BJC
www.bjcardio.co.uk

The British Journal of Cardiology

Supplement 1

Volume 16 Supplement 1 | January/February 2009

Moving forward in pulmonary arterial hypertension

ISSN 0969-6113 (Print) ISSN 1753-4313 (Online)

This supplement has been sponsored by:

gsk GlaxoSmithKline

This supplement has been comissioned by GSK. The material contained within has been reviewed and approved by GSK. Date of preparation January 2009 VOL/MTR/08/38380/1

BJC
www.bjcardio.co.uk

The British Journal of Cardiology

The peer-reviewed journal linking primary and secondary care

Editors
Kim Fox
Terry McCormack
Philip Poole-Wilson
Henry Purcell

Associate Editor
Katharine White

Supplement Editor
Rachel Arthur

Editorial Office and Publishers
MediNews (Cardiology) Limited
9 Langton Street,
London, SW10 0JL
(production@bjcardio.co.uk)
Tel: +44 (0)20 7823 3315

Design and Layout
Consultants in Design

Authors instructions
Can be obtained from the editorial office or from the website.
See contact details above.

Advertising and sales enquiries:
Michael Young
42 Avondale Avenue,
Hinchley Wood, Esher,
Surrey, KT10 0DA.
(michael-young@btconnect.com)
Tel: +44 (0)20 8339 0300
Fax: +44 (0)20 8398 3361

Annual subscriptions for 2009
UK & Europe:
Individual GBP 100.00
Institution GBP 150.00
Elsewhere:
Individual GBP 160.00
Institution GBP 215.00

Published bi-monthly and distributed on a controlled circulation to general practitioners with an interest in cardiology, hospital cardiologists, diabetologists, vascular and cardiothoracic surgeons. The Journal may be provided, free, on request to other registered medical practitioners and GP trainees.

ISSN 0969-6113 (Print)
ISSN 1753-4313 (Online)

www.bjcardio.co.uk

PULMONARY ARTERIAL HYPERTENSION

Moving forward in pulmonary arterial hypertension

Introduction

Pulmonary arterial hypertension (PAH) is a comparatively rare, chronic, progressive disease of unknown aetiology, which is characterised by increased pulmonary vascular resistance and which may ultimately lead to right heart failure and premature death.[1] In a recent French registry the estimated prevalence was 15 cases per million, with approximately twice as many women as men being diagnosed.[2] PAH is increasingly diagnosed in older people, who may have considerable co-morbidities compared to the younger PAH patients traditionally seen.[2]

Diagnosis can be challenging as its symptoms are often non-specific: they may include breathlessness, fatigue, weakness, angina, syncope and abdominal distension. In the mid-1980s, before the availability of 'targeted' therapy, median life expectancy from diagnosis in patients with idiopathic PAH (formerly termed primary pulmonary hypertension [PPH]) was only 2.8 years.[3]

In 1996, continuous intravenous prostacyclin (epoprostenol) was the first drug to demonstrate outcome benefit in PAH.[4] Subsequently, over the past ten years, randomised, placebo-controlled trials of other prostacyclin analogues, endothelin receptor antagonists and phosphodiesterase inhibitors have shown significant benefit to patients with PAH, with improvements in exercise capacity, functional class and other parameters.[5] For those patients who fail to respond to medical therapy, double-lung or heart-lung transplantation may be an option.[6]

This supplement is a report from the symposium 'Moving forward in pulmonary arterial hypertension', held on 1st September 2008 during

SPONSORSHIP

The symposium was sponsored by GlaxoSmithKline, who also sponsored the writing of this report and this supplement. Volibris™ ▼ is a registered trademark of Gilead (Nasdaq: GILD), used under license by the GlaxoSmithKline group of companies. Ambrisentan has been licensed to GlaxoSmithKline by Gilead Sciences Inc. in all countries of the world, except the United States (US).

Cover image shows a representation of the pathophysiology of pulmonary arterial hypertension (PAH). The yellow arrows represent the increased workload of the right ventricle. Credit: Foster Medical Communications

Printed in the UK by Caric Print Ltd, Bournemouth, Dorset in association with Stephens & George Magazines Ltd.
Printed on acid-free paper.

Trial acronyms

ARIES Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-controlled, Multicenter, Efficacy Studies (ARIES) Group

BREATHE Bosentan Randomized Trial of Endothelin Antagonist Therapy

EARLY Endothelin antagonist trial in mildly symptomatic pulmonary arterial hypertension patients

STRIDE Sitaxentan To Relieve ImpaireD Exercise Trial

SUPER The Sildenafil Use in Pulmonary Hypertension Trial

the European Society of Cardiology Congress in Munich, Germany. The meeting was chaired by Dr Sean Gaine, Mater Misericordiae University Hospital, Dublin, Ireland, and Dr Simon Gibbs, Imperial College London and Hammersmith Hospital, London, UK and was sponsored by an educational grant from GSK.

