365. Pulmonary circulation: clinical treatment

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Long-term safety and efficacy of imatinib in pulmonary arterial hypertension

Marius Hoeper[1], Robyn Barst[2], Nazzareno Galie[3], Paul Hassoun[4], Nicholas Morrell[5], Andrew Peacock[6], Gérald Simonneau[7], Victor Tapson[8], Fernando Torres[9], David Lawrence[10], Deborah Quinn[11], Hossein Ardeschir Ghofrani[12]. *[1]Respiratory Medicine, Medizinische Hochschule, Hannover, Germany; [2]Respiratory Medicine, Columbia University, New York, NY, United States; [3]Respiratory Medicine, Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; [4]Respiratory Medicine, Johns Hopkins University, Baltimore, MD, United States; [5]Respiratory Medicine, Addenbrookes and Papworth Hospitals, Cambridge, United Kingdom; [6]Respiratory Medicine, Golden Jubilee National Hospital, Glasgow, United Kingdom; [7]Respiratory Medicine, Université Paris-Sud XI, Orsay, France; [8]Respiratory Medicine, Duke University Medical Center, Durham, NC, United States; [9]Respiratory Medicine, UT Southwestern Medical Center, Dallas, TX, United States; [10]Respiratory Medicine, Novartis Horsham Research Centre, Horsham, West Sussex, United Kingdom; [11]Respiratory Medicine, Novartis Pharmaceuticals, Cambridge, MA, United States; [12]Respiratory Medicine, University Hospital Giessen and Marburg GmbH, Giessen, Germany*

IMPRES (IMP) was a 24-wk, randomised, double-blind study comparing imatinib vs. PBO in 202 symptomatic pts with severe PAH despite ≥2 PAH-therapies with PVR ≥800 dyn·s·cm-5. A 3-yr open-label extension is ongoing. In the extension, IMP imatinib pts continued on maintenance dose (200 or 400mg once daily [QD]) while IMP PBO pts received imatinib 200mg QD, increasing to 400mg QD, if tolerated. Data lock for the present analysis was 11 Nov 2011. 144/150 pts entered the extension (66 IMP imatinib, 78 IMP PBO). Median overall exposure in the extension was 276 days. At extension entry, mean±SD 6MWD had increased from IMP baseline by 43±55 vs. 5±63m for IMP imatinib vs. IMP PBO pts. In IMP imatinib pts, improvements in 6MWD were maintained after 48 wks of imatinib (24 wks in IMP + 24 wks in extension: 45±46m increase from IMP baseline [n=54]). In IMP PBO pts, 6MWD increased 16±46m from IMP baseline after 48 wks imatinib in extension (n=20). There were 6 deaths in the extension, all in IMP PBO pts. AEs in the extension included nausea (36.8%), peripheral oedema (27.8%), periorbital oedema (22.2%), vomiting (22.2%), and nasopharyngitis (20.8%). SAEs in ≥3% of patients included RV failure (7.0%), dyspnoea (4.2%), worsening PAH (4.2%), syncope (4.2%), subdural haematoma (SDH, 4.2%) and device-related infection (3.5%). Unexpectedly, SDH occurred in 8 pts (2 in IMP, 6 in ext), all in patients on imatinib and anticoagulation. 5 pts with SDH recovered, 1 died of SDH and 2 died of unrelated causes. Efficacy and safety assessments continue every 6 months to provide additional data regarding benefits and risks of imatinib in advanced PAH. Imatinib is currently not approved for treatment of PAH.

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Management of chronic thromboembolic pulmonary hypertension (CTEPH): A physician-based perception study

Henning Tiede[1], Barbara Hinzmann[2], Nicholas Bawden[3], Ioana Preston[4].
[1]Medical Clinic 2, University of Giessen Lung Centre, Giessen, Germany; [2]Global Market Research Department, Bayer HealthCare Pharmaceuticals, Berlin, Germany; [3]Healthcare Department, Ipsos MORI, London, United Kingdom; [4]Pulmonary and Critical Care and Sleep Medicine Departments, Tufts University School of Medicine, Tufts Medical Center, Boston, United States

