis or ABA was related to stability or improvement of RA-ILD in 83.9% and 88.6% of patients, respectively.**

Inflammopharmacology (2022) 30:705–712

★ Data are emerging in favor of tofacitinib to slowing the progression of CTD-ILD
★ Effect of tofacitinib on mice that developed arthritis and ILD, revealing a significant slowdown in ILD progression

JAKis in RA-ILD

POS0835

EFFECTIVENESS AND SAFETY OF JAK INHIBITORS IN RHEUMATOID ARTHRITIS-INTERSTITIAL LUNG DISEASE. NATIONAL MULTICENTER STUDY OF 57 PATIENTS

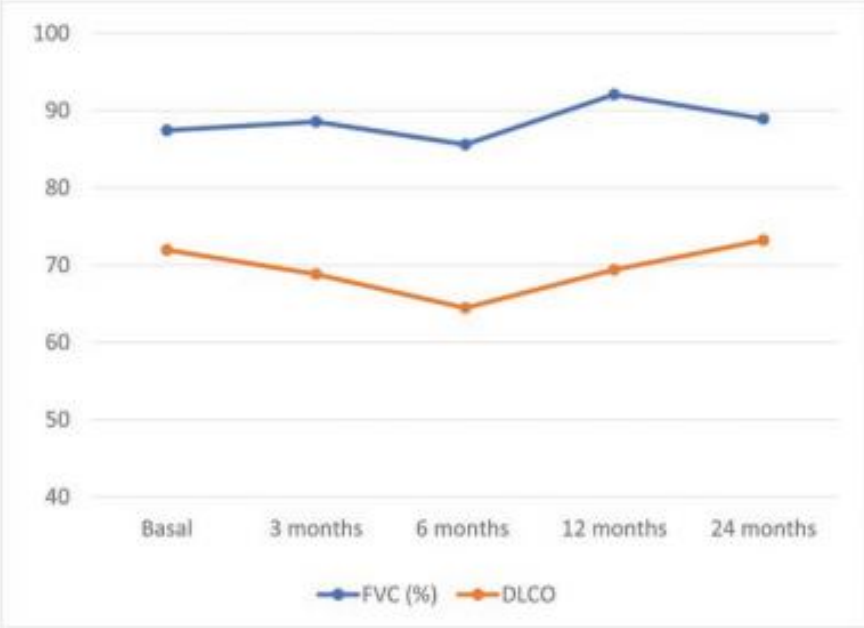
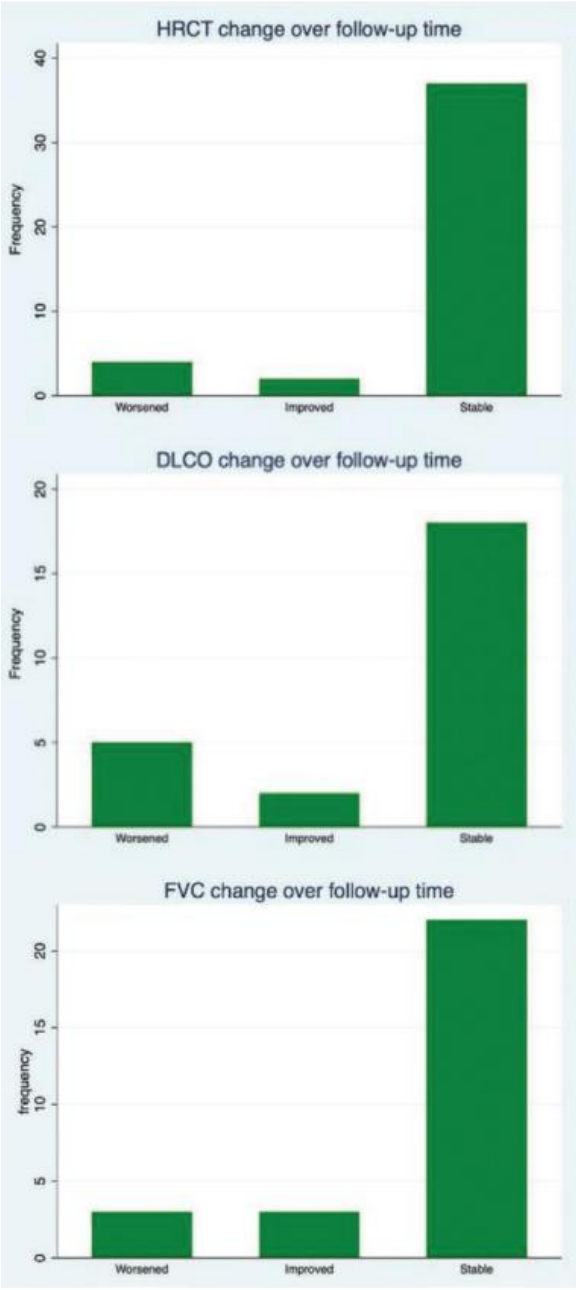


Figure 1. Evolution of pulmonary function tests (mean % of the predicted FVC and DLCO) in RA-ILD patients with BARI therapy at baseline and 24 months.

POS0855

EVOLUTION OF RHEUMATOID ARTHRITIS-ASSOCIATED INTERSTITIAL LUNG DISEASE IN PATIENTS TREATED WITH JAK INHIBITORS: A MULTICENTER RETROSPECTIVE STUDY



Tocilizumab

- ΄Εγκριση για SSc-ILD

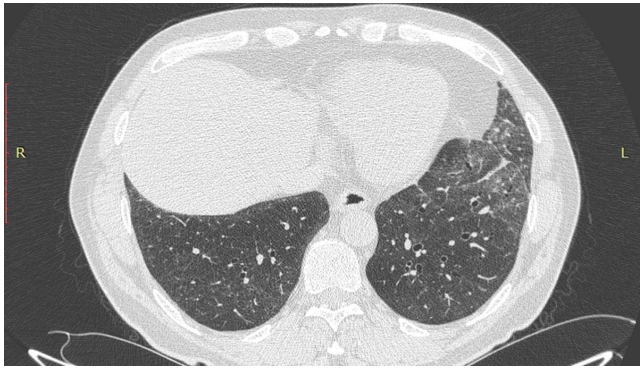
- RA-ILD

  - Retrospective study 28 RA-ILD patients, mean follow-up 30 months
  - FVC remained stable in 14 (56%) patients, improved in 5 (20%) and worsened in 6 (24%).
  - DLCO remained stable in 14 (56%) patients, improved in 5 (20%) and worsened in 6 (24%)
  - HRCT remained stable in the majority (25) of cases, worsened in 2 patients with a UIP pattern and improved in only one (NSIP pattern).

Intern Med J. 2020 Sep;50(9):1085-1090.