The symposium highlighted how understanding of the pathobiology of PAH has evolved over the past two decades, as has the treatment of this condition. With the availability of newer treatment agents, and with increasing use of combination therapy to enhance clinical benefit, along with the need to begin treatment earlier, the PAH picture continues to unfold. It offers many challenges for the years to come, which makes this one of the most rapidly evolving fields within cardiology, and indeed within medicine as a whole. We hope that this is an objective and informative review of the symposium.

Henry Purcell
Co-Editor,
British Journal of Cardiology.

WHO Functional Classification of Pulmonary Hypertension

WHO Class I	WHO Class II	WHO Class III	WHO Class IV
Class I – Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near syncope.	Class II – Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope.	Class III – Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope.	Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may be present even at rest. Discomfort is increased by any physical activity.

Adapted from: Barst RJ, McGoon M, Torbicki A *et al*. *J Am Coll Cardiol* 2004;**43**:40S–47S.

References

1. Galie N, Simmoneau G. Pulmonary hypertension. In: *The ESC Textbook of Cardiovascular Medicine*. Eds Camm AJ, Luescher TF, Serruys PS. Blackwell Publishing, 2006.

2. Humbert M, Sitbon O. Chaouat A *et al*. Pulmonary Arterial Hypertension in France. Results from a National Registry. *Am J Respir Crit Care Med* 2006;**173:**1023–30.

3. D'Alonzo GE, Barst RJ, Ayres SM *et al*. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991;**115**:343–9.

4. Barst RJ, Rubin LJ, Long WA *et al*. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med* 1996;**334**:296–302.

5. National Pulmonary Hypertension Centres of the UK and Ireland. Consensus statement on the management of pulmonary arterial hypertension in clinical practice in the UK and Ireland. *Heart* 2008;**94**:i1–i41.

6. Galie N, Torbicki A, Barst R et al. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. *Eur Heart J* 2004;**25**:2243–78.

Conflict of interest

Dr Gibbs has been an advisory board member and/or has received speaking honoraria from Actelion, GSK, Encysive/Pfizer and United Theraputics within the past year.

Dr Gaine is an advisory board member for and/or has received speaking honoraria from Actelion, GSK, Sanofi, Novartis and Encysive/Pfizer within the past year.

What scientific progress have we made in PAH?

Reviewing this topic, Professor Lewis J Rubin, University of California, San Diego, US, looked at both the successes and failures of the past 20 years. He described how, as little as two decades ago, there was no treatment algorithm for PAH: "we had absolutely no understanding of the fundamental mechanisms responsible for the development of PAH" and approaches to treatment were based on a simplistic extrapolation from systemic hypertension and left-sided heart disease.

Since then, there has been a steady exploration of the molecular mechanisms underlying PAH, which has led to development of effective targeted therapeutic options such as endothelin receptor antagonists and prostacyclin derivatives. In Professor Rubin's view, these options represent a major success, but he hoped that there would be further progress. Many patients may not respond to these therapies, and it remains a serious and life-threatening disease.

The characterisation of PAH into its clinical, pathobiological and epidemiological components has provided the opportunity to intervene therapeutically and to delay disease progression. Three factors appear to be associated with the increased pulmonary vascular resistance seen in PAH, including vasoconstriction, remodelling of the pulmonary vessel wall and thrombosis *in situ*. Early catheterisation studies led to the clinical characterisation of PAH, while landmark epidemiological studies such as the National Institutes of Health (NIH) Registry[1] have helped to define the natural history of this disease and its risk factors and to define treatment targets.

'We need to have a major focus on early diagnosis and early treatment'

The next pathobiological phase identified the role of endothelial dysfunction, demonstrating impaired production of prostacyclin and nitric oxide (NO) and overproduction of endothelin. For the first time, this offered pathobiological targets for the treatment of this disease. Similarly, the concept of vascular growth and proliferation meant that PAH was viewed not as a single dynamic disease but rather as a much more complex process. Finally, a further area of critical importance was identification of the role of genetics in PAH, and potentially in other forms of pulmonary hypertension.

