Προβληματισμοί και νεώτερα δεδομενα στην αντιμετώπιση της Ιδιοπαθούς Πνευμονικής Ίνωσης

Πασχάλης Ντόλιος

Πανεπιστημιακό Νοσοκομείο Αλεξανδρούπολης,
Πνευμονολογική κλινική

Ιδιοπαθής Πνευμονική Ίνωση

- Η συχνότερη ιδιοπαθής διάμεση πνευμονοπάθεια (~55%)
- Άγνωστη αιτιολογία
- Προοδευτικά επιδεινούμενη, καταλήγει πάντα στην αναπνευστική ανεπάρκεια και το θάνατο (διάμεση επιβίωση 2-5 χρόνια)
- Επίπτωση: 16-22 ασθενείς / 100.000 πληθυσμού
  - Μεγαλύτερη στους άντρες, αυξάνεται με την ηλικία
- Κυρίαρχος ρόλος της ινωτικής διεργασίας και όχι της φλεγμονής στην παθογένεση

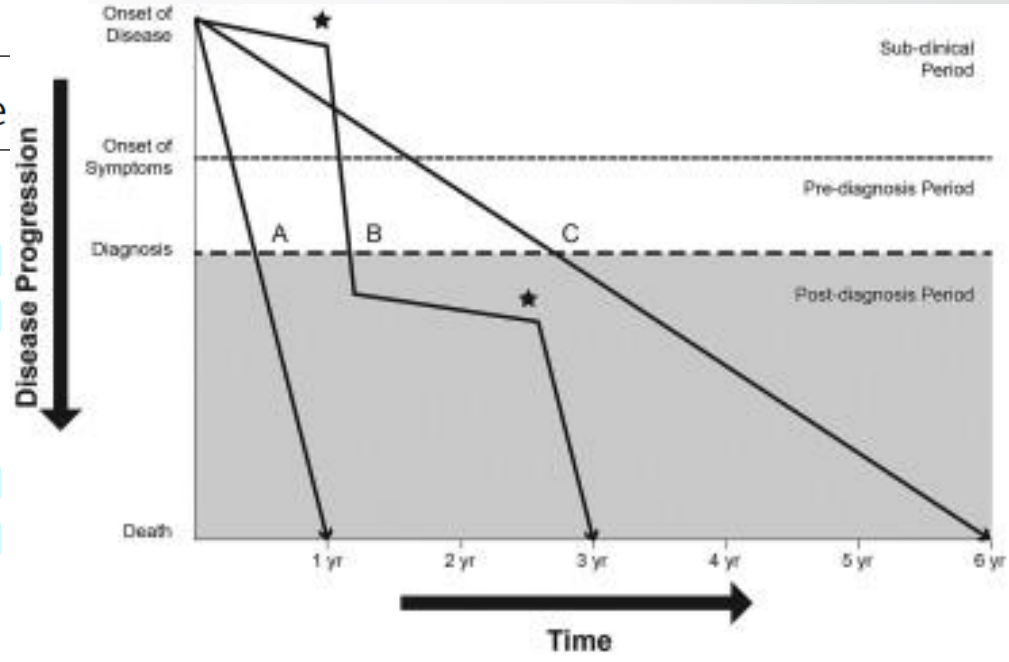
1. Meltzer EB and Noble PW. Orphanet J Rare Dis 2008;3:8–22;
2. Coultas DB et al. Am J Respir Crit Care Med 1994;150:967–997;
3. Hodgson U et al. Thorax 2002;57:338–342; 4. Hansell A eta l. Thorax 1999;54:413–419;
5. Eurostat News Release. Available at http://ec.europa.eu/eurostat. Accessed on 4 August 2013;
6. Ley B and Collard HR. Clin Epidemiol 2013;5:483–492;
7. Valeyre D. Eur Respir Rev 2011;20:108–113.

