Pulmonary hypertension due to lung diseases

Sergio Harari
U.O. di Pneumologia e Terapia Semi Intensiva
Servizio di Fisiopatologia Respiratoria ed Emodinamica Polmonare
Osp. San Giuseppe – MultiMedica IRCCS
Milano

COI disclosure

- Roche: investigator in trials, lectures, AB
- Actelion : investigator in trials, lectures, AB, grant for research
- Boehringer Ing. : investigator in trials, lectures, AB, grant for research

Task Force 10 – PH in chronic lung diseases

CHAIR: WERNER SEEGER, Giessen GERMANY

CHAIR: STEVEN D. NATHAN, Falls Church VA USA

JOAN ALBERT BARBERÀ, Barcelona SPAIN

SEAN P. GAINE, Dublin IRELAND

JOAN ALBERT , Barcellona SPAIN

SERGIO HARARI, Milan ITALY

FERNANDO JOSE MARTINEZ, Ann Arbor MI USA

HORST OLSCHEWSKI, Graz AUSTRIA

KAREN M. OLSSON, Hanover GERMANY

ANDREW J. PEACOCK, Glasgow UK

JOANNA PEPKE-ZABA, Cambridge UK

STEEVE PROVENCHER, Chemin Sainte-Foy CANADA

NORBERT WEISSMANN, Giessen GERMANY

Introduction

Pulmonary hypertension (PH) may be associated with chronic lung disease, mainly chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD).

However it is associated with other CLD, such as cystic fibrosis and bronchopulmonary dysplasia, and its presence is related to a reduced functional status and worse outcomes.

Even in patients who fulfill diagnostic criteria for Group 1 PAH, the presence of minor lung disease affects survival.

It is not still clear if the presence of PH is causative or a surrogate of other factors affecting outcomes.

Some data suggest that also mPAP ≤25 mmHg is associated with worse outcome in CLD-PH.

Seeger W et al. JACC 2013; Berge RMF et al. Lancet 2012
Manika K et al Pulm Med 2012; Medrek SK et al, COPD 2017
Poms AD et al. Chest 2013; Hamada et al. Chest 2007

COPD-PH: Epidemiology

The prevalence is dependent on the severity of the disease, but also on the definition of PH and method of diagnostic evaluation in the different studies.

Several studies in GOLD IV pts showed that up to 90% have a mPAP>20 mmHg (range 20-35 mmHg), and only 1-5% have mPAP >35-40 mmHg at rest

Under moderate exercise COPD pts may show a rapid rise in PAP, suggesting a loss of lung vasculature, vascular distensibility and/or vessel recruitment capability. Furthermore, exercise PH in COPD may be also related to left heart disease.

COPD-PH: Epidemiology

Hoffmann et al. demonstrated the presence of specific genetic signatures linked with the developmento of PH in COPD.

There is a cluster of patients representing a “pulmonary vascular COPD phenotype”, characterized by less severe airflow limitation, hypoxemia, very low DLCO, normo- or hypocapnia and a cardiovascular exercise limitation profile.

It has previously been established that the presence of PH has a stronger association with mortality in COPD than FEV1 or gas exchange variables. In addition, an enlarged pulmonary artery diameter, as detected at the CT scan, predicts hospitalization due to acute COPD exacerbation.

Major characteristics of patients with COPD
“Pulmonary vascular phenotype”

- Severe precapillary pulmonary hypertension
- Moderate airflow limitation
- No or very mild hypercapnia
- Very low DLCO (<45%predicted)
- Circulatory exercise limitation

Kovacs G et al. AJRCCM 2018

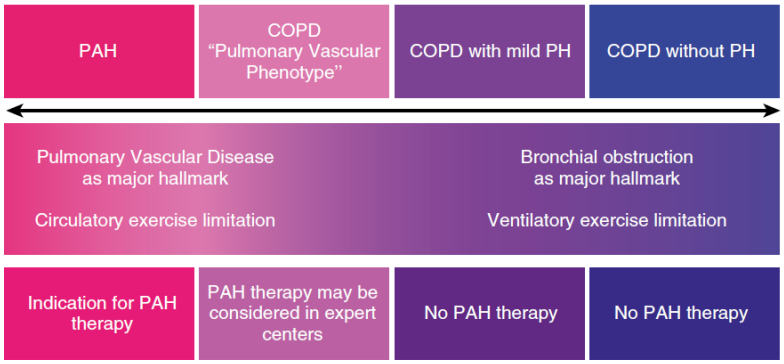
Pulmonary vascular phenotype in COPD

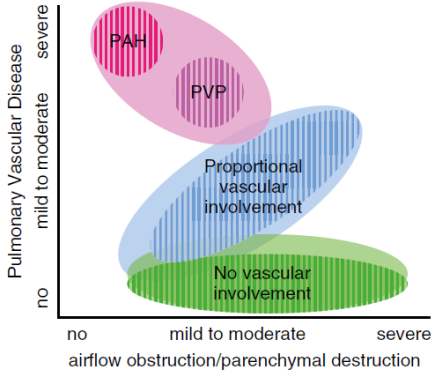
Pts with this phenotype share some important characteristics with pts affected by PAH. Especially, there is a potential overlap with idiopathic PAH (like very low DLCO).

