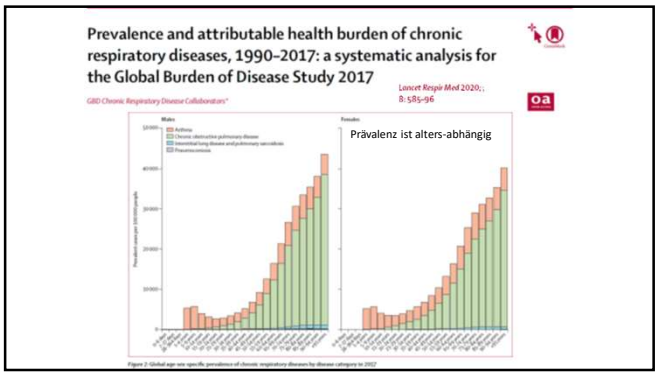
1



2

3

Male (GU), 18.11.1942

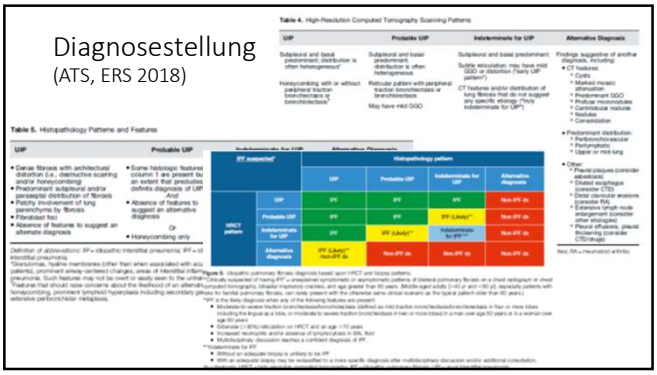
RISIKOFAKTOREN
- Ex-Raucher, zirka 10 PY, sistiert 1971, Negative FA, keine Exposition
- KLINIK
- Dyspnoe mMRC4 (e.g. Kleideranziehen), chronischer unproduktiver Husten
- Clubbing, BR 22/min, kachektisch
- Ko-MORBIDITÄT: schweres OSA, KHK, St.n. TIA, Osteoporose, leichte Anämie

BEFUNDE
- Histologie: UIP-Muster (VATS, 25.11.2010)
- Lungenfunktion: Restriktive Ventilationsstörung mit eingeschränkter Diffusionskapazität
- CT-Thorax vom 04.09.2013 : UIP-Muster
- 6-Minuten-Gehtest 610 m, minimale Sättigung 74% (14.05.2014)
- ILD-Board: Konsensdiagnose IPF 2010

30.10.2023 Martin Brutsche

4

Diagnosestellung
(ATS, ERS 2018)



5

Diagnosis of Idiopathic Pulmonary Fibrosis
An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline 2018

Question 7: Should Patients with Newly Detected ILD of Unknown Cause Who Are Clinically Suspected of Having IPF Be the Subject of MDD for Decision-Making?

Putting the evidence together. For every 1,000 patients who undergo diagnostic decision-making, SDD and MDD will derive the same diagnosis in 700 patients and different diagnoses in 300 patients. If one accepts MDD as the reference standard, then as many as 300 patients will be potentially subject to incorrect therapy, delayed therapy, or unnecessary additional diagnostic testing.

Conclusions. The guideline panel agreed that MDD is preferred, because the notion that as many as 300 patients may be subject to incorrect therapy, delayed therapy, or unnecessary additional diagnostic testing was deemed unacceptable.

6

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

Talmadge E. King, Jr., M.D., Williamson Z. Bradford, M.D., Ph.D., Socorro Castro-Bernardini, M.D., Elizabeth A. Fagan, M.D., Ian Glaspole, M.B., B.S., Ph.D., Marilyn K. Glassberg, M.D., Eduard Gorina, M.D., Peter M. Hopkins, M.D., David Kardatzke, Ph.D., Lisa Lancaster, M.D., David J. Lederer, M.D., Steven D. Nathan, M.D., Carlos A. Pereira, M.D., Steven A. Sahn, M.D., Robert Sussman, M.D., Jeffrey J. Swigris, D.O., and Paul W. Noble, M.D., for the ASCEND Study Group*

May 2014

N=555

7

Einschlusskriterien und Durchführung

- N=555
- 127 Zentren (87 in den USA - alle Kontinente ausser Afrika)
- 1:1 Randomisierung für Pirfenidon 3x3 Tbl à 267 mg per os oder Placebo für 52 Wochen

- Alter 40 – 80 Jahre
- IPF-Diagnose bestätigt durch zentrales Komitee
  - „definite IPF“
  - „possible IPF“ -> Bestätigung mit chirurgischer Biopsie
- DLCO 30-90%, FVC 50-90%, FEV1/FVC >0.8
- 6-Minuten Gehtest >150 m

8

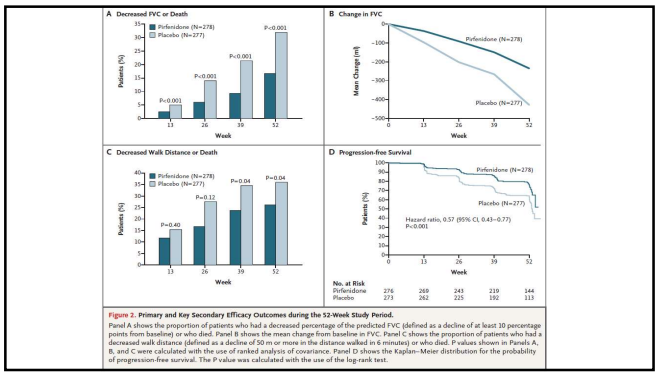


Figure 2. Primary and Key Secondary Efficacy Outcomes during the 52-Week Study Period.