Ιδιοπαθής Πνευμονική Ίνωση: φυσική πορεία της νόσου

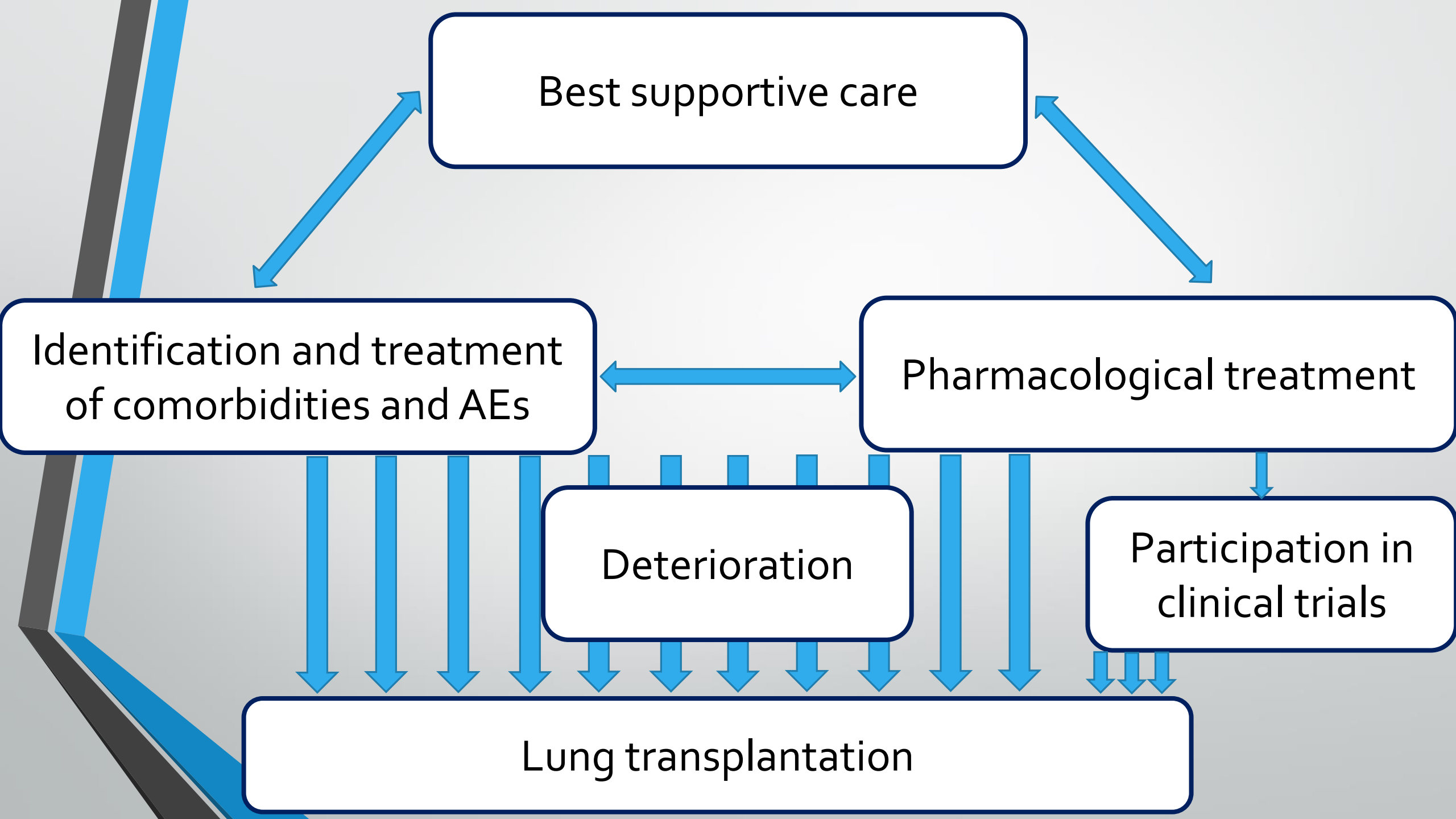
TABLE 6. COX PROPORTIONAL HAZARDS MODEL

			1-Year Risk of Death	
	Patient Visits (*n*)	Deaths (*n*)	HR (*95% CI*)	*P* Value
ΔFVC, % predicted				
⩽−10	166	39	4.78 (3.12–7.33)	<0.001
−5 to −10	373	45	2.14 (1.43–3.20)	<0.001
>−5	1,316	56		
FVC, % predicted				
⩽50	203	42	7.44 (3.28–16.87)	<0.001
51 to 65	691	65	4.09 (1.87–8.98)	<0.001
66 to 79	594	26	1.97 (0.85–4.55)	0.111
⩾80	374	7		

Definition of abbreviations: ΔFVC = 24-week absolute change in percent-predicted FVC (e.g., change from 70–65% = 5% absolute change); CI = confidence interval; HR = hazard ratio.