Pts with PAH may also present with COPD as a concomitant comorbid condition or with a mild peripheral airway obstruction due mainly to vascular rigidity leading to an impairment of lung elastic recoil.

Pts with pulmonary vascular phenotype should also be distinguished from subjects with severe airway obstruction and hypoxia or severe parenchymal derangement

Pts with COPD with completely or nearly normal PAP represent the other end of the clinical spectrum





Kovacs G et al. AJRCCM 2018

« Disproportionate PH » : cluster analysis

COPD

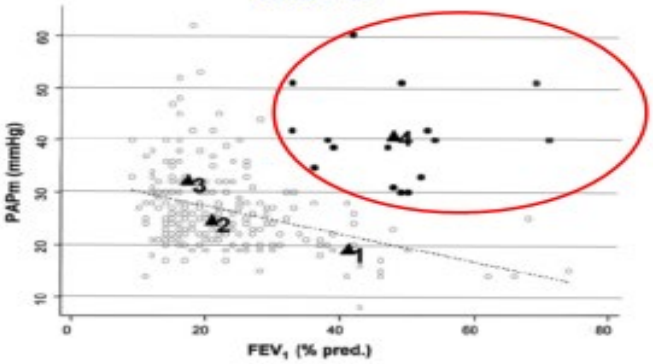
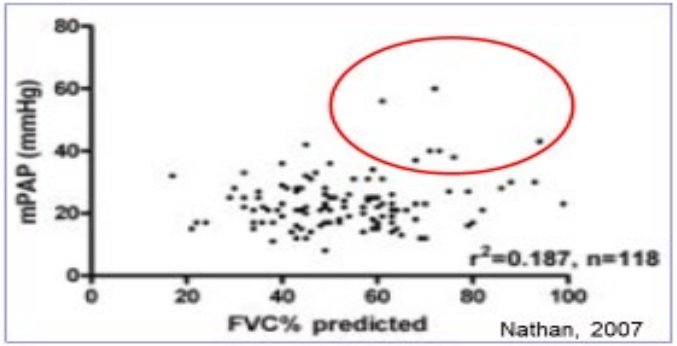


FIGURE 2. Characteristics of the four groups of patients disclosed by cluster analysis. Relationships between PAPm and FEV_1 are shown in groups 1, 2, and 3 (hollow circles) and group 4 (full circle). Triangles indicate the average of each group. A regression line is displayed.

Thabut G et al, *Chest* 2005;127:1531

IPF



Nathan SD Chest 2007;131:657

IPF- and IIP-PH: Epidemiology

Most of the data on prevalence of PH in fibrotic lung disorders comes from IPF studies.

In IPF, mPAP ≥25 mmHg have been reported in 8-15 % of pts upon initial work-up with greater prevalence in advanced (30-50%) and end-stage (>60%) disease.

Echocardiography and other non invasive tools (such as enlarged PA at CT scan) have a limited accuracy to detect PH and should be used only as screening.

There is limited correlation between PH severity and lung function impairment or HRCT fibrosis score, whereas distinct gene signatures have been observed in IPF-PH lungs.

PH may also be associated with an increased risk for acute exacerbation in advanced IPF.

Nadrons HF Chest 2005; Lettieri CJ Chest 2006; Shorr AF ERJ 2007; Nathan SD Respir Med 2008; Alhamed EH Radiology 2011; Mura M Chest 2012; Judge EP ERJ 2012; Kimura M, Respiration 2013; Raghu G ERJ 2015; Teramachi R Respirology 2017

Diagnosis of PH in Chronic Lung Disease (CLD)

Non invasive modalities helping to suspect PH in CLD are:

Echocardiography is the best non invasive tool. The determination of peak TRV is limited in COPD and IPF pts. In these group of pts alternate echocardiographic measures including right ventricular outflow tract diameter, tricuspid anular plane systolic excursion, and qualitative assessment of right chamber structure and function have been advocated in IPF and COPD.

-Circulating Biomarkers: BNP or pro BNP are helpful in severe PH, but less sensitive and specific in moderate PH and may be confonded by left heart abnormalities.

-DLCO, exercise capacity and main gas exchanges at rest lower than the one expected in the base of ventilatory impairment in COPD and IPF may rise the suspicion of PH.