Παρουσίαση περιστατικού #1

Άνδρας 65 ετών, πρώην καπνιστής



PA από 4ετίας
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- ~~MTX~~ 15mg/w + **Rituximab iv**
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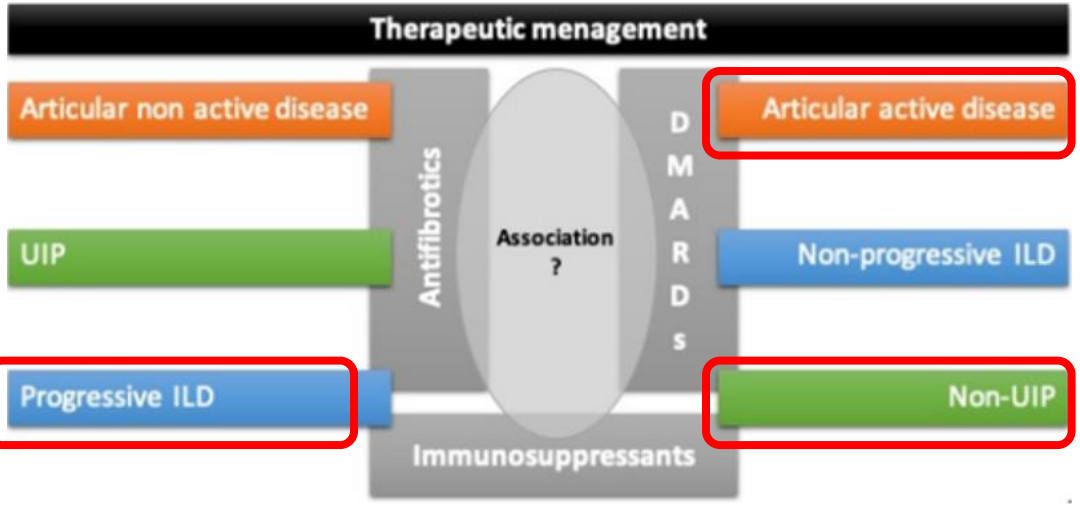

- Βήχας ξηρός από 9μήνου

- Velcro βάσεων άμφω
- FVC 82% (96% προ 2ετίας)

Προοδευτικός ινωτικός φαινότυπος

- Προοδευτική επιδείνωση ίνωσης
- Επιδείνωση αναπνευστικής λειτουργίας
- Επιδείνωση συμπτωμάτων
- Επιδείνωση Health associated QoL
- Μειωμένο προσδόκιμο επιβίωσης

Πώς ορίζεται η επιδείνωση?

- Μείωση της FVC
- Progressive pulmonary fibrosis (2022 ATS/ESR/JRS/ALAT guidelines)
- Progressive fibrosing ILD (INBUILD randomized clinical trial)
- Progression ILD (RELIEF randomized clinical trial)

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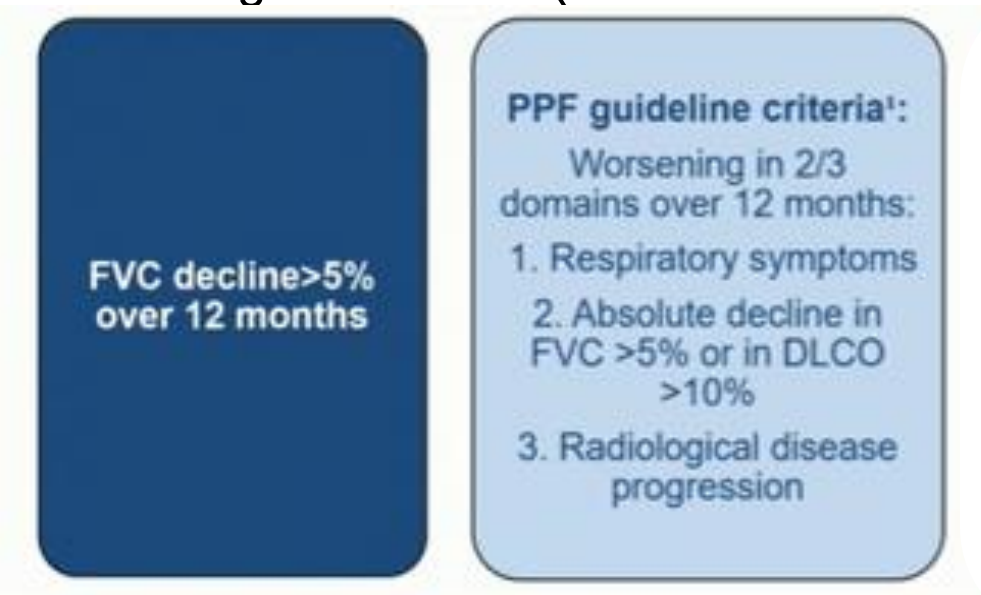

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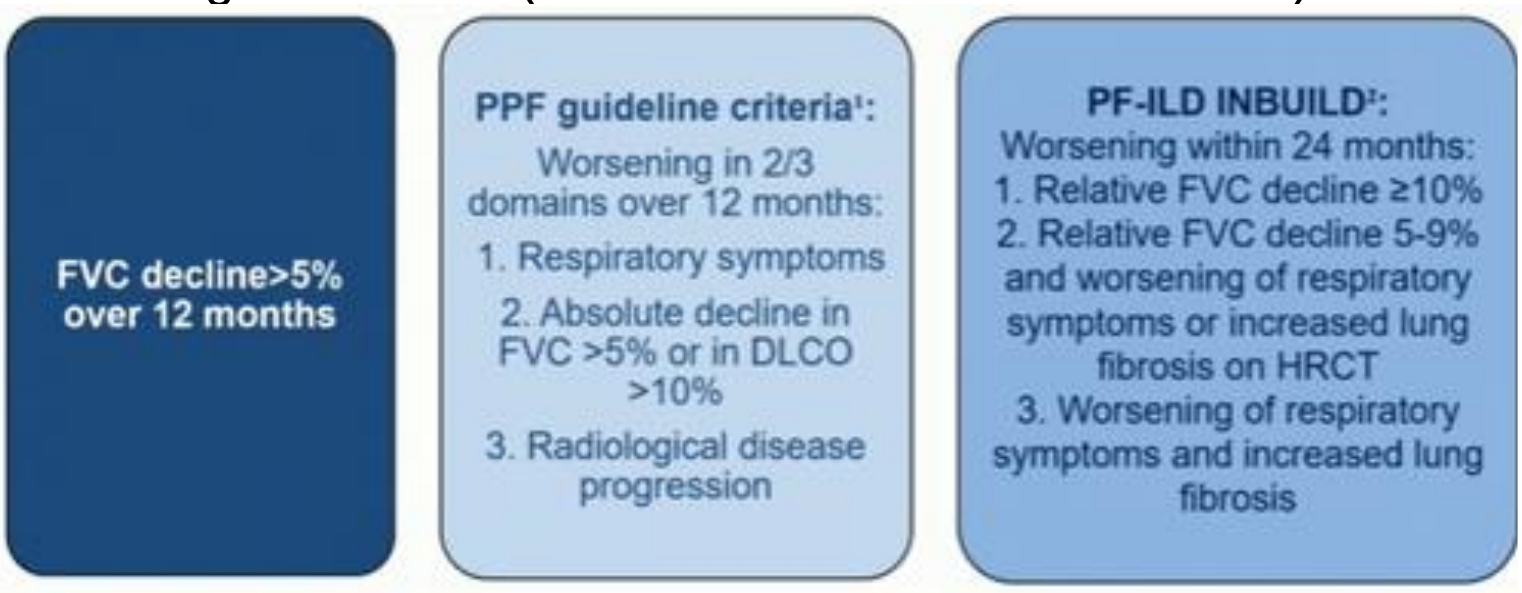