The natural history of primary pulmonary hypertension (PPH) was evaluated in the NIH Registry from 1981-87.[1] Reporting just over 20 years ago, it showed that of the 194 patients included in the study, 63% were female and 37% were male, and the mean age was 36 years. Median untreated survival after diagnosis was 2.8 years. It also highlighted "the haemodynamic severity of the disease relative to the normal range". (Pulmonary hypertension [PH] today is defined by a mean pulmonary artery pressure >25 mmHg at rest or >30 mmHg with exercise.)[2]

By the time patients presented, they had advanced disease and the Registry findings[1] also underscored the fact that there was an unacceptable delay from the onset of symptoms to the time of diagnosis, said Professor Rubin. This was true 20 years ago and "unfortunately it's still true today. It is one of our major failings that we still see patients present with advanced disease. We need to have a major focus on early diagnosis and early treatment…which is becoming more and more feasible".

Some forms, such as systemic sclerosis-associated pulmonary arterial hypertension (SScPAH), carry an even worse prognosis than that of patients with idiopathic PAH.[3] We should be able to identify such at-risk patients earlier if we invoke the right approaches to managing the condition.[4] Another important element in disease management is characterising the limitations and abnormalities that patients have. There are a number of determinants or markers of survival in PAH **(table 1)**. The six-minute walk distance, for example, has been used as an objective measure of exercise capacity and Professor Rubin stated that those who can walk longer do considerably better than those who cannot. Also, exercise distance improves with treatment. Haemodynamic markers include indices of right heart function, notably right atrial pressure and mean pulmonary artery pressure (mPAP). Echocardiographic indices include right atrial size. Useful biomarkers such as brain natriuretic peptide (BNP) are now being incorporated into management paradigms and also as end points in clinical trials.

PAH classification

There have been major developments in the classification of pulmonary hypertension since the First World Symposium on Diagnostic Classification in Geneva in 1973, which

Table 1: Determinants/markers of survival in pulmonary arterial hypertension (PAH)

- **Aetiology**
- **Severity of haemodynamic abnormalities**
- **Exercise capacity**
- **Echocardiographic indices**
- **Biomarkers-BNP, troponin**

Key: BNP=brain-type natriuretic peptide

basically divided the disease into primary and secondary pulmonary hypertension, depending on whether or not the patient had identifiable causes or risk factors.[4] Things have moved on to a more complex classification.[5] Although some may regard this classification as too complex, Professor Rubin believes that the classification is useful because it serves as the differential diagnosis, which is critical for assessing patients with pulmonary hypertension, who may share certain features in common or be quite different **(table 2).** This classification is a living document, he explained; it changes, and continues to change, as our thinking and experience evolve.

PAH pathophysiology

PAH is largely a vasoproliferative disease, a process which is characterised by growth and proliferation of all the layers of the vessel wall.[6] We have learned much about what may contribute to the transition from the normal to the remodelled pulmonary vessel. Studies have demonstrated a variety of abnormalities which are intrinsic to the smooth muscle cell or the endothelial cell, requiring cross-talk between the two cells. The hallmark is proliferation and probably altered apoptosis. Possibly, in the early phase of the disease, an intrinsic abnormality of contraction may occur as well, although this has not been confirmed.

Three important pathways have been identified in pulmonary hypertension **(table 3)**.[7]

These pathways are known from animal studies, and clinical trials have shown that targeting these three pathways does lead to improvements in patients with PAH.[8-12]

Table 2: Pulmonary arterial hypertension (PAH) current classification

1. Pulmonary Arterial Hypertension

- Idiopathic PAH
- Heritable
  - BMPR2
  - ALK1, endoglin (with or without HHT)
  - Unknown
- Drug and toxin induced
- Associated with:
  - connective tissue diseases
  - HIV infection
  - portal hypertension
  - systemic to pulmonary shunts
  - schistosomiasis
  - chronic haemolytic anemia
- PPHN

1. Pulmonary veno occlusive disease (PVO) and / or pulmonary capillary haemangiomatosis (PCH)

2. Pulmonary hypertension due to left heart disease

- Systolic dysfunction
- Diastolic dysfunction
- Valvular disease

3. Pulmonary hypertension due to lung diseases and / or hypoxia

- Chronic obstructive pulmonary disease
- Interstitial lung disease
- Other pulmonary diseases
- Sleep-disordered breathing
- Chronic exposure to high altitude
- Developmental abnormalities

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. PH with unclear or multifactorial mechanisms

- Haematological disorders, myeloproliferative disorders, splenectomy
- Systemic disorders: vasculitis, sarcoidosis, pulmonary Langerhans cell histiocytosis, neurofibromatosis
- Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- Congenital heart disease other than systemic to pulmonary shunt
- Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis, etc.