Right Heart Catheterization

RHC is the gold standard for the diagnosis of CLD-PH. However, it is not mandatory if there is no therapeutic or management consequence.

RHC should be performed in pts with CLD, when its result may influence the management of the underlying disease (i.e. refer to lung transplantation).

RHC may be considered when clinical worsening, progressive exercise limitation and/or gas exchange abnormalities are not deemed attributable to ventilatory impairment, or if an accurate prognostic assessment is deemed sufficiently important.

It is important underline that PH measurement should not be undertaken during acute exacerbation but under stable condition

RHC measurements

Due to high changes of the intrathoracic pressures during the breathing cycles in pts affected by CLD a floating average over several breaths (without a breath hold) is suggested for measurement of mean pressures, including the pulmonary capillary wedge pressure.

There is no valid data to support the use of acute vasodilator testing in this group of patients.

The definition of PH associated to CLD is:

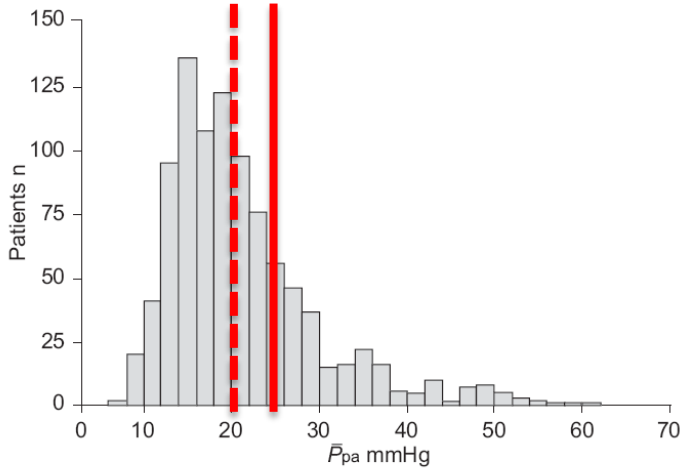
a) CLD without PH (mPAP <21 mmHg, or mPAP 21-24 with pulmonary vascular resistance (PVR) <3 WU)

b) CLD with PH (mPAP 21-24 mmHg with PVR >3 WU, or mPAP 25-34 mmHg (CLD-PH)

c) CLD with severe PH (mPAP >35 mmHg or mPAP >25 mmHg with low cardiac index (< 2.0 L/min/m2); (CLD-severe PH)

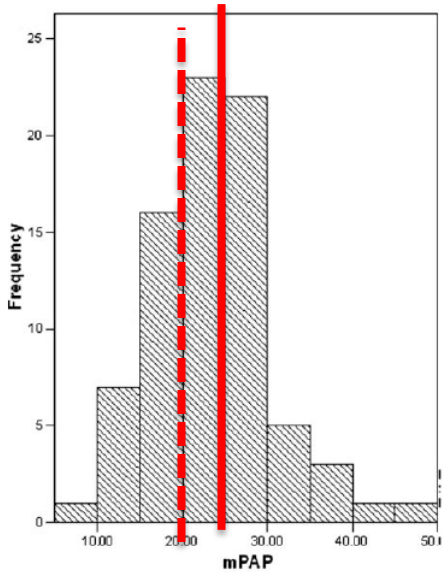
PH in chronic respiratory diseases: hemodynamics

COPD



Chaouat A et al, Am J Respir Crit Care Med 2005; 172: 189

IPF



Lettieri CJ *et al, Chest* 2006;129:746

How can I discriminate patients affected by PH group 3 and patiens affected by PAH in the context of CLD?

Lung diseases (especially COPD) are common conditions and PAH developing in such patients may not be attributable to these diseases, but may be co-incidental.