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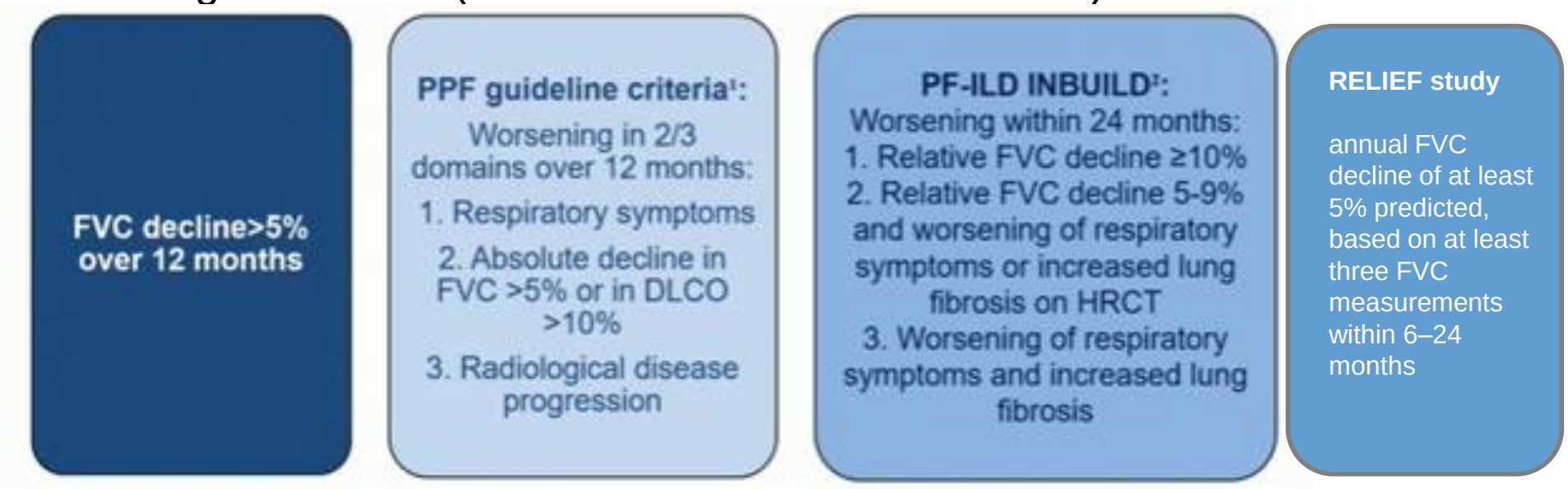
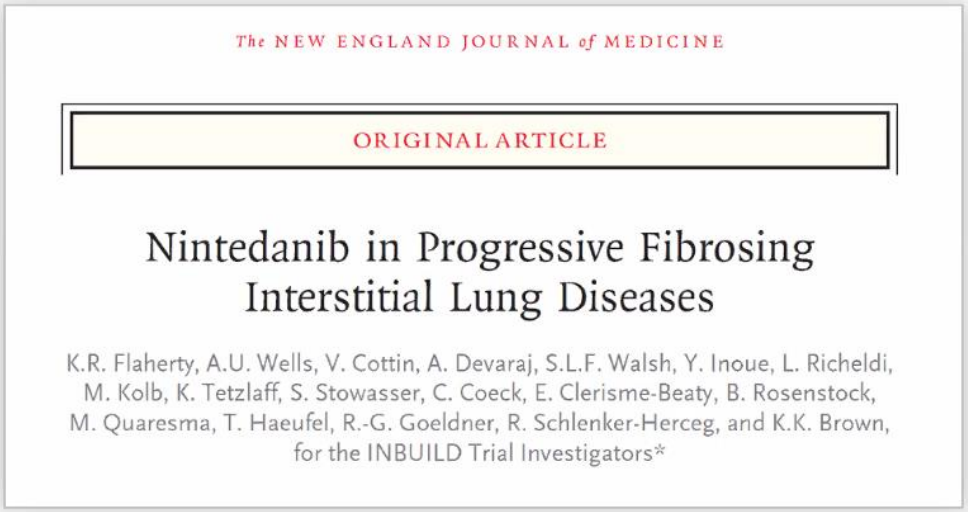


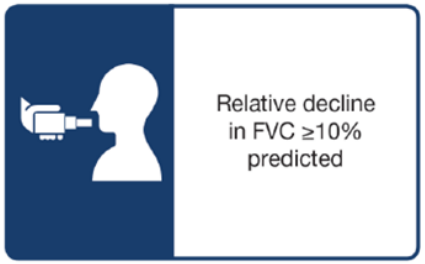
The INBUILD trial

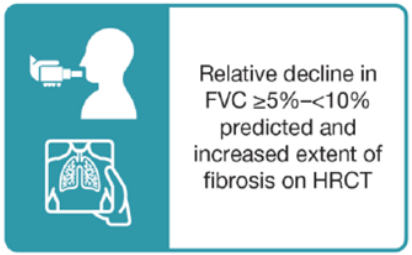


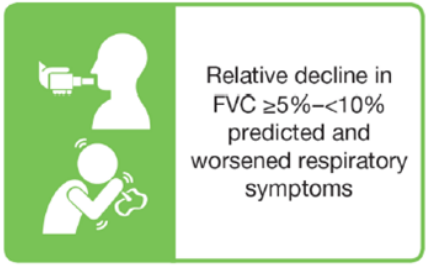
663 patients in 15 countries

- Fibrosis >10% extent on HRCT
- FVC ≥45% predicted
- DL_{CO} ≥30–<80% predicted
- ILD progression within previous 24 months

Flaherty KR, et al. N Engl J Med 2019; doi: 10.1056/NEJMoa1908681.