Key: PPHN=persistent pulmonary hypertension of the newborn

Adapted from: Simonneau 2004[5]

Table 3: Pathogenic pathways and treatment for pulmonary arterial hypertension (PAH)

Pathway	Target/Intervention
Endothelin	Endothelin receptor antagonists
Nitric oxide	Exogenous nitric oxide Phosphodiesterase-5 inhibitors
Prostacyclin	Prostacyclin derivatives

Adapted from: Humbert M 2004[7]

The endothelin pathway, or the so-called overproduction of endothelin, can be targeted with endothelin receptor antagonists. Underproduction of prostacyclin is addressed by the use of a prostacyclin analogue; and targeting underproduction of nitric oxide (NO) by augmenting the signal for its production and inhibiting its breakdown via a phosphodiesterase (PDE) inhibitor. There is of course a "whole variety of other pathways" which have been suggested to be abnormal and implicated in PAH, and many abnormalities have been demonstrated. The challenge for the future is to prioritise these and to try and gain an understanding of which of these abnormalities are causative

Conflict of interest

LJR serves on advisory committees for Actelion, Pfizer, MD Primer, Encysive, Novartis and Gilead.

References

1. D'Alonzo GE, Barst RJ, Ayres SM *et al*. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991;**115**:343–9.

2. Galie N, Torbicki A, Barst R *et al*. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. *Eur Heart J* 2004;**25**:2243–78.

3. Kawut SM, Taichman DB *et al*. Hemodynamics and survival in patients with pulmonary arterial hypertension related to systemic sclerosis. *Chest* 2003;**123**:344–50.

4. Hatano S, Strasser R, Eds. Primary pulmonary hypertension. World Health Organization, Geneva, 1975.

5. Simonneau G, Galie N, Rubin L *et al*. Clinical classification of pulmonary arterial hypertension. *J Am Coll Cardiol* 2004;**43**:S5–S12.

6. Humbert M, Morrell N, Archer S *et al*. Cellular and molecular pathobiology of pulmonary arterial hypertension. *J Am Coll Cardiol* 2004;**43**:S13–S24.

7. Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med* 2004;**351**:1425–36.

8. Galie N, Olschewski H, Oudiz RJ *et al*. Ambrisentan for the treatment of pulmonary arterial hypertension. Results of the ARIES Study 1 and 2. *Circulation* 2008;**117**:3010–19.

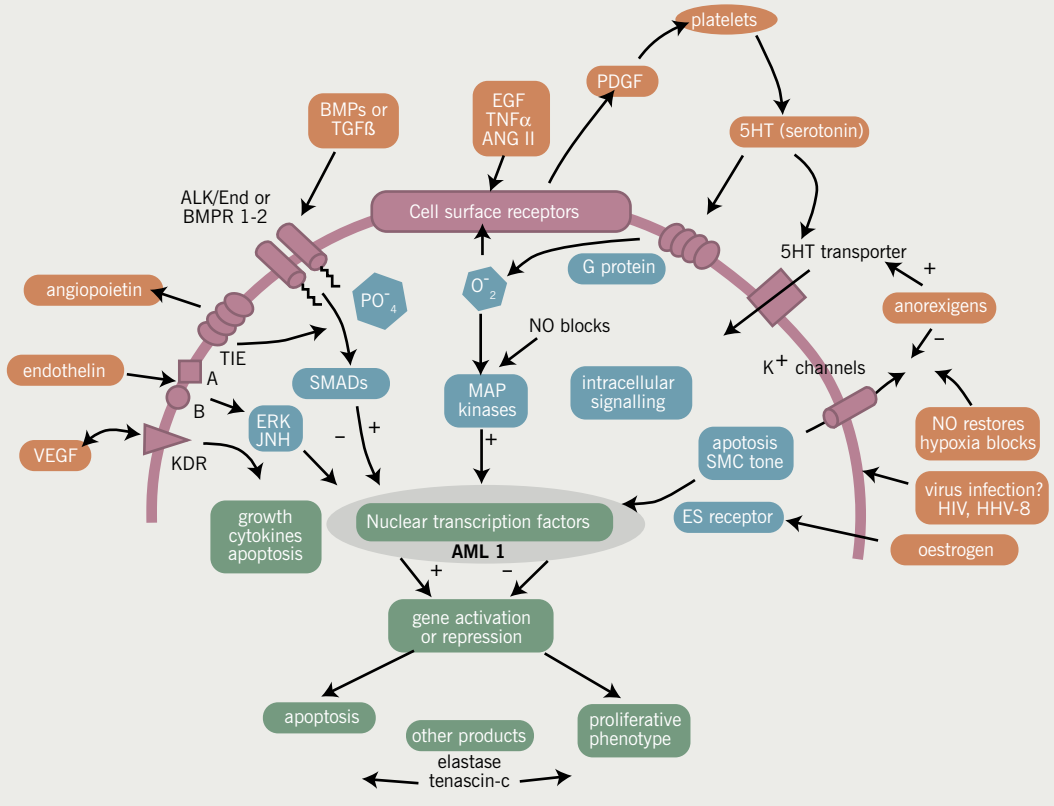
9. Rubin LJ, Badesch DB, Barst RJ *et al*. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;**346**:896–903.