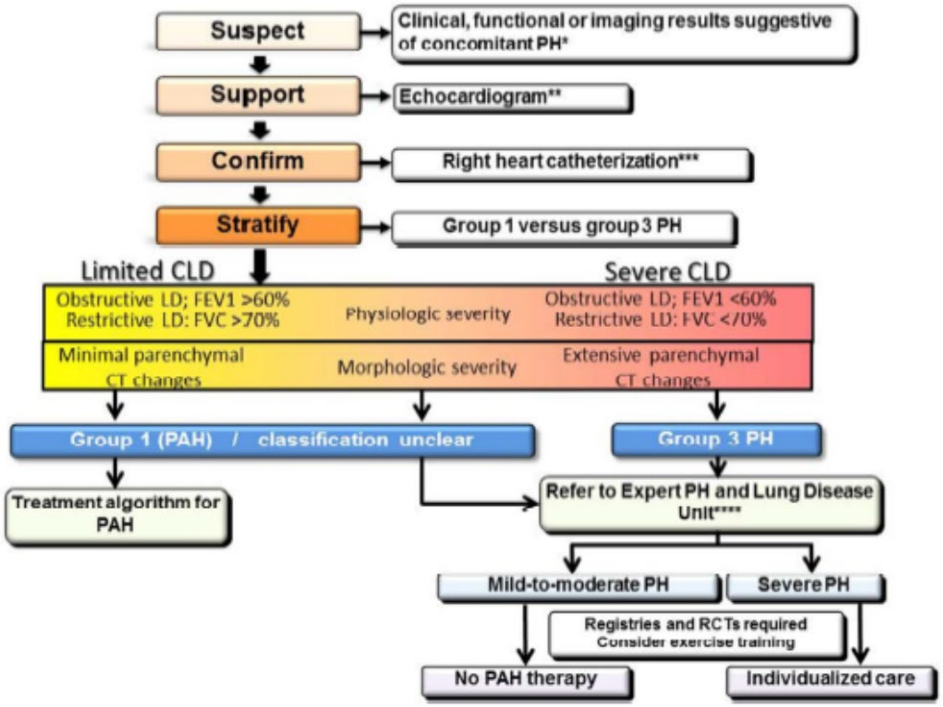
The spectrum of severity of both the pulmonary vascular and parenchymal lung disease is likely a continuum, which often makes the distinction between group 1 and group 3 PH very difficult.

How can I discriminate patients affected by PH group 3 and patiens affected by PAH in the context of CLD?

Table 1 – Criteria favoring Group 1 (PAH) versus Group 3 (PH due to Lung Disease) Pulmonary Hypertension*

Criteria favoring Group 1 (PAH)	Testing	Criteria favoring Group 3 (PH due to Lung Disease)
Extent of lung disease		
Normal or mildly impaired: FEV1 >60% pred. (COPD) FVC >70% pred. (IPF) Low diffusion capacity in relation to obstructive/restrictive changes	Pulmonary function testing	Moderate to very severe impairment: FEV1 <60% pred. (COPD) FVC <70% pred. (IPF) Diffusion capacity "corresponds" to obstructive/restrictive changes
Absence of or only modest airway or parenchymal abnormalities	High resolution CT scan**	Characteristic airway and/or parenchymal abnormalities
Hemodynamic Profile		
Moderate to severe PH	Right heart catheterization Echocardiogram	Mild to moderate PH
Ancillary Testing		
Present	Further PAH risk factors (as e.g. HIV, connective tissue disease, BMPR2 mutations, ...)	Absent
Features of exhausted circulatory reserve – Preserved breathing reserve – Reduced oxygen pulse – Low CO/VO2 slope – Mixed venous oxygen saturation at lower limit – No change or decrease in PaCO2 during exercise	Cardiopulmonary exercise test*** (particularly relevant in COPD)	Features of exhausted ventilatory reserve – Reduced breathing reserve – Normal oxygen pulse – Normal CO/VO2 slope – Mixed venous oxygen saturation above lower limit – Increase in PaCO2 during exercise
Predominant hemodynamic profile		Predominant obstructive/restrictive profile

How can I discriminate patients affected by PH group 3 and patiens affected by PAH in the context of CLD?



COPD-PH: Treatment

COPD should be treated according to the last guidelines.

LTOT makes intuitive sense in COPD patients who are hypoxemic.

Although in stabilized hypoxemic COPD patients, LTOT for 15 h/day prevented the progressive increase of mPAP and when used >18 h/day produced a slight decrease of mPAP, in COPD patients with moderate resting (SpO2 89-93%) or exercise-induced desaturation (<90% for ≥10 seconds), LTOT does not provide benefit in terms of survival or hospitalizations.

Timms et al. Ann Int Med 1985
Weitzenblum E et al. Am Rev Resp Dis 1985
Albert RK et al. NEJM 2016
Bell EC ERR 2017

COPD-PH: use of PAH targeted therapies

Long term use of PAH-targeted therapies improves pulmonary hemodynamic in COPD pts with PH.

Beneficial hemodynamic effects with long-term PAH treatment, assessed by RHC, demonstrate both with sildenafil and bosentan

The effect of these treatment on exercise capacity is controversial: 2 meta-analysis failed to show a significant improvement in 6MWD, while a 3rd one documented an improvement in 6MWD. Sildenafil was found to improve BODE index, MRC and SF-36 GHD.

Taken together, the available studies do not provide clear evidence that the effect of PAH-targeted therapy on pulmonary hemodynamics in COPD-PH translates into an improvement in exercise tolerance and symptoms.

Vasodilator treatment may worsen gas exchange due to the inhibitor of hypoxemic pulmonary vasoconstriction, increasing VA/Q mismatch. Gas exchanges deterioration was shown in some studies with bosentan and sildenafil, while no change was observed in others using sildenafil and tadalafil.