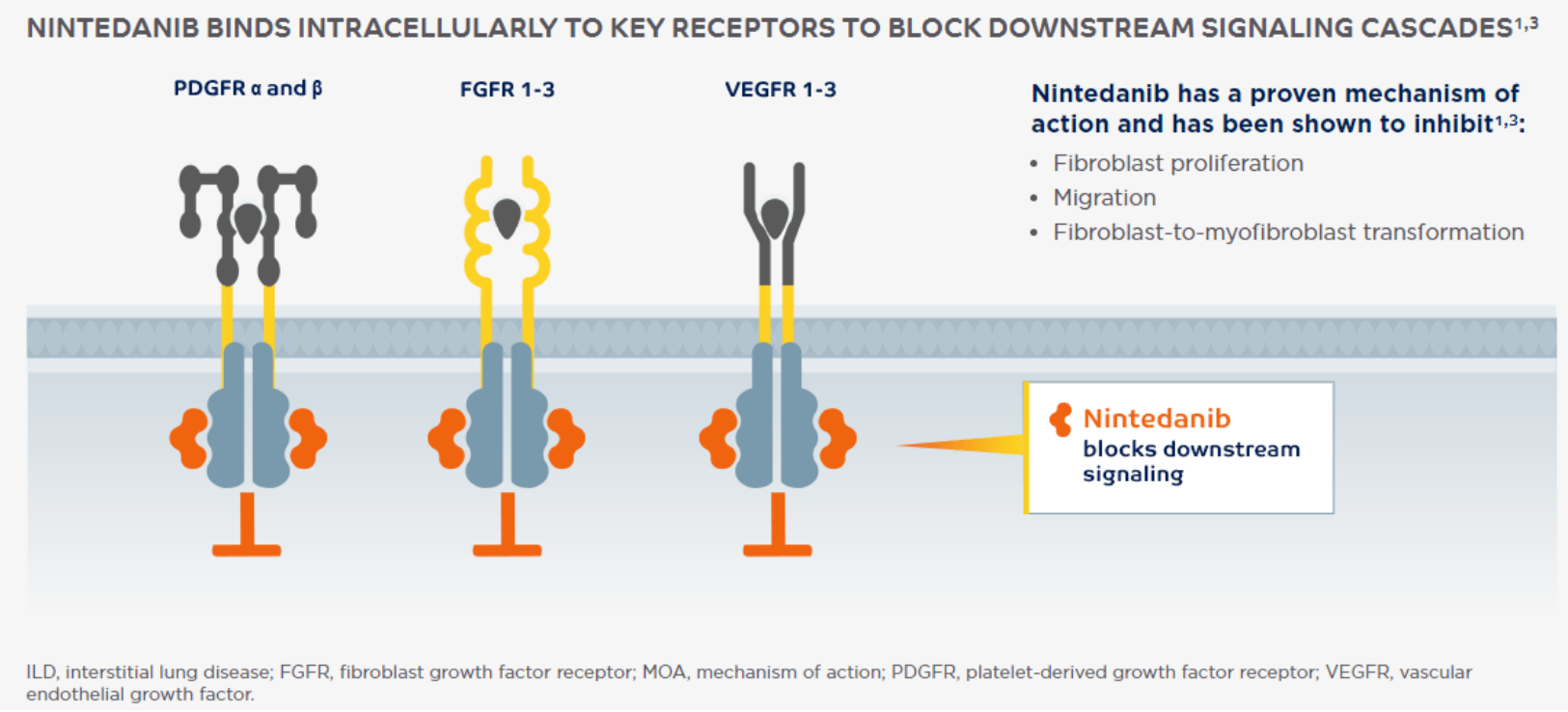






Nintedanib

- Oral small-molecule tyrosine kinase inhibitor that targets key receptors involved in pathways that lead to fibrosis
- Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of PDGF, FGF and VEGF receptors and thereby blocks the intracellular signalling cascades, which have been demonstrated to be involved in the pathogenesis of fibrotic tissue remodelling in interstitial lung diseases



INBUILD: Clinical ILD diagnoses in overall population

Clinical ILD diagnoses (grouped) in the overall population

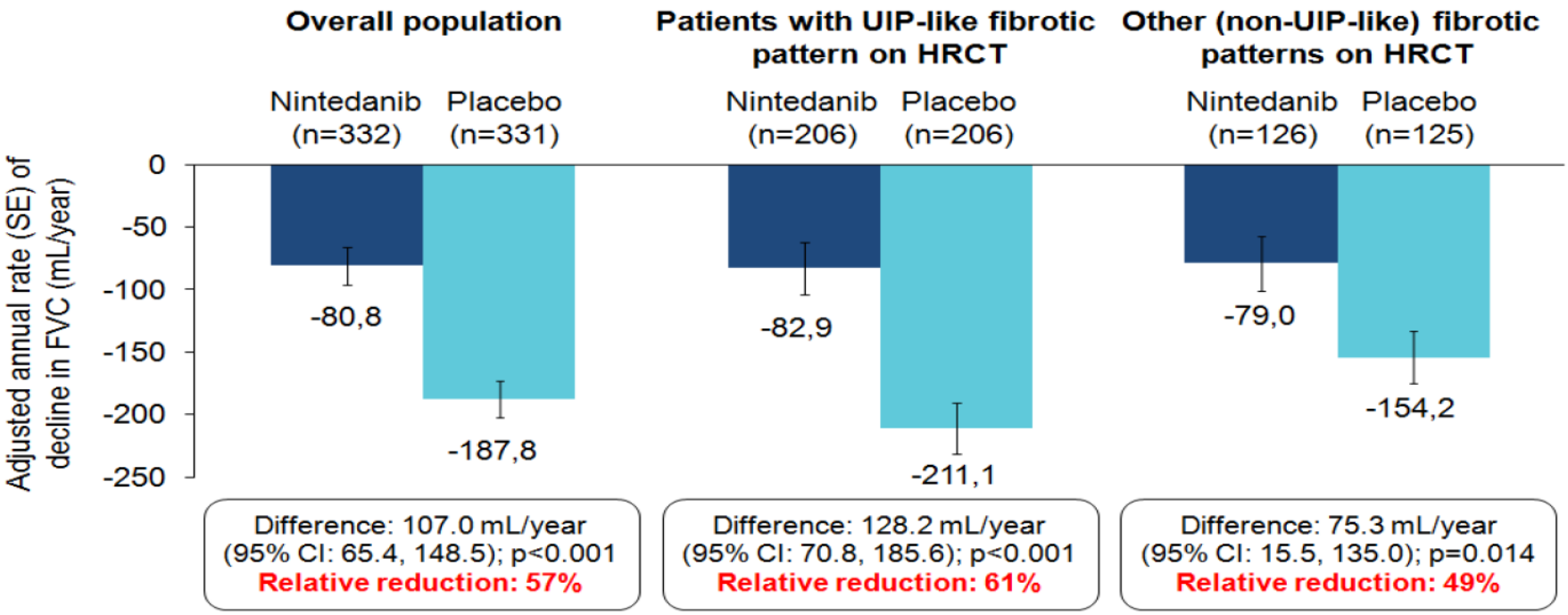
	Nintedanib (n=332)	Placebo (n=331)
Hypersensitivity pneumonitis	84 (25.3)	89 (26.9)
Autoimmune ILDs	82 (24.7)	88 (26.6)
Rheumatoid arthritis-associated ILD	42 (12.7)	47 (14.2)
Systemic sclerosis-associated ILD	23 (6.9)	16 (4.8)
Mixed connective tissue disease-associated ILD	7 (2.1)	12 (3.6)
Other autoimmune ILDs	10 (3.0)	13 (3.9)
Idiopathic non-specific interstitial pneumonia	64 (19.3)	61 (18.4)
Unclassifiable idiopathic interstitial pneumonia	64 (19.3)	50 (15.1)
Other ILDs*	38 (11.4)	43 (13.0)

Data are no (%) of patients.