Ley B, et al. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011;**183**:431–440.
Official Journal of the American Thoracic Society.


Best supportive care
Identification and treatment of comorbidities and AEs
Pharmacological treatment
Deterioration
Participation in clinical trials
Lung transplantation

Supportive Care

- Supplemental oxygen (SaO_2 < 88% during 6MWT)
- Pulmonary rehabilitation
  - Aerobic conditioning
  - Strength and flexibility training
- Education
  - Nutritional counseling
  - Psychosocial support
- Vaccination
- Palliative care

Φαρμακεύτικοί παράγοντες

Potentially harmful therapies

- Ambrisentan[81]
- Everolimus[82]
- Prednisolone, azathioprine, acetylcysteine[9]
- Warfarin[83]

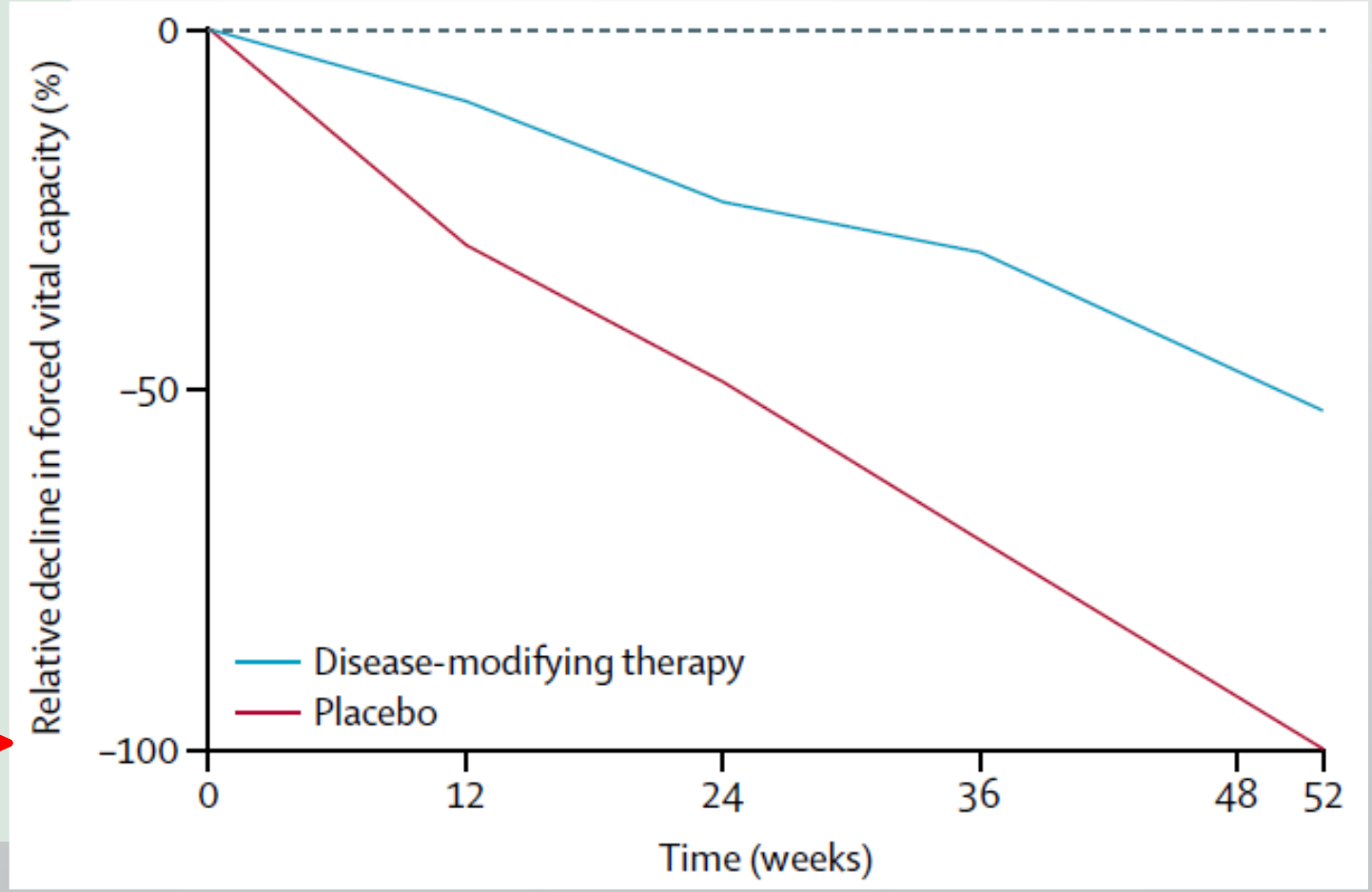
Potentially ineffective therapies

- Bosentan[84]
- Imatinib[85]
- Macitentan[86]
- Acetylcysteine[87]
- Sildenafil[88]

Effective disease-modifying therapies

- Nintedanib[89]
- Pirfenidone[90,91]

Richeldi L, et al, Lancet Resp Med 2017



Προβλήματα και προβληματισμοί

- Δεν αντιστρέφουν την ίνωση
- Βελτίωση επιβίωσης?
- Η βελτίωση της ποιότητας ζωής δεν είναι αισθητή από τον ασθενή → δύσπνοια, βήχας, διακοπή λόγω παρενεργειών
- Απουσία τυχαιοποιημενων μελετών για ασθενείς με FVC<50% ή/και Dlco<35%

- Personalized medicine: -επιλογή του κατάλληλου φαρμάκου για τον κάθε ασθενή, -πρόβλεψη των ασθενών που δεν θα ανταποκριθούν
- Αλλαγή αγωγής → πότε?
- Συγχορήγηση πιρφενιδόνης - νιντεδανίμπης