Chen X J Thor Dis 2015
Prins KW Pulm Circ 2017
Vitulo P et al. JHLT 2017

COPD-PH: Conclusions

Although preliminary evidence suggests that currently available vasoactive medications may have a benefit in COPD-PH patients with mPAP>35 mmHg, further studies are required before PAH therapies can be recommended.

Therefore, these patients should be a target population for larger prospective studies.

COPD patients with lower mPAPs should be enrolled in future studies, especially if the CI is low or the PVR is significantly elevated

IPF- and IIP-PH: use of PAH targeted- therapies

Treatment with PAH-targeted therapies in patients with IIP has yielded important safety signals in some RCTs: the ARTEMIS study was terminated prematurely because an interim analysis showed that ambrisentan-treated patients with IPF were more likely to have disease progression, particularly hospitalizations due to respiratory events. The RISE-IIP trial, that evaluated the effect of riociguat on 6MWD in patients with IIP, was terminated early on the basis of interim results showing increased mortality and risk of serious adverse events in the riociguat group.

RCTs did not find a significant improvement in pulmonary hemodynamic in pts treated with bosentan for 16 w or ambrisentan.

The effects of PAH-targeted therapies in patients with ILD-PH is controversial: STEP-IPF study (which used sildenafil in pts with DLCO <35%) failed its primary end point of a 20% increase in 6MWD. In contrast open-label studies with sildenafil, riociguat and treprostinil showed a significant improvement in 6MWD.

In ILD the acute administration of aerosolized iloprost or sildenafil does not worsen VA/Q. In contrast, acute administration of epoprostenol i.v. causes gas exchange deterioration due to increased perfusion in non ventilated alveolar units. In longer-term studies, treatment with PAH-targeted therapy did not result in worsening of gas exchange in patients with ILD.

The idiopathic Pulm Fibrosis Clin Res Net NEJM 2010
Sagger R Thorax 2014
Prins KW Pulm Cric 2017

Respiratory Medicine 138 (2018) 13–20

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Clinical Trial Paper

Sildenafil added to pirfenidone in patients with advanced idiopathic pulmonary fibrosis and risk of pulmonary hypertension: A Phase IIb, randomised, double-blind, placebo-controlled study – Rationale and study design

Jürgen Behr[a,*], Steven D. Nathan[b], Sergio Harari[c], Wim Wuyts[d], Klaus-Uwe Kirchgaessler[e], Monica Bengus[e], Frank Gilberg[e], Athol U. Wells[f]

[a] Department of Internal Medicine V, University of Munich and Asklepios Fachkliniken Gauting, Comprehensive Pneumology Center Munich, Germany
[b] INOVA Heart and Vascular Institute, Inova Fairfax Hospital, Vienna, VA, USA
[c] U.O. di Pneumologia e Terapia Semi-Intensiva Respiratoria, Servizio di Fisiopatologia Respiratoria ed Emodinamica Polmonare, Ospedale San Giuseppe, MultiMedica IRCCS, Milan, Italy
[d] Department of Pulmonary Medicine, Unit for Interstitial Lung Diseases, University of Leuven, Leuven, Belgium
[e] F. Hoffmann-La Roche Ltd., Basel, Switzerland
[f] Interstitial Lung Disease Unit, Royal Brompton Hospital, London, UK

ARTICLE INFO

Keywords:
6-Minute walk test
Clinical trial
Echocardiogram
Hypertension
Idiopathic pulmonary fibrosis
Phosphodiesterase-5 inhibitor
Pirfenidone
Sildenafil

ABSTRACT

Background: Pulmonary hypertension (PH) is commonly observed in patients with advanced idiopathic pulmonary fibrosis (IPF). Despite the availability of therapies for both IPF and PH, none are approved for PH treatment in the context of significant pulmonary disease. This study will investigate the use of sildenafil added to pirfenidone in patients with advanced IPF and risk of PH, who represent a group with a high unmet medical need.

Methods: This Phase IIb, randomised, double-blind, placebo-controlled trial is actively enrolling patients and will study the efficacy, safety and tolerability of sildenafil or placebo in patients with advanced IPF and intermediate or high probability of Group 3 PH who are receiving a stable dose of pirfenidone. Patients with advanced IPF (diffusing capacity for carbon monoxide ≤ 40% predicted) and risk of Group 3 PH (defined as mean pulmonary arterial pressure ≥ 20 mm Hg with pulmonary arterial wedge pressure ≤ 15 mm Hg on a previous right-heart catheterisation [RHC], or intermediate/high probability of Group 3 PH as defined by the 2015 European Society of Cardiology/European Respiratory Society guidelines) are eligible. In the absence of a previous RHC, patients with an echocardiogram showing a peak tricuspid valve regurgitation velocity ≥ 2.9 m/s can enrol if all other criteria are met. The primary efficacy endpoint is the proportion of patients with disease progression over a 52-week treatment period. Safety will be evaluated descriptively.