10. Barst RJ, Langleben D, Frost A. Sitaxsentan therapy for pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2004;**169**:441–7.

11. Galie N, Ghofrani HA, Torbicki A *et al*. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005;**353**:2148–57.

12. Barst RJ, Rubin LJ, Long WA *et al*. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med* 1996; **334**:296–302.

Diagram of the pathophysiology of pulmonary arterial hypertension showing circulating cells and mediators



Adapted from Newman J *et al*. *Circulation* 2004;**109**:2947–52.

Increasing complexities in PAH management

Current data show that PAH patients are now older than previously reported, and more patients are identified with associated co-morbidities, according to Professor Marius Hoeper, Hannover Medical School, Germany. One recent study in more than one thousand patients showed that over one half had two or more co-morbidities.[1] About one third had systemic hypertension, 16% had hypothyroidism, 15% scleroderma, 14% were clinically depressed (possibly as a consequence of pulmonary hypertension) and a further 13% had diabetes.[1] Some centres also report that the spectrum of PAH patients seems to be changing, he said. Whereas in the past idiopathic PAH was more common, in recent years PAH in association with connective tissue disorders and congenital heart disease has been more frequently observed in many centres.[2] The severity of pulmonary vascular resistance at presentation also seems to be (slightly) declining, which suggests that the disease is being diagnosed earlier. However, the vast majority of patients are still in functional class III or IV at diagnosis.[2] Professor Hoeper emphasised the improvements in available medical treatments, which have broadened from the limited options of intravenous epoprostenol and calcium channel blockers to include a wide range of prostanoids and the newer drug classes of endothelin receptor antagonists (three are currently available in some countries) and PDE-5 inhibitors.

It is very difficult to select PAH treatments, said Professor Hoeper, as there are only limited data to provide guidance. However, a number of factors are taken into consideration and these are shown in **table 1.**

Since many patients are being treated with combinations, the possibility of drug-drug interactions increases.[3] Similarly, the mode and convenience of administration must be considered; for example many patients might prefer oral administration. Treatment costs and approval status are also considerations. There are disparities in the indications for these drugs across Europe, which is potentially a source of disagreement for several more years.

For prescribers, it is important to know that the drugs work and to see haemodynamic evidence of improvement. Looking at data from randomised controlled trials (RCTs),

'Current data show that PAH patients are now older and more have co-morbidities'

Professor Hoeper expressed the view that improvements in pulmonary artery pressure (PAP) are often very modest. Reviewing data from the SUPER-1 trial with sildenafil,[4] some improvements in exercise capacity are observed but he argued that we do not yet know the most efficacious dose.

Endothelin receptor antagonists

Professor Hoeper then described the characteristics of the three clinically developed endothelin receptor antagonists (ERAs), bosentan, sitaxentan and ambrisentan **(table 2).**[5-7] These drugs have different chemical structures, with bosentan and sitaxentan belonging to the sulfonamide class and ambrisentan belonging to the propanoic acid class. Receptor affinities may confer differences in efficacy but presently this is difficult to determine. Six-minute walk distance data from placebo-controlled trials

Table 1: Selection of treatments in pulmonary arterial hypertension (PAH)

- **Type of PAH, functional class**
- **Efficacy**
- **Safety, including drug-drug interactions**
- **Route of administration and convenience**
- **Cost**
- **Approval status**

Table 2: Characteristics of bosentan, sitaxentan and ambrisentan

Bosentan (Tracleer®)[5]	Sitaxentan (Thelin®)[6]	Ambrisentan (Volibris®)[7]
Structure		
Etherocyclic sulfonamide	Amidothiophene sulfonamide	Diphenylpropanoic acid
Dose		
125 mg bid	100 mg qd	5–10 mg qd
ETA selectivity		
No	Yes	Yes

Key: ETA=endothelin A receptor

Table 3a: ALT and AST elevations during long-term follow-up with bosentan in the BREATHE-1 trial