Effect of pirfenidone on mortality: pooled analyses and meta-analyses of clinical trials in idiopathic pulmonary fibrosis

Steven D Nathan, Carlo Albera, Williamson Z Bradford, Ulrich Costabel, Ian Glaspole, Marilyn K Glassberg, David R Kardatzke, Monica Daigl, Klaus-Uwe Kirchgaessler, Lisa H Lancaster, David J Lederer, Carlos A Pereira, Jeffrey J Swigris, Dominique Valeyre, Paul W Noble

"…pirfenidone therapy is associated with a reduction in the relative risk of mortality compared with placebo over 120 weeks"

Pirfenidone improves survival in IPF: results from a real-life study

George A. Margaritopoulos[1,2†], Athina Trachalaki[1†], Athol U. Wells[2], Eirini Vasarmidi[1], Eleni Bibaki[1], George Papastratigakis[1], Stathis Detorakis[3], Nikos Tzanakis[1†] and Katerina M. Antoniou[1*†]

"…pirfenidone provides a survival benefit in a real-life IPF cohort compared to previously used medications"

Long-term safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis: results from the open-label extension study, INPULSIS-ON

Bruno Crestani, John T Huggins, Mitchell Kaye, Ulrich Costabel, Ian Glaspole, Takashi Ogura, Jin Woo Song, Wibke Stansen, Manuel Quaresma, Susanne Stowasser, Michael Kreuter

"…the effect of nintedanib on slowing the progression of idiopathic pulmonary fibrosis persists beyond 4 years"

Predicted Versus Observed Mortality in Clinical Trials of Nintedanib in Idiopathic Pulmonary Fibrosis (IPF)