Discussion: Combination treatment with sildenafil and pirfenidone may warrant investigation of the treatment of patients with advanced IPF and pulmonary vascular involvement leading to PH.

Sildenafil – Pirfenidone trial

- For the purpose of this study, patients have to present with:
- Advanced IPF
- (defined as a measurable %DLCO≤40% at screening)

AND

- Intermediate or high probability of Group 3 PH
- (defined as a mPAP≥ 20 mmHg with PAWP≤15 mmHg) on a previous RHC of acceptable quality

OR

- In the absence of a previous RHC, patients with ECHO intermediate or high probability of PH, as defined by the 2015 ESC/ERS guidelines (peak TRV ≥ 2.9 m/s), will be considered eligible for the study

Sildenafil + Pirfenidone trial - Primary end point

The primary efficacy endpoint will be evaluated based on a comparison of the proportion of patients showing disease progression over 52 weeks of treatment period, as evidenced by reaching the following combined endpoint:

Relevant decline in 6MWD of at least 15% from baseline (as defined per protocol)

Respiratory –related non-elective hospitalization, or all cause mortality

Sildenafil - nintedanib

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nintedanib plus Sildenafil in Patients with Idiopathic Pulmonary Fibrosis

Martin Kolb, M.D., Ganesh Raghu, M.D., Athol U. Wells, M.D., Jürgen Behr, M.D., Luca Richeldi, M.D., Birgit Schinzel, Dipl.Stat., Manuel Quaresma, Lic., Susanne Stowasser, M.D., and Fernando J. Martinez, M.D., for the INSTAGE Investigators*

ABSTRACT

BACKGROUND

Nintedanib is an approved treatment for idiopathic pulmonary fibrosis (IPF). A subgroup analysis of a previously published trial suggested that sildenafil may provide benefits regarding oxygenation, gas exchange as measured by the diffusion capacity of the lungs for carbon monoxide ($D_{L_{CO}}$), symptoms, and quality of life in patients with IPF and severely decreased $D_{L_{CO}}$. That idea was tested in this trial.

METHODS

From McMaster University and St. Joseph's Healthcare, Hamilton, ON, Canada (M.K.); the University of Washington, Seattle (G.R.); the National Institute for Health Research Respiratory Biomedical Research Unit, Royal Brompton and Harefield NHS Foundation Trust, and the National Heart and Lung Institute, Imperial College London (A.U.W.); Med-

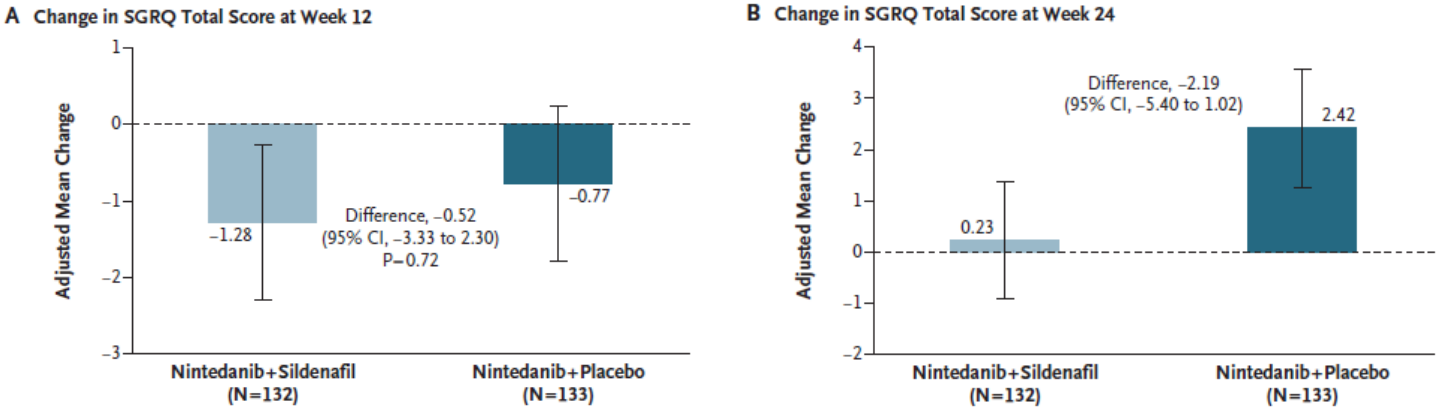
Sildenafil – nintedanib trial design

A 24-week, double-blind randomized parallel group study evaluating the efficacy and safety of oral nintedanib co-administered with oral sildenafil

Clinical phase: III b

Objective: To assess efficacy and safety of concomitant treatment with nintedanib and sildenafil in IPF patients with advanced lung function impairment

Sildenafil plus nintedanib in Patients with Idiopathic Pulmonary Fibrosis



Kolb M. et al. NEJM 2018 Sep 15

Sild – nintedanib trial - Conclusions

RESULTS

A total of 274 patients underwent randomization. There was no significant difference in the adjusted mean change from baseline in the SGRQ total score at week 12 between the nintedanib-plus-sildenafil group and the nintedanib group (–1.28 points and –0.77 points, respectively; P=0.72). A benefit from sildenafil treatment was not observed with regard to dyspnea as measured with the use of the University of California, San Diego, Shortness of Breath Questionnaire. No new safety signals were observed, as compared with previous trials.