*Included sarcoidosis, exposure-related ILDs and selected other terms in "Other fibrosing ILDs".

Flaherty KR, et al. N Engl J Med 2019; doi: 10.1056/NEJMoa1908681.

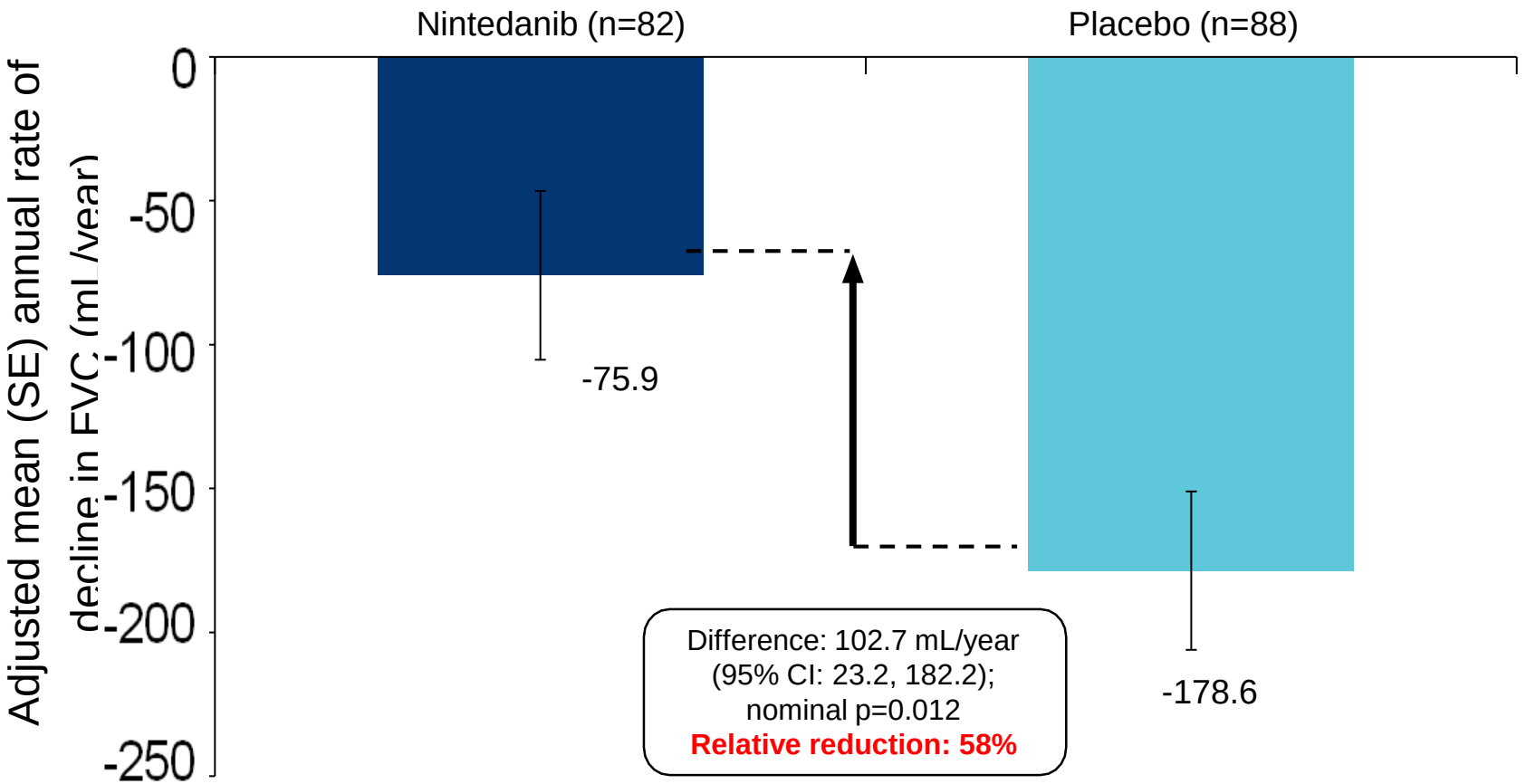
Nintedanib slowed the decline in FVC by 57% over 52 weeks



The relative reduction in the rate of FVC decline with nintedanib vs placebo was consistent irrespective of the fibrotic pattern on HRCT.

Flaherty KR, et al. N Engl J Med 2019; doi: 10.1056/NEJMoa1908681.

Nintedanib slowed the decline in FVC in patients with autoimmune disease-related ILDs

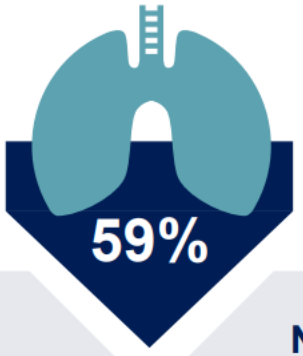


Matteson EL, et al. ACR 2019, Wells AU, et al. Lancet Respir Med 2020

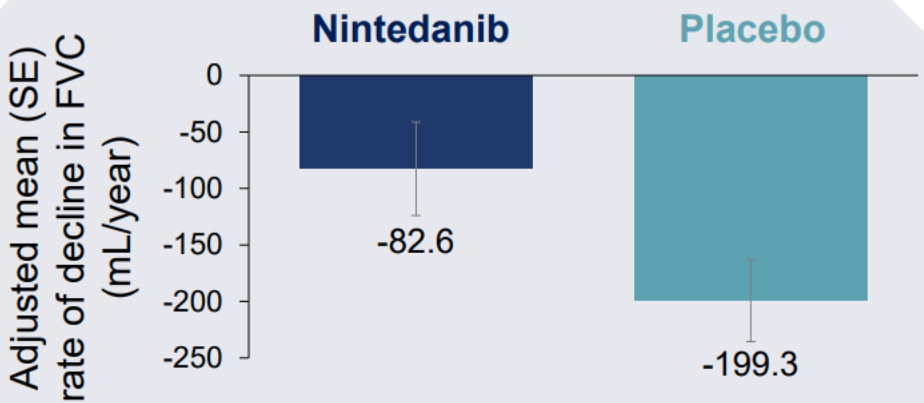
Effect of nintedanib in patients with progressive pulmonary fibrosis associated with rheumatoid arthritis: data from the INBUILD trial

Among the 89 patients with progressive fibrosing RA-ILD:

Nintedanib reduced the rate of decline in FVC over 52 weeks by 59% compared with placebo



relative reduction in rate of decline in FVC (mL/year) over 52 weeks



Difference: 116.7 (95% CI 7.4, 226.1); nominal p=0.037

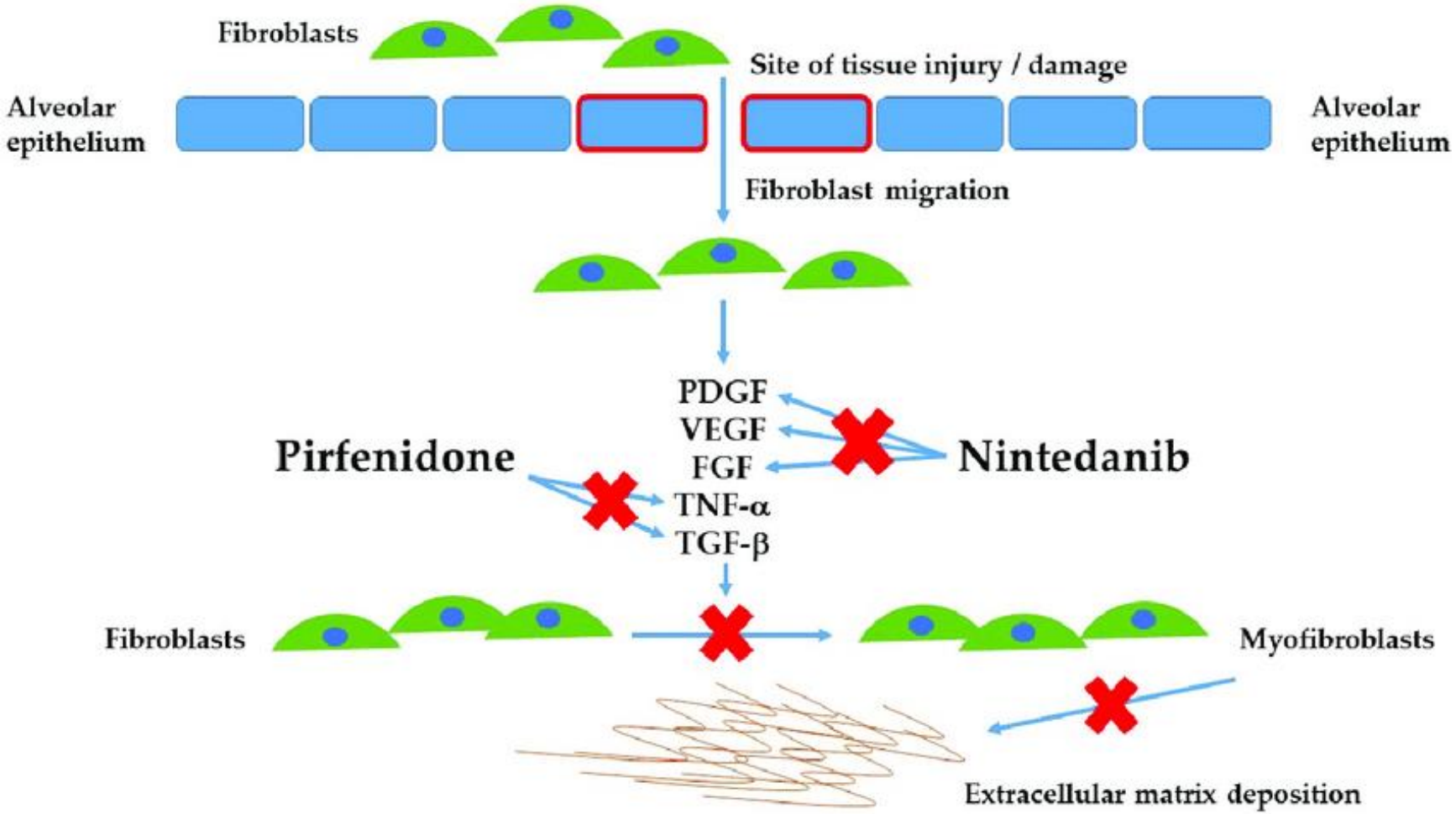
No heterogeneity was detected in the effect of nintedanib on decline in FVC across subgroups by:

- use of **DMARDs and/or glucocorticoids** at baseline
- **C-reactive protein (CRP)** at baseline

Diarrhoea was the most common adverse event over the whole trial (median exposure: 17.4 months)

Clin Rheumatol. 2023 May 20. doi: 10.1007/s10067-023-06623-7.

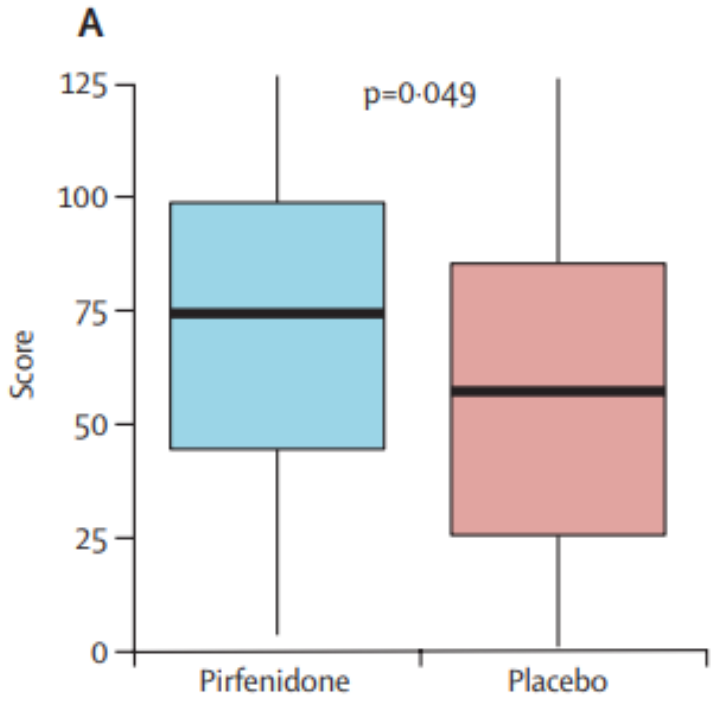
Pathophysiology of PF-
ILD and the major mechanisms by which pirfenidone and nintedanib modulate steps in the cycle of lung fibrosis



Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial

- patients aged 18–80 years with progressive fibrotic ILD due to:
  - collagen or vascular diseases
  - fibrotic non-specific interstitial pneumonia
  - chronic hypersensitivity pneumonitis
  - asbestos-induced lung fibrosis
- FVC: 40–90% predicted
- DLCO10–90% predicted
- annual decline of FVC of at least 5% predicted despite conventional therapy, based on at least three measurements within 6–24 months before enrolment