C. J. Ryerson[1], M. Wijsenbeek[2], F. Bonella[3], P. Spagnolo[4], W. Stansen[5], S. Stowasser[5], L. Richeldi[6]; [1]University of British Columbia, Vancouver, BC, Canada, [2]Erasmus MC, University

"…nintedanib treatment was associated with a reduction in the risk of mortality over 1 year compared with placebo"

Safety and efficacy of pirfenidone in severe Idiopathic Pulmonary Fibrosis: A real-world observational study

Argyrios Tzouvelekis [a, *, 1], Paschalis Ntolios [b, 1], Theodoros Karampitsakos [a], Vasilios Tzilas [a], Stavros Anevlavis [b], Evangelos Bouros [a], Paschalis Steiropoulos [b], Nikolaos Koulouris [a], Grigoris Stratakos [a], Marios Froudarakis [b], Demosthenes Bouros

"…safe when administered in patients with advanced IPF. …efficacy may diminish after 6 months of treatment"

Effect of pirfenidone in patients with more advanced idiopathic pulmonary fibrosis

Ulrich Costabel[1*], Carlo Albera[2], Marilyn K. Glassberg[3], Lisa H. Lancaster[4], Wim A. Wuyts[5], Ute Petzinger[6], Frank Gilberg[7], Klaus-Uwe Kirchgaessler[7] and Paul W. Noble[8]

"…pirfenidone is efficacious, well tolerated, and a feasible treatment option in patients with more advanced IPF"

Efficacy and Safety of Pirfenidone in Advanced Idiopathic Pulmonary Fibrosis

Hee-Young Yoon Dong Soon Kim Jin Woo Song

"…similar efficacy and safety to non-advanced IPF except for serious AEs"

A Real-Life Multicenter National Study on Nintedanib in Severe Idiopathic Pulmonary Fibrosis

Sergio Harari[a] Antonella Caminati[a] Venerino Poletti[b] Marco Confalonieri[c]
Stefano Gasparini[d] Donato Lacedonia[e] Fabrizio Luppi[f] Alberto Pesci[g]

"…slows down the rate of decline of absolute and % DLCO but does not have significant impact on FVC"

Efficacy and safety of nintedanib in advanced idiopathic pulmonary fibrosis

Hee-Young Yoon, Sojung Park, Dong Soon Kim and Jin Woo Song

"…efficacy and safety profiles in the advanced group were comparable to those in the non-advanced group"

First Data on Efficacy and Safety of Nintedanib in Patients with Idiopathic Pulmonary Fibrosis and Forced Vital Capacity of ≤50 % of Predicted Value

Wim A. Wuyts[1] · Martin Kolb[2] · Susanne Stowasser[3] · Wibke Stansen[3]
John T. Huggins[4] · Ganesh Raghu[5]

"…similar effect on disease progression in patients with advanced disease as in less advanced disease"

Efficacy of pirfenidone in patients with idiopathic pulmonary fibrosis with more preserved lung function

Carlo Albera[1], Ulrich Costabel[2], Elizabeth A. Fagan[3], Marilyn K. Glassberg[4], Eduard Gorina[3], Lisa Lancaster[5], David J. Lederer[6], Steven D. Nathan[7], Dominique Spirig[8] and Jeff J. Swigris[9]

"These findings support the initiation of treatment irrespective of stage of baseline lung function"

Nintedanib in patients with idiopathic pulmonary fibrosis and preserved lung volume

Martin Kolb,[1] Luca Richeldi,[2] Jürgen Behr,[3] Toby M Maher,[4,5] Wenbo Tang,[6] Susanne Stowasser,[7] Christoph Hallmann,[7] Roland M du Bois[8]

"Patients with IPF and preserved lung volume have the same rate of FVC decline and receive the same benefit"

Επιλογή σκευάσματος

- Δεν υπάρχουν μελέτες ανωτερότητας του ενός εκ των δύο
- Δεν υπάρχουν υποομάδες ασθενών που να οφελούνται περισσότερο από το ένα εκ των δύο
- Η συνδυαστική θεραπεία και με τα δύο σκευάσματα είναι υπό μελέτη →Σημαντικό ρόλο παίζουν οι αναμενόμενες παρενέργειες:
  - Διάρροια με την νιντεδανίμπη
  - Ναυτία, φωτοευαισθησία και εξάνθημα με την πιρφενιδόνη