Panel A shows the proportion of patients who had a decreased percentage of the predicted FVC (defined as a decline of at least 10 percentage points from baseline) or who died. Panel B shows the mean change from baseline in FVC. Panel C shows the proportion of patients who had a decreased walk distance (defined as a decline of 50 m or more in the distance walked in 6 minutes) or who died. P values shown in Panels A, B, and C were calculated with the use of ranked analysis of covariance. Panel D shows the Kaplan–Meier distribution for the probability of progression-free survival. The P value was calculated with the use of the log-rank test.

9

Table 2. Mortality in the ASCEND and CAPACITY Trials.*

Variable	Pirfenidone	Placebo	Hazard Ratio (95% CI)†	P Value‡
ASCEND trial				
No. of patients	278	277		
Death — no. (%)				
From any cause	11 (4.0)	20 (7.2)	0.55 (0.26–1.15)	0.10
Related to idiopathic pulmonary fibrosis§	3 (1.1)	7 (2.5)	0.44 (0.11–1.72)	0.23
Pooled data from ASCEND and CAPACITY trials				
No. of patients	623	624		
Death — no. (%)				
From any cause	22 (3.5)	42 (6.7)	0.52 (0.31–0.87)	0.01
Related to idiopathic pulmonary fibrosis§	7 (1.1)	22 (3.5)	0.32 (0.14–0.76)	0.006

10

Table 3. Adverse Events.*

Adverse Event	Pirfenidone (N=278)	Placebo (N=277)
	no. of patients (%)	
Cough	70 (25.2)	82 (29.6)
Nausea	100 (36.0)	37 (13.4)
Headache	72 (25.9)	64 (23.1)
Diarrhea	62 (22.3)	60 (21.7)
Upper respiratory tract infection	61 (21.9)	56 (20.2)
Fatigue	58 (20.9)	48 (17.3)
Rash	78 (28.1)	24 (8.7)
Dyspnea	41 (14.7)	49 (17.7)
Dizziness	49 (17.6)	36 (13.0)
Idiopathic pulmonary fibrosis†	26 (9.4)	50 (18.1)
Bronchitis	39 (14.0)	36 (13.0)
Constipation	32 (11.5)	38 (13.7)
Back pain	30 (10.8)	37 (13.4)
Dyspepsia	49 (17.6)	17 (6.1)
Nasopharyngitis	33 (11.9)	30 (10.8)
Anorexia	44 (15.8)	18 (6.5)
Vomiting	36 (12.9)	24 (8.7)
Decrease in weight	35 (12.6)	22 (7.9)
Gastroesophageal reflux	33 (11.9)	18 (6.5)
Insomnia	31 (11.2)	18 (6.5)

11

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 MAY 29, 2014 VOL. 370 NO. 22

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

Luca Richeldi, M.D., Ph.D., Roland M. du Bois, M.D., Ganesh Raghu, M.D., Arata Azuma, M.D., Ph.D., Kevin K. Brown, M.D., Ulrich Costabel, M.D., Vincent Cottin, M.D., Ph.D., Kevin R. Flaherty, M.D., David M. Hansell, M.D., Yoshikazu Inoue, M.D., Ph.D., Dong Soon Kim, M.D., Martin Kolb, M.D., Ph.D., Andrew G. Nicholson, D.M., Paul W. Noble, M.D., Moisés Selman, M.D., Hiroyuki Taniguchi, M.D., Ph.D., Michèle Brun, M.Sc., Florence Le Maulf, M.Sc., Mannaig Girard, M.Sc., Susanne Stowasser, M.D., Rozsa Schlenker-Herceg, M.D., Bernd Disse, M.D., Ph.D., and Harold R. Collard, M.D., for the INPULSIS Trial Investigators*

N=1061

12

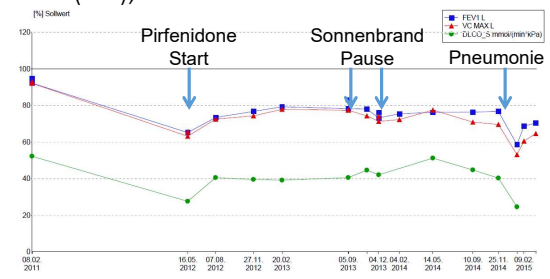
An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis
An Update of the 2011 Clinical Practice Guideline 2015

Therapieoptionen

- Lungentransplantation!
- Empfohlen und in der CH zugelassen
  - Pirfenidone (Esbriet)
  - Nintedanib (Ofev)
- PPIs, LOT bei Hypoxämie, APR
- Nicht empfohlen: Immunosuppression, Etanercept, Bosentan, IFNγ, OAK, NAC, Imatinib

13

Male (GU), 18.11.1942



30.10.2023 Martin Brutsche

14

Male (GU), 18.11.1942

VERLAUF

- makrozytäre, hyperchrome Anämie, frühes Ergrauen der Haare
- DD: Short-Telomer-Syndrom (…ist assoziiert mit IPF…)
- Telomerlängenmessung (Inselspital Bern) 08.05.2018 : kurze Telomerlängen für alle Lc-Subpopulationen, bei Granulozyten und naive T-Zellen unter der 1. Perzentile → Telomeropathie wahrscheinlich.
- Germline Panel für Telomer Störungen NGS im Blut (Inselspital) 06.9.2018: keine Mutationen nachweisbar
- Zytogenetik Knochenmark 16.07.2018 : del(20 q11.2-q13.3)