ALT/AST elevations	Bosentan
> 3 x ULN	11.6%
> 8 x ULN	2.1%
BREATHE-1 excluded ALT/AST > 3 x ULN at baseline	
ALT/AST elevations > 3 x ULN in control populations varied between 0% and 6%	

Key: ALT=alanine aminotransferase; AST=aspartate aminotransferase; BREATHE=bosentan randomized trial of endothelin antagonist therapy; ULN=upper limits of normal

Table 3b: ALT and AST elevations during long-term follow-up with sitaxentan in the STRIDE trials

ALT/AST elevations	Sitaxentan
> 3 x ULN	7%
> 8 x ULN	4%
STRIDE-2 excluded ALT/AST > 1.5 x ULN at baseline	
STRIDE-1 excluded ALT/AST > 3 x ULN at baseline	
ALT/AST elevations > 3 x ULN in control populations varied between 0% and 6%	

Key: ALT=alanine aminotransferase; AST=aspartate aminotransferase; STRIDE=sitaxentan to relieve impaired exercise; ULN=upper limits of normal

Table 3c: ALT and AST elevations during long-term follow-up with ambrisentan in the ARIES trials

ALT/AST elevations	Ambrisentan
> 3 x ULN	2.1%
> 8 x ULN	0.3%
ARIES 1+2 excluded ALT/AST > 1.5 x ULN at baseline	
ALT/AST elevations > 3 x ULN in control populations varied between 0% and 6%	

Key: ALT=alanine aminotransferase; AST=aspartate aminotransferase; ARIES=ambrisentan in pulmonary arterial hypertension, randomised, double-blind, placebo-controlled multicenter efficacy study; ULN=upper limits of normal

show very similar changes in most of the trials.[8-10] Likewise, we do not yet have long-term survival data from RCTs, just the open-label extension data from several short-term RCTs. The survival observed at one year is in the high nineties: it appears to be very similar for the three ERAs, which makes choice of drug difficult**.**

Factors such as safety also need to be taken into consideration. In Professor Hoeper's view, rises in hepatic aminotransferases (e.g. alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) are a problem with these drugs in general and something that has to be monitored when on the drug continuously. The STRIDE 2 trial,[9] sought to determine the optimal dose of the ERA, sitaxentan in PAH patients, and included an open-label bosentan arm for observation only. Although powered for efficacy, the study did report safety results as well, which showed that the incidence of elevated aminotransferases (>3 x upper limit of normal [ULN]) was 6% in the placebo group; 5% in the sitaxentan 50 mg group; 3% in the sitaxentan 100 mg group; and 11% for open-label bosentan. But in the long-term extension data,[10] the difference seemed to be less pronounced **(tables 3a-3c).** For ambrisentan, the newest of the three ERAs, it appears that the incidence of aminotransferase elevation is lower than for the other two but this drug still has to stand the test of long-term administration, Professor Hoeper noted.

Table 4: ERA and drug-drug interactions*

	Bosentan[5]	Sitaxentan[6]	Ambrisentan[7]
Initial dose	2 x 62.5 mg		
Target dose	2 x 125 mg	1 x 100 mg	1 x 5 (10) mg
Dosing with warfarin Sildenafil inhibits, Bosentan induces CYP 2C9	↑	↓	↔
Sildenafil plasma level Bosentan metabolized via CYP 3A4/5 Sildenafil: no interaction	↓	↔	↔

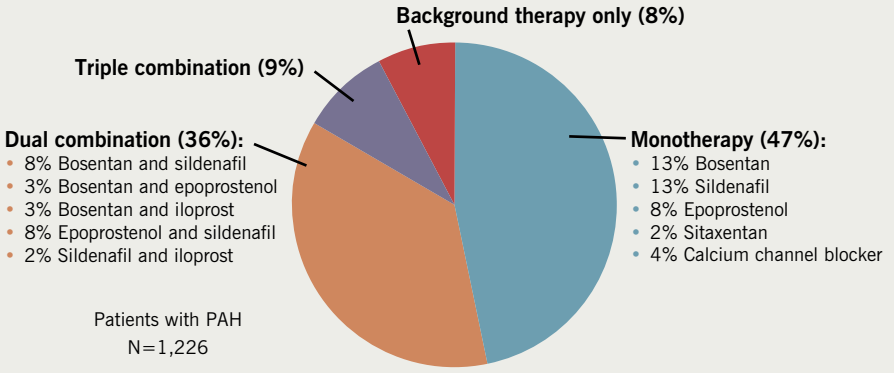
Key: CYP=cytochrome, *includes healthy volunteer and preclinical data