Nintedanib with Add-on Pirfenidone in Idiopathic Pulmonary Fibrosis
Results of the INJOURNEY Trial

Carlo Vancheri[1], Michael Kreuter[2], Luca Richeldi[3], Christopher J. Ryerson[4], Dominique Valeyre[5], Jan C. Grutters[6,7], Sabrina Wiebe[8], Wibke Stansen[9], Manuel Quaresma[2,9], Susanne Stowasser[9], and Wim A. Wuyts[10]; on behalf of the INJOURNEY Trial Investigators

"…manageable safety and tolerability profile"

Safety and pharmacokinetics of nintedanib and pirfenidone in idiopathic pulmonary fibrosis

Takashi Ogura[1], Hiroyuki Taniguchi[2], Arata Azuma[3], Yoshikazu Inoue[4], Yasuhiro Kondoh[2], Yoshinori Hasegawa[5], Masashi Bando[6], Shinji Abe[3], Yoshiro Mochizuki[7], Kingo Chida[8], Matthias Klüglich[9], Tsuyoshi Fujimoto[1], Kotaro Okazaki[10], Yusuke Tadayasu[10], Wataru Sakamoto[10] and Yukihiko Sugiyama[6]

"…trend towards lower nintedanib exposure"

Safety of Nintedanib Added to Pirfenidone Treatment for Idiopathic Pulmonary Fibrosis

Kevin R. Flaherty, Charlene D. Fell, J. Terrill Huggins, Hilario Nunes, Robert Sussman, Claudia Valenzuela, Ute Petzinger, John L. Stauffer, Frank Gilberg, Monica Bengus, Marlies Wijsenbeek

"Combined pirfenidone and nintedanib was tolerated by the majority of patients with IPF, encouraging further study"

Randomised, double-blind, placebo-controlled pilot trial of omeprazole in idiopathic pulmonary fibrosis

Prosenjit Dutta,[1] Wendy Funston,[1] Helen Mossop,[2] Vicky Ryan,[2] Rhys Jones,[1] Rebecca Forbes,[3] Shilpi Sen,[4] Jeffrey Pearson,[5] S Michael Griffin,[6] Jaclyn A Smith,[4,7] Christopher Ward,[1] Ian A Forrest,[8] A John Simpson[1,8]

cough frequency at the end of treatment, adjusted for baseline, was 39.1% lower (95% CI 66.0% lower to 9.3% higher) in the omeprazole group compared with placebo. Omeprazole was well tolerated and adverse event profiles were similar in both groups, although there was a small excess of lower respiratory tract infection and a small fall in forced expiratory volume and forced vital capacity associated with omeprazole.

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Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1		Not yet recruiting NEW	Evaluation of Efficacy and Safety of Pamrevlumab in Patients With **Idiopathic Pulmonary Fibrosis**	• **Idiopathic Pulmonary Fibrosis**	• Drug: Pamrevlumab • Drug: Placebo	
2		Recruiting	Safety, Tolerability, and Pharmacokinetic Study of TRK-250 for Patients With **Idiopathic Pulmonary Fibrosis**	• **Idiopathic Pulmonary Fibrosis**	• Drug: TRK-250 • Drug: Placebo	• Pulmonary Associates Phoenix, Arizona, United States • Mayo Clinic Jacksonville, Florida, United States

Emerging targets and drugs

- Target: Lysophosphatidic acid (LPA)
  - Promotes fibroblast recruitment
  - Increased in IPF lung tissue
- GLPG1690 → inhibits LPA production through autotaxin inhibition
  - Phase IIa: minimal adverse reactions, stable FVC against placebo
  - Phase III studies recruiting (NCT03711162, NCT03733444)
- BMS-986020 → inhibits LPA1 receptor
  - Phase II: Reduction in FVC decline rate, **however** increased liver enzymes and 3 cases of cholecystitis