THERAPIE

- Seit 11/2018: Danazol 100mg 1-0-0

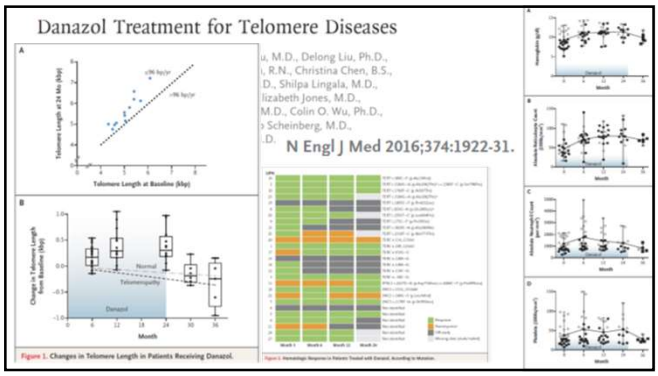
30.10.2023 Martin Brutsche

15

Danazol Treatment for Telomere Diseases

Danielle M. T
Angélique Bia
Nathan Ha
Yun Ju
Bernadette
Rodri

16



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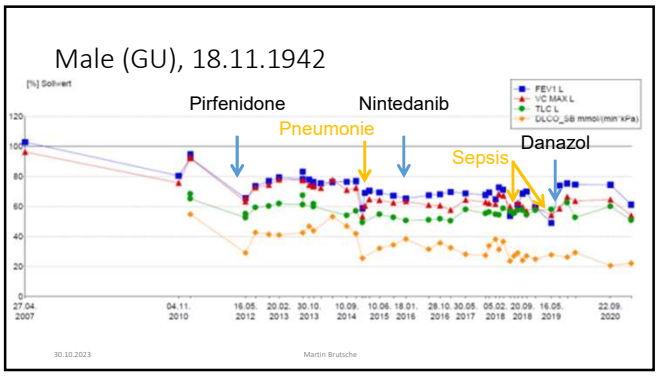


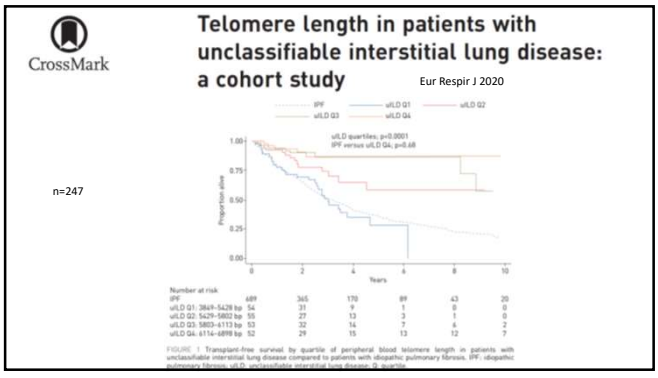
18

Telomer-Länge und fibrosierende ILDs

- Short Telomer-Syndrome sind assoziiert mit ILD
- Patienten mit IPF haben häufig eine verkürzte Telomer-Länge
- Eine verkürzte PBL-Telomer-Länge ist assoziiert mit:
  - Sterblichkeit bei IPF, cHP, nicht-klassifizierbare ILD, IPAF, Kollagenose-assoziierter ILD
  - FVC-Verschlechterung bei IPF, IPAF, Kollagenose-assoziierter ILD
- Im Mausmodell führt eine verkürzte Telomer-Länge von alveolären Epithelzellen Typ 2 (AEC2) zu fibrotischem Lung remodeling

➢Telomer-Dysfunktion wird als pathogenetischer Faktor bei fibrosierenden ILDs unterschiedlicher Äetiologie vermutet

19



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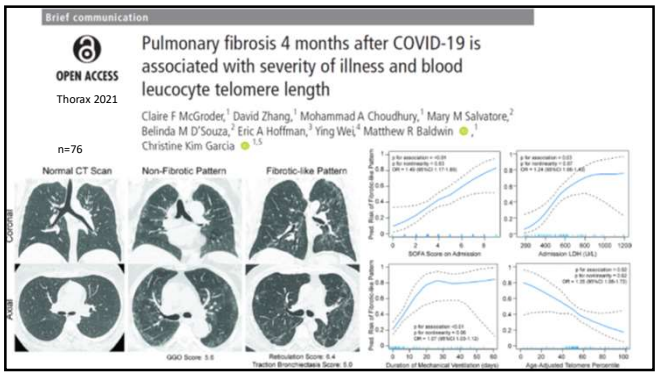

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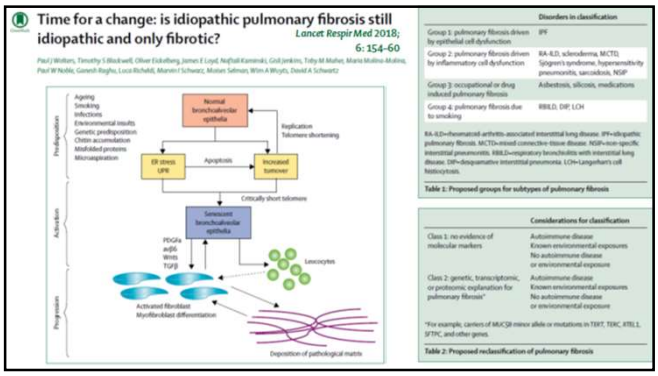