Background: Therapeutic approach to CTEPH includes surgical and medical management. Pulmonary endarterectomy (PEA) is the standard of care in eligible patients (pts). Medical therapy with pulmonary arterial hypertension (PAH)-specific drugs has not been formally studied in this population.
Objectives: To compare therapeutic management of CTEPH between different countries.
Methods: Quantitative online survey conducted in 7 countries in Europe and North America, during 2010, of 331 physicians with experience in managing CTEPH for ≥2 years and who were treating ≥3 pts.
Results: CTEPH pts were mostly treated by cardiologists (38%) and pulmonologists (34%) and 59% of physicians were affiliated with a pulmonary hypertension (PH) centre. Only 26% of pts were evaluated for PEA; 10% of all pts had undergone or were awaiting PEA. The proportion of pts who had been evaluated for and undergone/awaiting PEA was higher in PH centres compared with non-specialist centres (31% vs 17%; 12% vs 6%, respectively). A subset of physicians in the US was found to 'self-screen' pts for PEA using subjective criteria. 59% of CTEPH pts were receiving PAH-specific therapies with little variation between countries. Comparison with a similar perceptual study in PAH pts demonstrated that the treatment of CTEPH mirrors that of PAH in terms of PAH-specific therapy usage and combination therapy.
Conclusions: Despite PEA being the standard of care and a potentially curative treatment for CTEPH, a low referral rate for PEA evaluation was observed in clinical practice. There is a need for education about CTEPH, implementation of specific CTEPH management guidelines, and an established referral process after diagnosis.

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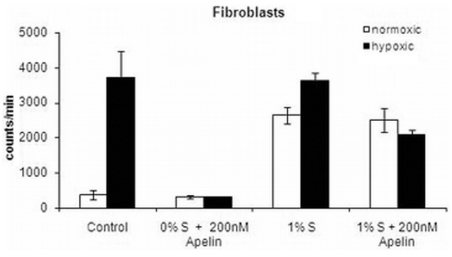
The anti-proliferative effects of apelin on pulmonary adventitial fibroblasts

Lauren Brash[1], Colin Church[1], Roger Wadsworth[2], Andrew Peacock[1], David Welsh[1]. *[1]Scottish Pulmonary Vascular Unit, Western Infirmary, Glasgow, United Kingdom; [2]Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, United Kingdom*

Background: Pulmonary arterial hypertension (PAH) involves remodelling of the pulmonary artery resulting in right heart failure. Apelin is an endogenous peptide with physiological actions in the cardiovascular system. Pre-clinical models indicate that apelin deficiency may mediate or contribute to the pathogenesis of PAH which involves pulmonary artery fibroblasts (PAF).
Aims: To determine if Apelin had an effect on the proliferation and migration of rat PAF.
Methods: PAF were isolated from Sprague Dawley rats. The PAF were incubated in normoxic and hypoxic conditions (35mmHg for 24h) and proliferation in response to Apelin was assessed. The presence of the Apelin receptor (APJ) was detected by Western Blotting. PAF were also cultured to 100% confluency and the cell monolayer was scratched and cell migration was determined after incubation with Apelin.
Results: APJ receptor was detected in PAF cells. Hypoxia alone increased the proliferation of PAF and this effect was abrogated with the addition of 200nM Apelin.



Hypoxia caused PAF migration both alone and to a higher degree with serum. The addition of Apelin prevented this migration.
Conclusions: Apelin can reduce the increased proliferation of PAF to hypoxia and reduce the migratory capacity of these cells. Apelin may have anti-remodelling properties that require further investigation.

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Hemodynamics and response to therapy of pulmonary hypertension in patients with interstitial lung disease: Preliminary results of the "HYPID" prospective study

Vincent Cottin[1], Martine Reynaud-Gaubert[2], Julie Traclet[1], David Montani[3], Hilario Nunes[4], Benoit Wallaert[5], Boubou Camara[6], Chahera Khouatra[1], David Launay[7], Sylvain Marchand-Adam[8], Dominique Israel-Biet[9], Romain Magnier[10], Laurent Tétu[11], Sabrina Zeghmar[1], Lize Kiakouama[1], Marc Humbert[3], Jean-François Cordier[1]. *[1]Respiratory Medicine, Hospices Civils de Lyon, Lyon, France; [2]Respiratory Medicine, AP-HM, Marseille, France; [3]Respiratory Medicine, AP-HP, Clamart, France; [4]Respiratory Medicine, AP-HP, Bobigny, France; [5]Respiratory Medicine, CHRU, Lille, France; [6]Respiratory Medicine, CHU, Grenoble, France; [7]Internal Medicine, CHRU, Lille, France; [8]Respiratory Medicine, CHU, Tours, France; [9]Respiratory Medicine, AP-HP HEGP, Paris, France; [10]Respiratory Medicine, CHU, Caen, France; [11]Cardiology, CHU, Toulouse, France*