CONCLUSIONS

In patients with IPF and a $D_{L_{CO}}$ of 35% or less of the predicted value, nintedanib plus sildenafil did not provide a significant benefit as compared with nintedanib alone. No new safety signals were identified with either treatment regimen in this population of patients. (Funded by Boehringer Ingelheim; INSTAGE ClinicalTrials.gov number, NCT02802345.)

IPF- and IIP-PH: Conclusions

Riociguat and Ambrisentan are both contraindicated in IIP-PH.

There is no evidence of benefit for other endothelin receptor antagonists in IIP-PH.

Data on the use of sildenafil in IIP-PH is conflicting while evidence for prostanoid therapy is too limited for any current recommendations.

Further RCTs are encouraged.

Future Perspectives

Although the association between PH and CLD with impaired functional status and worse outcomes is well proved, it is not still clear whether PH is the driver of outcomes or a consequence of the underling disease.

Further investigation must be supported and encouraged.

Studies should be addressed to develop:

-better animal models of PH in COPD and ID in order to identify different molecular mechanism (parenchymal vs vascular) and novel molecular targets.

-The identification of biomarkers for group 3 PH (circulating DNA, volatile exhaled compounds and exhaled “genomic fingerprint”).-

-The optimal phenotipization of patients for target therapy

Which principal end-point in clinical trial in PH with CLD?

In Phase 2 studies, physiological variables (RV function, hemodynamics, 6MWT) and biomarkers (e.g. BNP) are acceptable.

In Phase 3 studies a comprehensive patient centric clinical outcomes are preferable: composite end points, time to clinically meaningful change (clinical worsening and/or improvement)

Clinical worsening event may include mortality, hospitalization, changes in functional test, QOL measurements, NYHA changes, need for supplement oxygen, disease exacerbation, lung transplantation.

What should we improve?

6MWT should take in consideration other informative values in group 3 patients such as integrate distance, deoxygenation, Borg dyspnea score, heart rate recovery

Use of cardiopulmonary exercise test should be encouraged as it may offer more elaborate distinction between respiratory vs circulatory limitation, although supplemental oxygen dependency is a major issue in this group of patients.

Hemodynamic assessment while exercising is encouraged and has to be standardized

Future studies should also target role of the vascular compartment in driving parenchymal abnormalities (“vascular therapy beyond PH”).

Group 10: Lung Disease

Back –up slides

PH in systemic sclerosis: a grey zone

Although patients with SS are at high risk of developing isolated PAH, they may also develop significant parenchymal lung disease and/or a component of left heart disease.

It is often difficulty in discriminating group 1 PAH from group 3 PH in systemic sclerosis patients, since these patients have evidence of parenchymal lung disease on HRCT, not necesseraly be accompanied by restrictive physiology.

As the assessment of the extension of the fibrosis was based in several studies on the respiratory function tests, and not on the HCRT patients with preserved lung volumes can be safely treated with PAH drugs, but there is no evidence for treatment of PH-SSc with more advanced.

To best evaluate the extent of lung disease in relation to the patient´s hemodynamic profile CT scan imagines are required. In the absence of RCTs, systemic sclerosis patients with PH and more than minimal fibrosis on HRCT should be referred to expert centers for individualized treatment.

CPFE-PH

CPFE is the simultaneous presence of emphysema in the upper lobes and fibrosis in the lower lobes.

30-50% of CPFE pts develop PH

The PH appear to contribute to the functional limitation in CPFE and it is associated with a poor survival.

Treatment options remain limited with currently little evidence to support PAH therapies in this disease.

Sarcoidosis

The prevalence of PH in sarcoidosis range from 5.7 to 74%, with a 5 years-survival of 50-60%

It mainly affects pts with a major lung parenchymal involvement, but it may occur even in patents without lung fibrosis.

The pathogenic mechanisms include remodeling and obliteration of pulmonary vessels, extrinsic compression of central pulmonary vessels by lymphadenopathy or mediastinal fibrosis, pulmonary veno-occlusive-like lesions, granulomatous involvement of pulmonary vessels, left ventricular dysfunction and portopulmonary PH.