22

Male (SE), 1941

RISIKOFAKTOREN

- Nie-Raucher, ehem. Lokführer, neg. FA

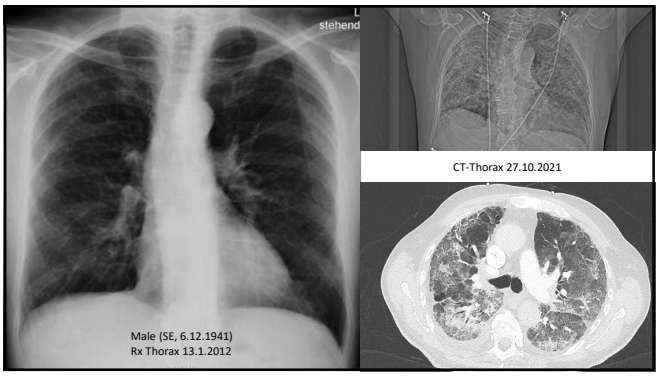
KLINIK

- seit 3 Tagen Fieber nachts und trockener Husten, progrediente Dyspnoe

BEFUNDE

- Respiratorische Partialinsuffizienz, BNP 100 pg/l, CRP 98 mg/l, Procalcitonin 0.48 ug/l, LDH 315 U/l, D-Dimer 1.71 ug/ml, Leukozyten 16 g/l, Neutrophile 92% Lymphozyten 3.8%
- Legionella pneumophila und Pneumokokken Ag: negativ, SARS-CoV-2 NP PCR: 2x negativ, SARS-CoV-2 Spike IgG >2080 BAU/ml, SARS-CoV-2 IgG und IgM negativ

23



24

Male (SE), 1941

BEFUNDE (bis)

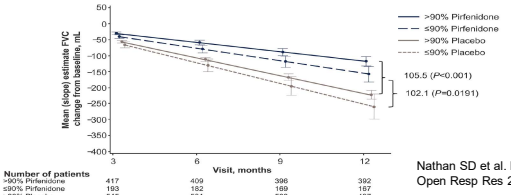
- Bronchoskopie-BAL: Bakt, Pilze, Mykobakterien, säurfeste Stäbchen, SARS-CoV-2 PCR, respiratorische Viren-Multiplex-PCR, Pneumocystis jiroveci, Legionella-PCR: negativ
- Reaktiv leicht erhöhte Gammafraktion, ANA 1:80, Myositis-Blot: Mi-2-Alpha und SRP schwach positiv (unspezifisch)
- Rheumatologisches Konsil: kein Anhalt für Systemerkrankung

THERAPIE

- Amoxcillin/Clavulansäure 24.10.2021 - 31.10.2021, Clarythromycin 27.10.2021 - 31.10.2021
- Sauerstoff-/nasale High-Flow-Therapie 28.10.2021 - 31.10.2021
- Kortisonstoss 75mg 29.10. - 12.22.2021; 25 mg vom 13.11. - 15.11.2021, erneut 75 mg bei resp. Verschlechterung vom 15.11 - 20.11.2021
- ILD-Board 19.11.2021: Konsensusdiagnose AIP bei Erstmanifestation einer IPF

25

Lungenfibrose – Verlauf unter Therapie



Number of patients				
>90% Pirfenidone	417	409	396	392
≤90% Pirfenidone	193	182	169	167
>90% Placebo	545	531	508	497
≤90% Placebo	59	60	52	52

Nathan SD et al. BMJ Open Resp Res 2018

Figure 5 Modelled mean (SEM) observed forced vital capacity (FVC) volume change from baseline (mL) over time by dose intensity (>90%, ≤90%), based on actual dose (modified intention-to-treat population). No imputation for missing values and deaths. Months 3, 6, 9 and 12 correspond to weeks 12, 24, 36 and 48 for CAPACITY (004 and 006) studies and weeks 13, 26, 39 and 52 for ASCEND (016), respectively. The annual rate of decline was estimated from the linear mixed-effects model comparing pirfenidone with placebo for each of the dose intensity groups (>90%, ≤90%), with change from baseline as the outcome variable. Study (CAPACITY 004 and 006 and ASCEND 016), treatment, sex, age and height were evaluated as fixed effects, and patient and assessment time were evaluated as random effects in an unstructured variance–covariance matrix.

26

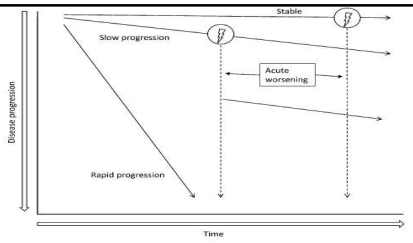


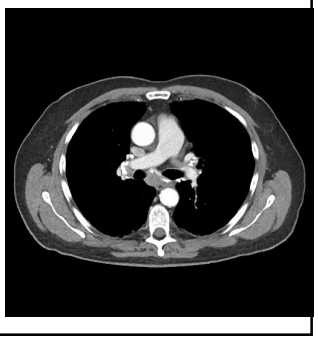
Figure 4. Natural history of IPF. There appear to be several possible natural histories for patients with IPF. The majority of patients experience a slow but steady worsening of their disease ("Slow progression"). Some patients remain stable ("Stable"), while others have an accelerated decline ("Rapid progression"). A minority of patients may experience unpredictable acute worsening of their disease (lightning bolt), either from a secondary complication such as pneumonia, or for unrecognized reasons. This event may be fatal or may leave patients with substantially worsened disease. The relative frequency of each of these natural histories is unknown.