Maher TM., et al; Lancet Respir Med, 2018

Palmer SM., et al; Chest, 2018

Emerging targets and drugs

- Target: Connective Tissue Growth Factor (CTGF)
  - Promotes fibroblast differentiation and activation of myofibroblasts
  - Increases TGF-b expression and ECM deposition
  - Increased in IPF lung BALf
- FG-3019 (pamrevlumab)→ binds CTGF with great affinity
  - Phase IIa, open label: acceptable safety profile, 140 mL FVC decline over 48 weeks BUT with improvement of 0.2-14.1% in 30% of patients
  - Phase II, double-blind (NCT03733444): slowed progression as assessed by quantitative HRCT at weeks 24 and 48
  - Fast-track from FDA for phase III trials

Raghu G., et al; Eur Resp J 2016

Corina E., et al; AJRCCM 2018

Emerging targets and drugs

- Target: αvβ6 Integrin
  - Strongly expressed in alveolar epithelial cells in fibrotic areas of IPF lung tissue
  - Higher levels associated with increased risk of death
- BG00011→ humanized anti-αvβ6 immunoglobulin (Ig) G1 monoclonal antibody
  - Phase IIa: no treatment-related AEs, reduction of TGF-b signal transducer pSMAD2 in BALf
  - Phase IIb: recruiting (NCT03573505)

Raghu G., et al; AJRCCM 2018

Emerging targets and drugs

- Target: G-protein-coupled receptors GPR40 and GPR84
- PBI-4050→ Agonist for GRP40, antagonist for GPR84
  - Reduces activation and profibrotic gene expression by fibroblasts
  - Phase II (NCT02538536): well tolerated, no significant decline in FVC when used alone and in combination with nintedanib. However: A drug–drug interaction with pirfenidone resulted in a significant decline in FVC over 12 weeks

Khalil N., et al; Eur Resp J 2018

Emerging targets and drugs

- Target: Pentraxin-2 (PTX2-2) or serum amyloid P (SAP)
  - Blood plasma pattern recognition receptor
  - Downregulates monocyte and macrophage activity
  - Reduces M2 polarized macrophages
- PRM-151→ Intravenous recombinant human pentraxin-2
- Phase I: well tolerated, one episode of treatment-related hypotension
- Phase II: permitted concomitant pirfenidone or nintedanib, reduced FVC decline. However: increases cough, trial included patients with possible UIP on HRCT

Khalil N., et al; Eur Resp J 2018

Stem cells - Clinical studies in IPF

A phase 1b study of placenta-derived mesenchymal stromal cells in patients with idiopathic pulmonary fibrosis

DANIEL C. CHAMBERS,[1,2] DEBRA ENEVER,[1] NINA ILIC,[3] LISA SPARKS,[4] KYLIE WHITELAW,[1] JOHN AYRES,[5] STEPHANIE T. YERKOVICH,[1,2] DALIA KHALIL,[6] KERRY M. ATKINSON[7,8] AND PETER M.A. HOPKINS[1,2]

"Intravenous MSC administration is feasible and has a good short-term safety profile in patients with moderately severe IPF"

Allogeneic human mesenchymal stem cells in patients with idiopathic pulmonary fibrosis via intravenous delivery (AETHER): a phase I, safety, clinical trial

Marilyn K. Glassberg, M.D., Julia Minkiewicz, Ph.D., Rebecca L. Toonkel, M.D., Emmanuelle S. Simonet, M.A., Gustavo A. Rubio, M.D., Darcy Difede, R.N., B.S.N., Shirin Shafazand, M.D., Aisha Khan, Ph.D., Marietsy V. Pujol, M.B.A., Vincent F. LaRussa, Ph.D., Lisa H. Lancaster, M.D., Glenn D. Rosen, M.D., Joel Fishman, M.D., Ph.D., Yolanda N. Mageto, M.D., M.P.H., Adam Mendizabal, Ph.D., Joshua M. Hare, M.D.