RELIEF study



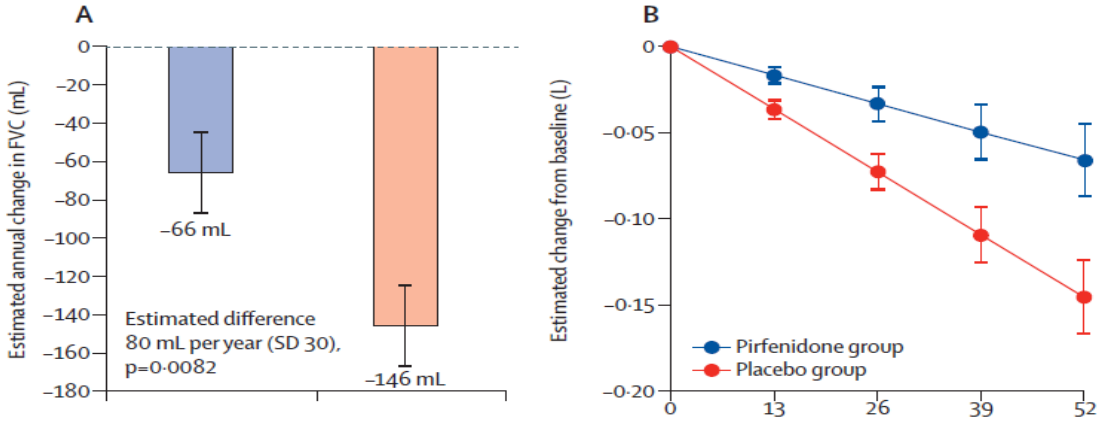
absolute change in percentage of predicted FVC (FVC % predicted) from baseline to week 48

	Baseline				Change from baseline to week 48: within groups				Change from baseline to week 48: pirfenidone *vs* placebo	p value
	n	Pirfenidone	n	Placebo	n	Pirfenidone	n	Placebo		
FVC, mL	64	2332·5 (798·9)	63	2123·0 (715·7)	35	−36·6 (281·5)	32	−114·4 (225·3)	80·0 (−40·0 to 210·0)	0·21
DLCO, mmol/kPa per min	64	3·4 (1·4)	63	3·2 (1·2)	32	−0·1 (1·0)	26	−0·4 (0·6)	0·4 (0·1 to 0·7)	0·023
6MWD, m	64	357·7 (99·2)	63	345·2 (110·0)	33	−2·7 (74·2)	30	−34·1 (91·0)	28·0 (−15·0 to 75·0)	0·15
TLC, L	64	4·1 (1·2)	63	4·0 (1·0)	35	−0·1 (0·5)	32	−0·3 (0·4)	0·2 (0·0 to 0·4)	0·089
FEV_1, mL	64	2004·2 (636·2)	63	1761·7 (552·2)	35	−76·9 (259·3)	32	−103·1 (182·1)	50·0 (−50·0 to 140·0)	0·27

TRAIL1 study

Safety, tolerability, and efficacy of pirfenidone in patients with rheumatoid arthritis-associated interstitial lung disease: a randomised, double-blind, placebo-controlled, phase 2 study

- 231 patients (3/2017 – 3/2020)
- The primary endpoint was the incidence of the composite endpoint of a decline from baseline in FVC% ≥10% or death (over 52-weeks)
- The trial was stopped early due to slow recruitment and the COVID-19 pandemic.
- primary endpoint: NOT significant (11%, 7/63 patients in the pirfenidone group *vs* 15%, 9/60 patients in the placebo group; OR 0·67 [95% CI 0·22 to 2·03]; p=0·48).
- secondary endpoints
  - reduction in the decline in absolute FVC and FVC% over 52 weeks in the pirfenidone group compared with the placebo group.
  - frequency of progressive disease, change in Dyspnea-12 scores, and admissions to hospital due to a respiratory cause, were all better in the pirfenidone group.



Lancet Respir Med 2022

Παρουσίαση περιστατικού #1

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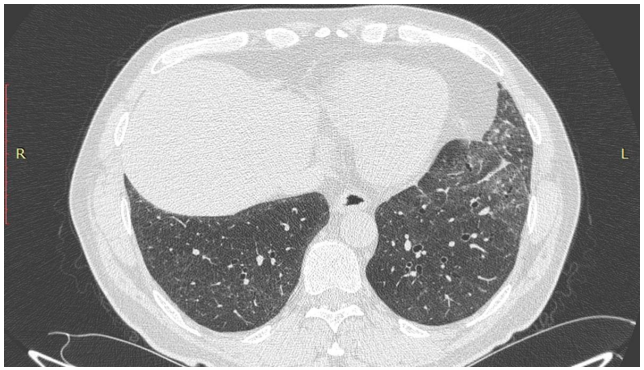


PA από 4ετίας
- Συμμετρική πολυαρθρίτιδα άκρων χειρών

- RF+++, aCCP-

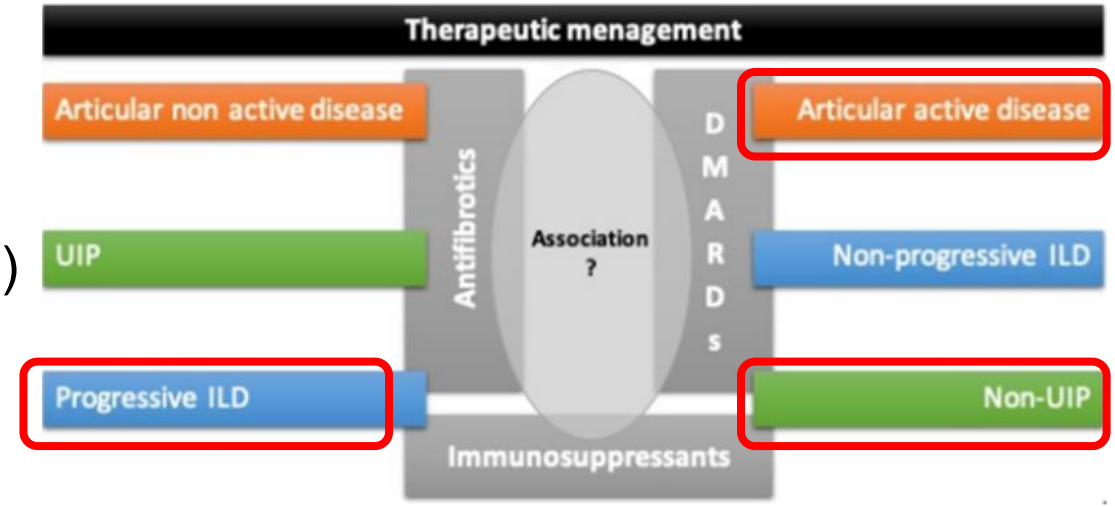
- ~~MTX~~ 15mg/w
- ~~a-TNF~~

+ **Rituximab iv**

+ **Nintedanib**

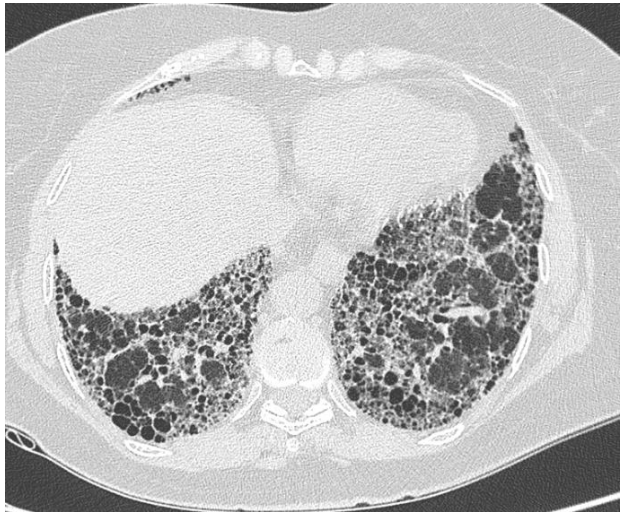
- Βήχας ξηρός από 9μήνου
- Velcro βάσεων άμφω
- FVC 82% (96% προ 2ετίας)