27

Male (JW), 1951

- History
  - Chronic cough, dyspnea mMRC1
  - 15 PY, stopped 35 y ago
- Risikofaktoren
  - Construction manager, grandfather was stonemason (exposure?)
  - Neg. family history
- Findings 2011
  - CT: calcified bihilar LAP
  - BAL: 39% lymph, CD4/CD8 4
  - Blood: ACE, sIL-2R norm

➢Sarcoidosis w/o systemic activity



28

Progression 15.10.2019

- Progressive restriction and dyspnea mMRC2
- Blood: ACE, sIL-2R norm
- Bronchoscopy to find a granuloma…

Zytologische Diagnose MAM/ns
5337-1:
Differenzierte bronchioloalveoläre Lavage mit erhöhter Gesamtzellzahl (301,19 M/l) aufgrund deutlicher Vermehrung der Lymphozyten (58,5%).
Der CD4/CD8-Quotient mit 7,7 erhöht.

Pathologisch-anatomische Diagnose DBO/cm
34602-1:
Rechter Unter- und Mittellappen: Ein Kryobiopsat mit Anschnitten grösserer Bronchus- und Blutgefässe mit wenigen Herden einer organisierenden Pneumonie mit beginnender Konsolidierung und Proliferate glatter Muskulatur. Ein weiteres unauffälliges Kryobiopsat mit alveolärem Lungenparenchym und geringer Anthrakose sowie ein drittes bestehend aus Blutbestandteilen.

29

Case Report

Cryptogenic Organizing Pneumonia with Sarcoidosis Overlap: An Atypical Case Study

Case Reports in Medicine 2018

Ajmal Nazir Neelambra,[1] **Vishak Acharya**,[2] **and Sowmya Sundararajan**[3]

[1]*Department of General Medicine, Kasturba Medical College, Mangalore, India*
[2]*Department of Pulmonary Medicine, Kasturba Medical College, Mangalore, India*
[3]*Kasturba Medical College, Mangalore, India*

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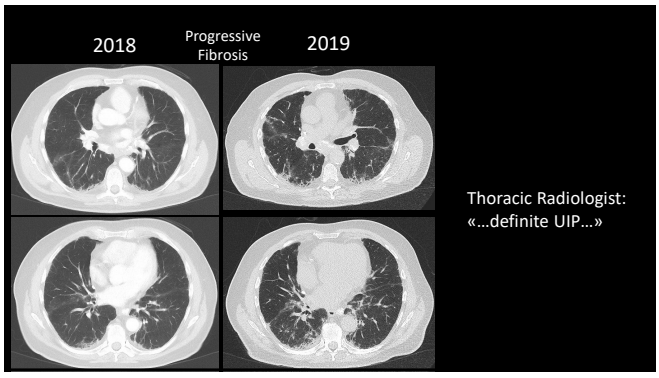
Received 30 January 2018; Revised 9 May 2018; Accepted 15 May 2018; Published 20 June 2018

Academic Editor: Ting Fan Leung

Case Summary. We present a case of a young female with subacute symptoms of cough and progressive dyspnoea. On evaluation, the patient was diagnosed as cryptogenic organizing pneumonia based on her histopathological reports. However, her significant elevation of serum angiotensin-converting enzyme (SACE) levels which drop after treatment with oral steroids, relapse, and clinical presentation pointed towards sarcoidosis as clinical diagnosis. *Discussion.* Here, in this patient, transbronchial biopsy was suggestive of cryptogenic organizing pneumonia along with chest X-ray, and the HRCT finding was also favouring the same. But in this case, we have also seen elevated levels of serum ACE which dropped significantly to the normal level along with a complete clearance of lesions with systemic steroids, and this favours sarcoidosis. Also, the recurrence was in different areas of the lung, and lesions once again responded both clinically and radiologically to steroids with a consistent drop in serum angiotensin-converting enzyme (SACE) levels, which again is a feature common in sarcoidosis. In COP, often complete clearance of the lesions is seldom seen, even though they do respond to steroids but not as dramatically as in our case. Also, recurrence of the lesion with BOOP at different sites is uncommon as it generally progresses in the same site. *Conclusion.* This case report suggests that sarcoidosis as a possible cause of cryptogenic organizing pneumonia is worth considering with the mixed spectrum of presentation as in our case. And to our knowledge, this type of presentation of cryptogenic organizing pneumonia with sarcoidosis as an overlap disease is very rare, and this possibility needs to be explored by more series of such cases.

30



31

Sarcoidosis and IPF in the same patient-a coincidence, an association or a phenotype?☆

Respiratory Medicine 2018

Bridget F. Collins[a], Robyn L. McClelland[b], Lawrence A. Ho[a], Carmen R. Mikacenic[a], Jennifer Hayes[a], Carolyn Spada[a], Ganesh Raghu[a,*]

[a] *Center for Interstitial Lung Diseases, University of Washington Medical Center, Seattle, WA, USA*
[b] *Department of Biostatistics, University of Washington School of Public Health, Seattle, WA, USA*

ABSTRACT

Background: Idiopathic Pulmonary Fibrosis (IPF) and Sarcoidosis are distinct clinical entities. Fibrotic disease in pulmonary sarcoidosis is typically upper lobe predominant. In IPF fibrosis is basilar and peripheral predominant [usual interstitial pneumonia (UIP) pattern]. Sarcoidosis and UIP have rarely been observed in the same patient. We sought to characterize patients manifesting both sarcoidosis and IPF and compare clinical features and survival to that of patients with "Lone-IPF" (IPF only) and pulmonary sarcoidosis with fibrosis in a non-UIP pattern.