At present, no PAH-targeted therapy can routinely be recommended for patients with sarcoidosis-PH However. Only a single RCT has been performed in this group of patients and the results were inconclusive.

Shorr AF ERJ 2005
Nunes H Thorax 2006
Boughman RP Chest 2014
Boucky A ERJ 2017
Boughman RP Res Med 2018

Other Chronic Lung disease

The prevalence of PH in patients with Pulmonary Langerhans Cell Histiocytosis is high

PH complicating lymphangioleiomatosis tends to be mild-to-moderate and mostly related to the extent of parenchymal involvement.

PH may complicate the course of adults with a history of bronchopulmonary dysplasia and cystic fibrosis and may also develop in patients with chronic hypersensitivity pneumonitis and lung cancer.

Only case series suggest beneficial effects of PAH conventional treatments in some patients with PLCH and LAM, for this reason there is not any recommendation to use these therapies in this group of pts.

Harari S JHLT 1997
Fartoukh M AJRCCM 2000
Le Pavec J Chest 2012
Cottin V, Harari S ERJ 2012
Oliveira RH ERJ 2014

Hemodynamic Mechanisms of Exercise-Induced Pulmonary Hypertension in Patients with Lymphangioleiomyomatosis: The Role of Exercise Stress Echocardiography

Andrea Sonaglioni, MD, Massimo Baravelli, MD, Roberto Cassandro, MD, Olga Torre, MD, Davide Elia, MD, Claudio Anza, MD, and Sergio Harari, MD

J Am Soc Echocardiogr 2018

AIM

To conduct a non invasive evaluation of the main hemodynamic mechanisms of exercise-induced PH in patients with LAM, assessed using exercise stress echocardiography.

METHODS

Fifteen patients with LAM without resting PH were enrolled in a prospective single-center study and compared with 15 healthy female control subjects.

A complete echocardiographic study with Doppler tissue imaging was performed at baseline and during semisupine symptom-limited exercise testing to evaluate (1) left ventricular systolic and diastolic function, (2) right ventricular contractile function, (3) estimated pulmonary capillary wedge pressure, (4) estimated systolic and mean pulmonary artery pressure, and (5) estimated pulmonary vascular resistance.

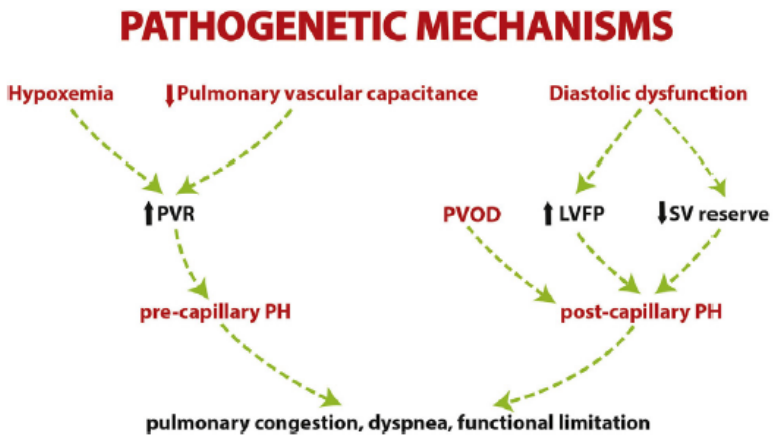
RESULTS

Compared with healthy control subjects, patients with LAM during exercise showed echocardiographic signs of right ventricular overload and right ventricular systolic dysfunction and significant increases in mean pulmonary artery pressure (14.4 ± 6.5 vs 4.2 6 3.1 mm Hg, $P < .0001$), pulmonary vascular resistance (+68.3 ± 42.1 vs -0.1 ± 18.3 dyne-sec/cm5, $P < .0001$), and, unexpectedly, pulmonary capillary wedge pressure (+8.3 ± 5.3 vs -0.5 ± 1.3 mm Hg, $P < .0001$).

Hemodynamic Mechanisms of Exercise-Induced Pulmonary Hypertension in Patients with Lymphangioleiomyomatosis: The Role of Exercise Stress Echocardiography

Andrea Sonaglioni, MD, Massimo Baravelli, MD, Roberto Cassandro, MD, Olga Torre, MD, Davide Elia, MD, Claudio Anza, MD, and Sergio Harari, MD

J Am Soc Echocardiogr 2018



We observed two major pathophysiologic components underlying the increase in estimated MPAP

1. A significant exercise-induced increase in estimated PVR (precapillary component), as assessed by previous studies
2. A significant exercise-induced increase in estimated PCWP (postcapillary component), probably secondary to a diastolic dysfunction, with subsequent decrease in LV SV reserve.

These two components contributed to generate pulmonary congestion, dyspnea, and functional limitation.