"No treatment-related AEs, at 60 weeks FVC mean decline was 3% and Dlco mean decline was 5.4%"

Stem cells - Clinical studies in IPF

A prospective, non-randomized, no placebo-controlled, phase Ib clinical trial to study the safety of the adipose derived stromal cells-stromal vascular fraction in idiopathic pulmonary fibrosis

Argyris Tzouvelekis[1], Vassilis Paspaliaris[2], George Koliakos[3,4], Paschalis Ntolios[1], Evangelos Bouros[5], Anastasia Oikonomou[6], Athanassios Zissimopoulos[7], Nikolaos Boussios[7], Brian Dardzinski[3,4], Dimitrios Gritzalis[8], Antonis Antoniadis[9], Marios Froudarakis[1], George Kolios[5] and Demosthenes Bouros[1,10*]

"**No serious AEs during the 1st year, absence of decline of FVC or Dlco after 1 year**"

Longitudinal outcomes of Patients Enrolled in a Phase Ib Clinical Trial of the Adipose Derived Stromal Cells-Stromal Vascular Fraction in Idiopathic Pulmonary Fibrosis

"Significant functional decline occurred at 24 months … median survival and time to progression are in line with published epidemiologic data"

Stem cells - Clinical studies in IPF

Safety and Tolerability of Alveolar Type II Cell Transplantation in Idiopathic Pulmonary Fibrosis

Anna Serrano-Mollar, PhD [1,15] *, Gemma Gay-Jordi, PhD [1,15], Raquel Guillamat-Prats, PhD [1,15], Daniel Closa, PhD [1], Fernanda Hernandez-Gonzalez, MD [1, 2, 15], Pedro Marin, PhD [3], Felip Burgos, PhD [2,15], Jaume Martorell, PhD [4], Marcelo Sánchez, MD [5], Pedro Arguis, MD [5], Dolors Soy, PhD [6,15,16], José M Bayas, PhD [7], José Ramirez, PhD [8,14, 15], Teresa D. Tetley, PhD [9], Laureano Molins, PhD [10, 16], Jordi Puig de la Bellacasa, PhD [11,16], Camino Rodríguez-Villar; PhD [12], Irene Rovira, PhD[13], Juan José Fiblà, MD [14], Antoni Xaubet, PhD [2,15,16 *], for the Pneumocyte Study Group[#]

"no significant adverse events, … pulmonary function, respiratory symptoms and disease extent did not deteriorate during 12-months of follow-up"

Διαχείριση της οξείας παρόξυνσης

- Δεν υπάρχουν τυχαιοποιημένες μελέτες
- Συνήθως η αντιμετώπιση περιλαμβάνει ενδοφλέβια αντιβιοτικά, υποστηρικτική αγωγή και κορτικοστεροειδή
  - χωρίς ωστόσο να υπάρχουν έγκυρα δεδομένα από μελέτες
  - Αντικρουόμενα δεδομένα από σειρές ασθενών
- Ο μηχανικός αερισμός ενδείκνυται μόνο ως γέφυρα για μεταμόσχευση πνεύμονα
- Δεν υπάρχουν δεδομένα για τον ρόλο των υπάρχοντων αντι-ινωτικών παραγόντων στην αντιμετώπιση της AE-IPF

Raghu G, et al., AJRCCM, 2011

Papiris SA, et al., BMC Pulm Med, 2015

Συμπεράσματα

- Δεν υπάρχουν δεδομένα για υπεροχή ενός εκ των δύο διαθέσιμων φαρμάκων
- Κανένα εκ των δύο δεν προσφέρει αισθητά αποτελέσματα όσον αφορά την ποιότητα ζωής
- Η χρήση τους στην προχωρημένη νόσο είναι ασφαλής και πιθανότατα επωφελής
- Δεν υπάρχουν ακόμα αρκετά δεδομένα όσον αφορά την συγχορήγηση
- Η ομεπραζόλη βοηθά στη βελτίωση του βήχα
- Υπάρχουν πλέον, σε αντίθεση με το παρελθόν, πολλές κλινικές μελέτες – σημαντική η ένταξη των ασθενών σε αυτές
- Ζητούμενο η επιλογή του κατάλληλου φαρμάκου για τον κάθε ασθενή