Method: Patients were identified from a clinical database and data abstracted from medical records (1995-2016): 1) 25 patients with combined sarcoidosis and IPF (CSIPF) defined by clinical and histological features of sarcoidosis and HRCT features of possible or definite UIP or UIP by histopathology; 2) Randomly selected control patients during the same period: 28 Lone-IPF, 25 stage III/IV pulmonary sarcoidosis.

Results: The gender and race of patients with CSIPF and Lone-IPF patients were similar (68% male and 84% Caucasian), as were survival outcomes. Mean time from IPF diagnosis to death: 3.2 years CSIPF, 3.6 years Lone-IPF (log rank p value 0.49). Among patients with pulmonary sarcoidosis, mean time from diagnosis to death: 21.4 years.

Conclusions: Clinical characteristics/behavior of patients with CSIPF was similar to Lone-IPF patients. It is possible that patients with sarcoidosis coincidentally developed IPF and/or have occult genetic predisposition factors to manifest both diseases at different time points. Further study is needed.

32

ILD-Board 18.10.2019

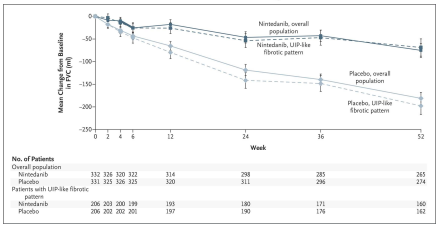
Konferenzergebnis

Empfehlungsfreitext	radiologisch UIP defnitie im Rahmen von vorbestehender Sarkoidose 1. Steroidtherapie je nach Ansprechen antifibrotische Therapie

33

Nintedanib in Progressive Fibrosing Interstitial Lung Diseases

K.R. Flaherty, A.U. Wells, V. Cottin, A. Devaraj, S.L.F. Walsh, Y. Inoue, L. Richeldi, M. Kolb, K. Tetzlaff, S. Stowasser, C. Coeck, E. Clerisme-Beaty, B. Rosenstock, M. Quaresma, T. Haeufel, R.-G. Goeldner, R. Schlenker-Herceg, and K.K. Brown, for the INBUILD Trial Investigators*



No. of Patients							
Overall population							
Nintedanib	332	326	320	322	314	298	285	265
Placebo	331	325	326	325	320	311	296	274
Patients with UIP-like fibrotic pattern							
Nintedanib	206	203	200	199	193	180	171	160
Placebo	206	202	202	201	197	190	176	162

Flaherty KR et al. N Engl J Med 2019;381:1718-1727

34

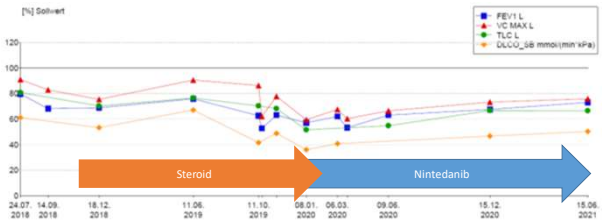
Table S2: Clinical ILD diagnoses (grouped) in the overall population

	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".

35

Lung function over time



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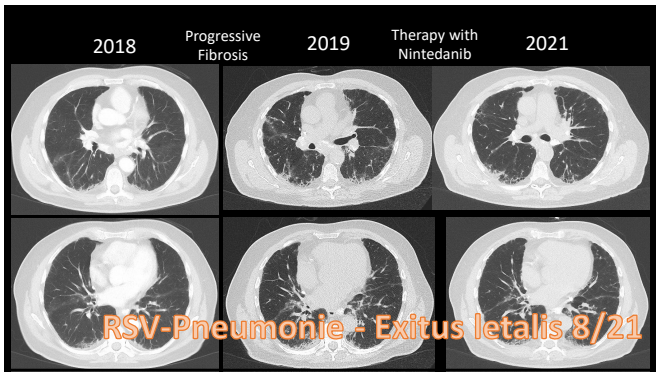

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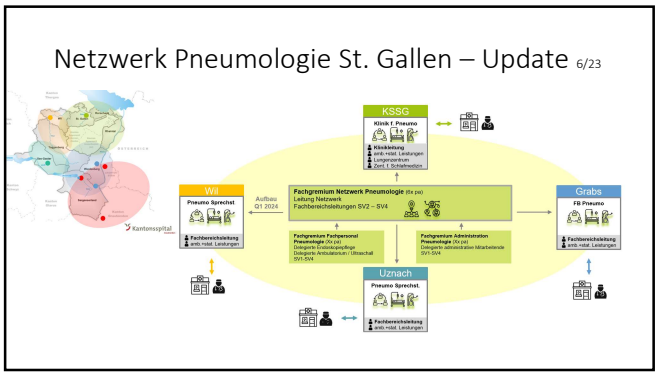
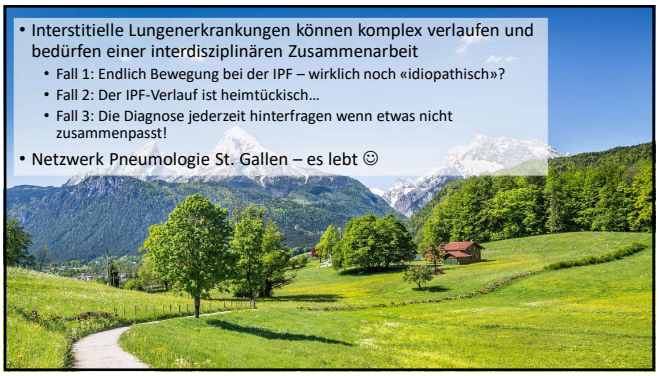