Another factor of concern, in his view, is drug-drug interaction, which is "becoming an issue in the treatment of pulmonary hypertension at the present time". Bosentan and sitaxentan have the propensity to interact with warfarin (**table 4):** this is important because up to 75% of PAH patients are being treated with warfarin or other anticoagulants.[11] With bosentan, the dose of warfarin has to be increased[12] whereas with sitaxentan, the dose of warfarin has to be decreased in order to avoid bleeding problems.[13] There is also an interaction between bosentan and sildenafil, which leads to lower concentrations of the latter.[14] We don't know if this has any clinical relevance, said Professor Hoeper, and this interaction is not seen with sitaxentan[6] or ambrisentan.[7]

Summarising, he said that the majority of PAH patients in functional classes II/III are receiving oral medications such as PDE-5 inhibitors or ERAs. There are not sufficient data to compare their long-term efficacy, but there appears to be no difference in terms of efficacy among the three ERAs**.**[8-10] Other factors such as side effects and costs must also be taken into consideration. Monotherapy, regardless of the agent used, is often not sufficiently effective in some of these patients, according to Professor Hoeper. Current clinical data from combination studies are limited but the results are promising. He presented findings from the REVEAL Registry,[7] a multicentre, observational US-based study, looking at PAH treatment. It showed **(figure 1)** from a sample of 1,226 patients, that at the time of enrolment, 44% were receiving only oral medications and 31% a prostacyclin combined with other agents. PAH-specific medications included 9% calcium channel blockers, 44% prostacyclin analogue, 47% ERAs and 46% PDE-5 inhibitors; 47% of patients were being treated with monotherapy. Eight percent of patients were receiving no PAH-specific medications.[15]

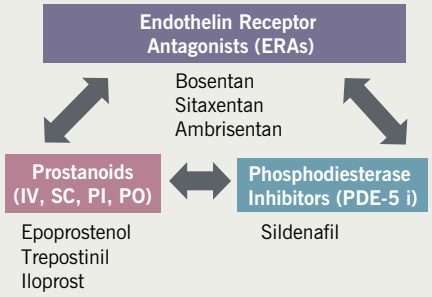
He commented that more than half of the patients were receiving combination therapy although there are as yet insufficient data to support this. The number of drugs and therefore the number of potential combinations of drugs that could be used is increasing rapidly (**figure 2).** The cost of combination therapy is likely to compound the

Figure 1: Combination therapy: a frequently used strategy in the treatment of pulmonary arterial hypertension (PAH)



Key: PO=oral; IV=intravenous; SC=subcutaneous; PI=inhaled. Data from McGoon MD 2007[15]

Figure 2: Combining various therapies in pulmonary arterial hypertension (PAH)



challenges faced by physicians managing PAH patients, in Professor Hoeper's view.

Findings from a small study of nine patients with idiopathic PAH from his centre[16] showed that adding sildenafil to bosentan improves six-minute walk distance. In a similar study from Johns Hopkins University[17] in patients with idiopathic PAH and in others with scleroderma, benefit was shown in the latter patients but not in the idiopathic cohort, suggesting that the PAH population is becoming increasingly complex and that not all forms of PAH may respond similarly to medical therapy. Also, new treatment options are rapidly emerging but comparative data are lacking. He believes that many questions will remain unanswered for some time.

"Treatment goals are becoming more ambitious year by year, and this is one of the reasons why combination therapy is now increasingly used. As PAH therapy is more complex than ever, this makes a strong case to treat these patients in experienced centres," he said

Conflict of interest

MMH has received lecturing fees and consultancy honoraria from Actelion, Bayer, Encysive, GSK, LungRx and Pfizer.

References

1. Elliott GC. *Chest* 2007; **132**: 631S.

2. Thenappan T, Shah SJ, Rich S, Gomberg-Maitland M. A USA-based registry for pulmonary arterial hypertension. *Eur Respir J* 2007;**30**:1103–10.

3. Gibbs JSR. Consensus statement on the management of pulmonary hypertension in clinical practice in the UK and Ireland. *Heart* 2008;**94**:1–41.

4. Galie N, Ghofrani HA, Torbicki A *et al*. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005;**353**:2148–57.

5. www.emea.europa.eu/humandocs/PDFs/EPAR/tracleer/H-401-PI-en.pdf

6. www.emea.europa.eu/humandocs/PDFs/EPAR/thelin/H-679-PI-en.pdf

7. www.emea.europa.eu/humandocs/PDFs/EPAR/volibris/H-839-PI-en.pdf

8. Rubin LJ, Badesch DB, Barst RJ *et al*. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;**346**:896–903.

9. Barst RJ, Langleben D, Badesch D *et al*: STRIDE-2 Study Group. Treatment of pulmonary arterial hypertension with the selective endothelin-A receptor antagonist sitaxsentan. *J Am Coll Cardiol* 2006;**47**:2049–56.