FVC 86% (1y)

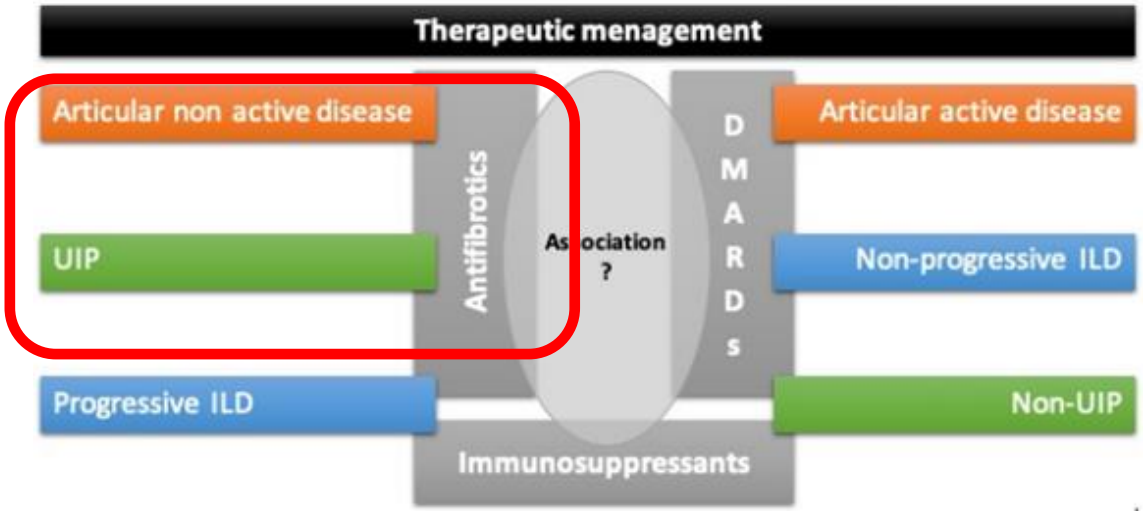


Παρουσίαση περιστατικού #2

- Γυναίκα 75ετών, μη καπνίστρια
- Οροθετική ΡΑ από το 1998
- Πνευμονική ίνωση από το 2007
- Φ.Α.: Στο παρελθόν είχε λάβει λεφλουνομίδη, υδροξυχλωροκίνη, μεθοτρεξάτη, mabthera
- prezolon 5mg και κατ'οίκον O_2
- Δύσπνοια στην ελάχιστη κόπωση, βήχα και επεισόδια αποκορεσμού (από έτους χειρότερα)
- FVC 51.3%, FEV1 63%



Παρουσίαση περιστατικού #2



- ❖ Όχι ανοσοκαταστολή
  - δεν έχει αποδείξει αποτελεσματικότητα σε UIP
  - αυξημένος κίνδυνος λοιμώξεων
- ❖ Αντινωτικό
  - τεκμηριώνεται προοδευτικός ινωτικός φαινότυπος ?

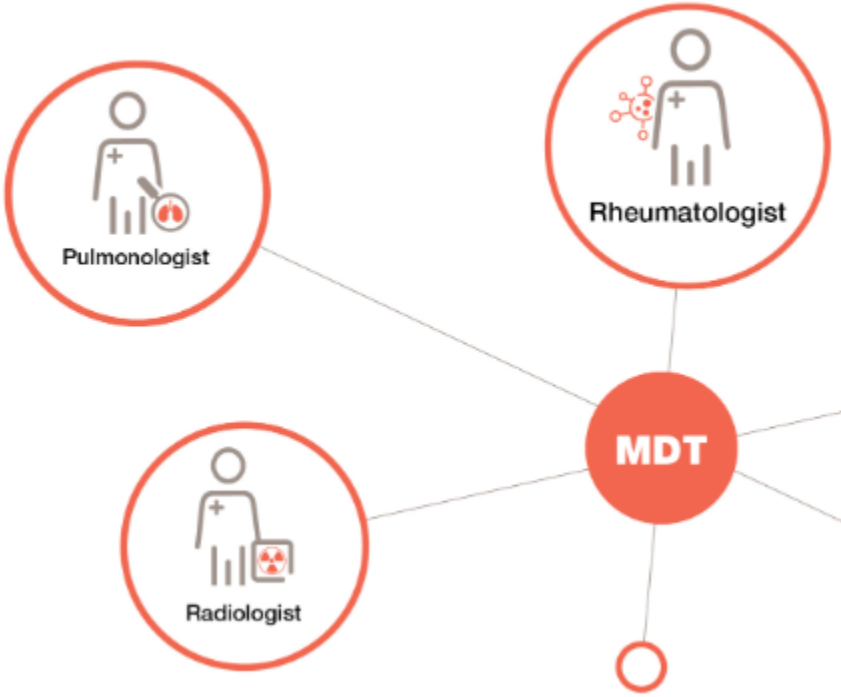
- αύξηση έκτασης ίνωσης στη HRCT
- χειρότερα κλινικά (βήχας, δύσπνοια, επεισόδια αποκορεσμού, επισκέψεις στο ΤΕΠ)
- κακή συνεργασία στη σπιρομέτρηση (μη αξιόπιστη μέτρηση)

Μετά 1.5 έτος

- υποκειμενική βελτίωση της συμπτωματολογίας της δύσπνοιας
- κλινικά σημαντικά λιγότερους παροξυσμούς βήχα
- σημαντικά λιγότερα επεισόδια αποκορεσμού στην προσπάθεια.
- Κατά την διάρκεια του τελευταίου ενάμιση έτους ελάχιστες επισκέψεις στο τμήμα επειγόντων περιστατικών.

Συμπερασματικά

- ★ Οι ασθενείς με PA έχουν αυξημένο κίνδυνο ανάπτυξης ILD
- ★ Η RA-ILD (UIP πρότυπο) σχετίζεται με αυξημένη νοσηρότητα και θνητότητα
- ★ Έγκαιρη διάγνωση
  - εκτίμηση παραγόντων κινδύνου
  - ακρόαση
  - σπιρομέτρηση - διάχυση
  - απεικόνιση (α/α, HRCT)



- ★ Θεραπευτικές επιλογές
  - εξατομίκευση θεραπείας
  - ανοσοκαταστολή
  - αντινωτική θεραπεία
    - έγκριση nintedanib για προοδευτικά επιδεινούμενη RA-ILD

Ευχαριστώ