38

			7/2018		5/2022		1/2024	
	Angebot	Durchführung	Angebot	Durchführung	Angebot	Durchführung	Angebot*	Durchführung
Pneumologische Sprechstunde	X	täglich	X	täglich	X	1.5 d p. W.	X*	2d p. W.
Ambulatorium Lungenfunktion	X	täglich	X	täglich	X	1.5 d p. W.	X*	2d p. W.
Bettenstation	X	24/7						
Beatmungsweaning Unit	X	24/7						
Endoskopie	X	täglich	X		X	2xp. W.	X*	
Zentrumspneumologie	X	täglich						
Notfalldienstabdeckung (durch KSSG)	X	24/7/365	KSSG	24/7/365	KSSG	24/7/365	KSSG	24/7/365
Schlafmedizin	X	täglich	X	täglich	X	1.5 d p. W.	X*	2d p. W.
Amb. Pulm. Rehabilitation (Lungenliga)	X	extern	X	extern				
Digitale Service (Online Sprechstunde)	X	täglich			X	täglich		
Rauchstoppberatung	X	täglich	X**		X**		X**	
Forschung	X	täglich	X***	täglich	X***	täglich	X***	täglich
Exteme Sprechstunden	X****	Rehazentrum Walensadberg	X	PizolCare				

39



40

Therapie bei ILD-assoziierter pulmonal-arterieller Hypertonie

- Systemsklerose: Behandlung analog zur WHO-Gruppe 1 (aggressive Therapie bis hin zur upfront-Kombinationstherapie)
- Sarkoidose: Riocyguat (Verbesserung im 6MGT, weniger clinical worsening; B. Baughman. CHEST 2021)
- Übrige Fälle von ILD-assoziierter PAH…

41

Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease

The NEW ENGLAND JOURNAL of MEDICINE

Aaron Waxman, M.D., Ph.D., Ricardo Restrepo-Jaramillo, M.D., Thenappan Thenappan, M.D., Ashwin Ravichandran, M.D., Peter Engel, M.D., Abubakr Bajwa, M.D., Roblee Allen, M.D., Jeremy Feldman, M.D., Rahul Argula, M.D., Peter Smith, Pharm.D., Kristan Rollins, Pharm.D., Chunqin Deng, M.D., Ph.D., Leigh Peterson, Ph.D., Heidi Bell, M.D., Victor Tapson, M.D., and Steven D. Nathan, M.D. Jan 2021

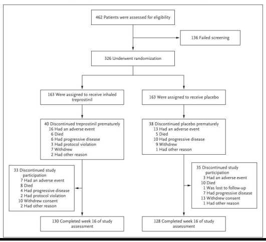
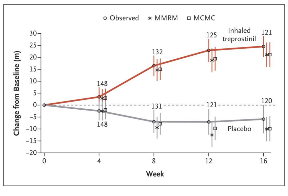

462 Patients were assessed for eligibility
136 Failed screening
326 Underwent randomization
163 Were assigned to receive inhaled treprostinil
163 Were assigned to receive placebo
40 Discontinued treprostinil prematurely
16 Had an adverse event
6 Died
6 Had progressive disease
3 Had protocol violation
7 Withdrew
2 Had other reason
38 Discontinued placebo prematurely
13 Had an adverse event
5 Died
10 Had progressive disease
9 Withdrew
1 Had other reason
33 Discontinued study participation
7 Had an adverse event
8 Died
4 Had progressive disease
2 Had protocol violation
10 Withdrew consent
2 Had other reason
35 Discontinued study participation
3 Had an adverse event
10 Died
1 Was lost to follow-up
7 Had progressive disease
13 Withdrew consent
1 Had other reason
130 Completed week 16 of study assessment
128 Completed week 16 of study assessment