Background: Pulmonary hypertension (PH) is associated with a shorter survival in patients with interstitial lung disease (ILD).
Objective: To study the characteristics and response to specific PH therapy in patients with ILD and precapillary PH at right heart catheterization.
Methods: A prospective multicenter observational study was conducted in French expert centers for rare pulmonary diseases or PH (NCT01443598).
Results: The first 100 patients were studied (mean age 64±10 years; 63 males). ILD was idiopathic pulmonary fibrosis (n=25), combined pulmonary fibrosis and emphysema syndrome (n=21), systemic sclerosis with ILD (n=26), sarcoidosis (n=8) and other ILD (n=20). Overall, NYHA class was I-II in 24% of patients and III-IV in 76%. Six-min walk distance was 289±140m. Hemodynamic characteristics were mPAP 38±9.8 mmHg, CI 2.7±0.65 L/min/m^2, and PVR 515±243 dyn.s.cm-5. mPAP was >35 mmgHg ("disproportionate" PH) in 56% of the cases. No correlation was found between pulmonary function and hemodynamic parameters. No differences were found between the 4 etiological groups for hemodynamic parameters. 36 patients with mPAP >35 mmHg received PH therapy and were evaluated at 3-6 months; mPAP decreased from 46 to 38 mmHg ($p<0.0001$), CI improved from 2.6 to 2.9 L/min/m^2 ($p<0.05$), and PVR decreased from 640 to 460 dyn.s.cm-5 ($p<0.0001$), but no difference was observed in 6 min walk distance or NYHA class.
Conclusion: Hemodynamic characteristics do not correlate with pulmonary function and are comparable between etiological categories of ILD with PH. Preliminary data suggest that PH therapy may improve hemodynamics.

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Cicletanine in pulmonary arterial hypertension (PAH): Results from a phase 2 randomized placebo-controlled trial

Aaron Waxman[1], Ronald Oudiz[2], Shelley Shapiro[3], Mardi Gomberg-Maitland[4], Anne Keogh[5], David Badesch[6], Robert Frantz[7], C. Gregory Elliott[8], Hunter Gillies[9], Gennyne Walker[9]. *[1]Department of Medicine, Pulmonary and Critical Care, Brigham and Women's Hospital, Boston, MA, United States; [2]Division of Cardiology, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, United States; [3]Department of Cardiology, West Los Angeles VA HealthCare Center, Los Angeles, CA, United States; [4]Department of Medicine, Pulmonary Hypertension Center, Univeristy of Chicago, IL, United States; [5]Heart Failure and Transplant Unit, St. Vincent's Hospital, Sydney, NSW, Australia; [6]Divisions of Pulmonary Sciences and Critical Care Medicine, and Cardiology, University of Colorado, Denver, CO, United States; [7]Division of Cardiovascular Disease, Mayo Clinic, Rochester, MN, United States; [8]Department of Medicine, Intermountain Medical Center and The University of Utah, Murray, UT, United States; [9]Cardiovascular Clinical Research, Gilead Sciences, Inc., Foster City, CA, United States*

Cicletanine (CIC) is an antihypertensive with vasorelaxant and diuretic properties. Potential efficacy was observed with compassionate use of CIC in worsening PAH. A controlled study investigating the safety and efficacy of CIC for PAH was performed.
162 subjects were randomized to 12 weeks of placebo (n=41) or CIC at doses of 150 mg qd (n=39), 150 mg bid (n=40) or 300 mg qd (n=42). Subjects could be on stable doses of an endothelin receptor antagonist, phosphodiesterase type 5 inhibitor, parenteral prostanoid, or any 2-drug combination. The primary analysis was comparison of change in 6-minute walk distance (6MWD) following 12 weeks of treatment with daily doses of CIC 300 mg (150 mg bid+300 mg qd; n=80) to placebo. Secondary analyses included dyspnea, WHO functional class, NT-proBNP, and a subset analysis of pulmonary hemodynamics (n=50).
57.4% of subjects had idiopathic PAH and 42.6% associated PAH; 38.9% of subjects were WHO Class II, 61.1% WHO Class III and the mean baseline 6MWD was 370±64 meters (m). For the 300 mg combined group (n=80), the placebo-adjusted mean and median changes from baseline in 6MWD were +19.4 m (95% CI: 0.3, 38.4) and +7.0 m (95%: CI -8.0, 24.0), respectively (p=0.50). There were no clinically relevant improvements in the secondary assessments, including pulmonary vascular resistance (mean change 35 dyne·s/cm5). The adverse events reported more frequently with CIC were nausea, hypokalemia, and fatigue, consistent with known properties of diuretics.
Although CIC was generally well-tolerated, no improvements in exercise tolerance, symptoms or hemodynamics were observed in patients with PAH after 12 weeks of CIC treatment.