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Inhaled Treprostinil (N=163)	Placebo (N=163)	All Patients (N=326)
Female sex — no. (%)	85 (52.1)	68 (41.7)	153 (46.9)
Mean age at randomization (range) — yr	65.6 (26–90)	67.4 (36–85)	66.5 (26–90)
Age distribution — no. (%)			
<65 yr	64 (39.3)	48 (29.4)	112 (34.4)
65 to <80 yr	83 (50.9)	100 (61.3)	183 (56.1)
≥80 yr	16 (9.8)	15 (9.2)	31 (9.5)
Race or ethnic group — no. (%)†			
White	112 (68.7)	126 (77.3)	238 (73.0)
Black or African American	41 (25.2)	30 (18.4)	71 (21.8)
American Indian or Alaska Native	2 (1.2)	1 (0.6)	3 (0.9)
Asian	7 (4.3)	5 (3.1)	12 (3.7)
Multiple	0	1 (0.6)	1 (0.3)
Unknown	1 (0.6)	0	1 (0.3)
Hispanic or Latino ethnic group — no. (%)†			
Yes	11 (6.7)	16 (9.8)	27 (8.3)
No	152 (93.3)	146 (89.6)	298 (91.4)
Data missing	0	1 (0.6)	1 (0.3)
Mean time since diagnosis — yr	0.54±1.16	0.54±1.31	0.54±1.23
Cause of lung disease — no. (%)			
Idiopathic interstitial pneumonia	65 (39.9)	81 (49.7)	146 (44.8)
Chronic hypersensitivity pneumonitis	10 (6.1)	9 (5.5)	19 (5.8)
Occupational lung disease	5 (3.1)	1 (0.6)	6 (1.8)
Combined pulmonary fibrosis and emphysema	42 (25.8)	40 (24.5)	82 (25.2)
Connective tissue disease	40 (24.5)	32 (19.6)	72 (22.1)
Other	1 (0.6)	0	1 (0.3)
Idiopathic interstitial pneumonia subcategory — no. (%)			
Idiopathic pulmonary fibrosis	37 (22.7)	55 (33.7)	92 (28.2)
Idiopathic nonspecific interstitial pneumonia	21 (12.9)	16 (9.8)	37 (11.3)
Respiratory bronchiolitis associated with interstitial lung disease	2 (1.2)	0	2 (0.6)
Desquamative interstitial pneumonia	0	1 (0.6)	1 (0.3)
Acute interstitial pneumonia	0	1 (0.6)	1 (0.3)
Unclassified idiopathic interstitial pneumonia	5 (3.1)	8 (4.9)	13 (4.0)
Use of supplemental oxygen — no. (%)	119 (73.0)	114 (69.9)	233 (71.5)
Background therapy — no. (%)			
None	133 (81.6)	119 (73.0)	252 (77.3)
Pirfenidone only	19 (11.7)	25 (15.3)	44 (13.5)
Nintedanib only	11 (6.7)	19 (11.7)	30 (9.2)

* Plus–minus values are means ±SD. Additional patient characteristics at baseline are provided in Table S2 in the Supplementary Appendix. Percentages may not total 100 because of rounding.
† Race and ethnic group were reported by the patient.

42



Waxman A et al. N Engl J Med 2021;384:325-334

Table 2. Summary of Primary and Secondary End Points.*

End Point	Inhaled Treprostinil (N=163)	Placebo (N=163)	Treatment Effect (95% CI)	P Value
Primary end point				
Change in peak 6-minute walk distance from baseline to wk 16 — m†	21.08±5.12	−10.04±5.12	31.12±7.25 (16.85 to 45.39)‡	<0.001
Secondary end points§				
Change in plasma concentration of NT-proBNP from baseline to wk 16¶				
Mean (±SD) change — pg/ml	−396.35±1904.90	1453.95±7296.20		
Median — pg/ml	−22.65	20.65		
Range — pg/ml	−11,433.0 to 5373.1	−5483.3 to 87,148.3		
Ratio to baseline	0.85±0.06	1.46±0.11	0.58±0.06 (0.47 to 0.72)‖	<0.001
Occurrence of clinical worsening — no. (%)			0.61 (0.4 to 0.92)**	0.04
Any event	37 (22.7)	54 (33.1)		
Hospitalization for cardiopulmonary indication	18 (11.0)	24 (14.7)		
Decrease in 6-minute walk distance of >15% from baseline	13 (8.0)	26 (16.0)		
Death from any cause	4 (2.5)	4 (2.5)		
Lung transplantation	2 (1.2)	0		
Least-squares mean change in peak 6-minute walk distance from baseline to wk 12 — m†	18.77±4.99	−12.52±5.01	31.29±7.07 (17.37 to 45.21)‡	<0.001
Least-squares mean change in trough 6-minute walk distance from baseline to wk 15 — m	9.3±5.5	−12.7±5.5	21.99±7.7 (6.85 to 37.14)‡	0.005††

* Plus–minus values are means ±SE, unless otherwise indicated. For secondary end points, the confidence intervals (CIs) have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects. NT-proBNP denotes N-terminal pro–B-type natriuretic peptide.
† The effect of inhaled treprostinil as compared with placebo on the change in 6-minute walk distance was evaluated with the use of a mixed-model repeat measurement with the change from baseline in peak 6-minute walk distance as the dependent variable; treatment, week, and treatment-by-week interaction as the fixed effects; baseline 6-minute walk distance as the covariate; and subject as the random effect. Results are shown in Figures S1 and S3.
‡ This is a least-squares mean difference between the groups.
§ The effect of inhaled treprostinil as compared with placebo on the change in log-transformed NT-proBNP was evaluated with the use of a mixed-model repeat measurement with the change from baseline in log-transformed NT-proBNP as the dependent variable; treatment, week, and treatment-by-week interaction as the fixed effects; and log-transformed baseline NT-proBNP as the covariate. Ratio to baseline is the least-squares mean of the change from baseline in log-transformed data.
¶ The change in plasma concentration of NT-proBNP from baseline to week 16 was assessed in 156 patients in the treprostinil group and 160 in the placebo group.
‖ This is the treatment ratio, which is the ratio of ratios between two treatment groups.
** This is a hazard ratio, calculated from a Cox proportional-hazards model. The P value was calculated with the use of a log-rank test stratified by the baseline 6-minute walk distance category.
†† The P value was obtained from 100 multiple imputations with Markov chain Monte Carlo estimation with the use of analysis of covariance (ANCOVA) modeling, with the change from baseline in peak 6-minute walk distance as the dependent variable, treatment as a fixed effect, and baseline 6-minute walk distance as a covariate.

43