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Pulmonary hypertension due to alveolar hypoventilation: Functional impact and improvement of haemodynamics and exercise capacity under non-invasive positive pressure ventilation

Matthias Held, Johanna Walthelm, Stefan Baron, Christine Roth, Berthold Jany.
Department of Internal Medicine, Mission Medical Hospital, Würzburg, Bavaria, Germany

Background: For pulmonary hypertension (PH) due to lung diseases guidelines recommend treatment of the underlying disease. Due to preserved cardiac index (CI) in alveolar hypoventilation the functional impact of elevated pulmonary artery pressure (PAP) is not clear. The impact of non-invasive positive pressure ventilation (NIPPV) on exercise capacity of patients with PH due to alveolar hypoventilation is unclear.
Objective: To characterize the functional impact of PH due to alveolar hypoventilation and the haemodynamic and functional consequences of NIPPV.
Methods: Analysis of hemodynamics and functional capacity of 18 patients with daytime PH due to alveolar hypoventilation. The analysis included the data from baseline after a complete diagnostic work-up and after 3 months of NIPPV.
Results: Patients presented with a mean PAP (mPAP) of 49±12 mmHg, a CI (3,21±0,66), a 6-minute walking distance (6-MWD) of 303±133 m and severely elevated nt-pro-BNP levels. mPAP correlated negatively with maximal workload (R=-0,71667, p=0,029) and six-minute-walking distance (R=-0,621, p= 0,010). Under NIPPV, we found a significant reduction of mPAP (-17,75 mmHg, p=0,0005), NT-pro-BNP serum levels (-2110 pg/ml, p= 0,0014), improvement of the 6-MWD (+66 m, p=0,0082) and maximal workload (+18 W, p=0,028). CI did not change significantly. Changes of workload and mPAP correlated negatively (R= -0,7545, p= 0,0305).
Conclusions: Despite preserved CI elevated mPAP has a functional impact for patients with PH due to alveolar hypoventilation. NIPPV leads to a significant reduction of PH and improvement of exercise capacity.

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Improved right ventricular function after substantial afterload reduction in patients with pulmonary arterial hypertension

Marielle van de Veerdonk[1], Tim Marcus[2], Harm-Jan Bogaard[1], Nico Westerhof[3], Anton Vonk-Noordegraaf[1]. *[1]Pulmonary Diseases, VU University Medical Center, Amsterdam, Netherlands; [2]Physics and Medical Technology, VU University Medical Center, Amsterdam, Netherlands; [3]Physiology, VU University Medical Center, Amsterdam, Netherlands*

Introduction: In pulmonary arterial hypertension (PAH), increased load leads to right ventricular (RV) dysfunction. We showed that despite a modest reduction in pulmonary vascular resistance (PVR) after treatment, RV function can decrease resulting in poor prognosis[1].
Aims: We hypothesize that RV function can be sustained when therapies reduce RV load to a larger extent. We will compare RV load in PAH patients with improved/stable RV function to patients with decreased RV function during follow-up.
Methods: 76 patients underwent right heart catheterization to measure mean pulmonary artery pressure (mPAP) and PVR and MRI to assess RV ejection fraction (RVEF) at baseline and after 1 year of therapy. During a subsequent follow-up of 47months, 17 patients died.
Results: After therapy, 61% of the patients showed an improved/stable RVEF and had a better prognosis than patients with decreased RVEF (p=0.01). Patients with improved/stable RVEF showed a larger reduction in load (ΔmPAP: -9±12mmHg; ΔPVR: -231±301dyne·s·cm^{-5}) than patients with decreased RVEF (ΔmPAP: 3±10mmHg; ΔPVR: 20±313dyne·s·cm^{-5}, both p<0.001). Cardiac output (CO) increased in case of improved/stable RVEF (0.9±2.1L/min) and declined in case of decreased RVEF (0.4±1.8L/min, p=0.01). No differences were observed in 6-min walk distance or NT-proBNP.
Conclusions: PAH patients with sustained RV function showed a substantial load reduction after therapy and had a better prognosis than patients with decreased RV function. This might imply that preserved RV function and improved survival can be achieved if mPAP is substantially reduced, which requires a strong decrease in PVR.
References:
[1] vd Veerdonk et al. JACC 2011.