10. Galie N, Olschewski H, Oudiz RJ *et al*. Ambrisentan for the treatment of pulmonary arterial hypertension. Results of the ARIES Study 1 and 2. *Circulation* 2008;**117**:3010–19.

11. Johnson RS, Mehta S, Granton JT. Anticoagulation in pulmonary arterial hypertension: a qualitative systematic review. *Eur Respir J* 2006; **28**:999–1004.

12. Murphey LM, Hood EH. Bosentan and warfarin interaction. *Annals Pharmacotherapy* 2003;**37**:1028–31.

13. Waxman AB. A review of sitaxsentan sodium in patients with pulmonary arterial hypertension. *Vasc Dis Risk Manage* 2007;**3**:151–7.

14. Paul GA, Gibbs JSR, Boobis AR *et al*. Bosentan decreases the plasma concentration of sildenafil when coprescribed in pulmonary hypertension. *Br J Clin Pharmacol* 2005;**60**:1007–12.

15. McGoon MD. REVEAL Registry: treatment history and treatment at baseline. *Chest* 2007;**132**:631S.

16. Hoeper MM, Faulenbach C, Golpon H *et al*. Combination therapy with bosentan and sildenafil in idiopathic pulmonary arterial hypertension. *Eur Respir J* 2004;**24**:1007–10.

17. Mathai SC, Girgis R, Fisher MH *et al*. Addition of sildenafil to bosentan monotherapy in idiopathic pulmonary arterial hypertension. *Eur Respir J* 2007;**29**:469–75.

The optimal time to treat PAH patients

Professor Nazzareno Galiè, University of Bologna, Italy, outlined the pathophysiological mechanisms of pulmonary arterial hypertension (PAH). These are initiated by the progressive obstructive changes of the pulmonary resistance vessels which lead to the increase in afterload of the right ventricle (RV). In turn, this responds with functional and structural adaptations, leading ultimately to heart failure and death.[1] The hope is to have some treatment to help in reverse remodelling. Over the past 15 years or so there have been 22 randomised controlled studies, using a variety of PAH agents. He showed some 'hypothesis-generating' data from trials, using historical controls (prior to 1992) and then including patients treated with prostacyclin and more recently (after 2000) with oral agents. Although these patients are not identical or comparable at baseline, it appears that survival of patients who are referred to us today is much better than survival 15 or more years ago,[2] said Professor Galiè.

Despite greater awareness of PAH in recent years and the availability of targeted therapies, the majority of patients are at an advanced symptomatic stage by the time they are diagnosed.[3] A French registry of 674 patients has highlighted that 75% of patients were in New York Heart Association (NYHA) Class III or IV at presentation **(figure 1).**[3]

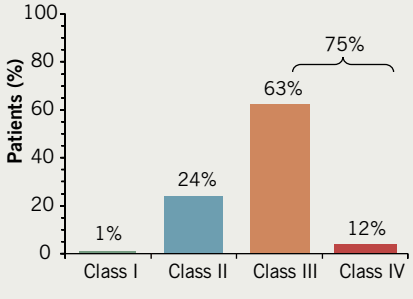
'Evidence is now sufficient to justify the treatment of early symptomatic (class II) patients'

Clinical investigations to date have focused largely on these more compromised patient populations. However, some recent studies have included patients in the early symptomatic stages of the disease. This is supported by findings from the University of Bologna pulmonary vascular diseases centre **(figure 2)** showing in recent months ("probably because there is more attention to the disease"), that referral of patients in the early symptomatic stages of the disease appears to be increasing, said Professor Galiè. Studies with epoprostenol show significantly improved survival rates when patients are treated at NYHA class III compared to class IV.[4]

EARLY and...

He presented further data from trials including the EARLY study, showing benefit of treatment in less compromised individuals in World Health Organization (WHO) Functional Class (FC) I and II. EARLY was a double-blind, randomised controlled trial of six months' treatment with bosentan (n=93) or placebo (n=92) in patients with WHO FC II PAH.[5] The primary end points were pulmonary vascular resistance (PVR) at six months (expressed as percentage of baseline) and change from baseline to month six in six-minute walk distance. Results showed the mean PVR at six months was 83.2% of baseline value with bosentan and 107.5% with placebo (p=0.0001); mean six-minute walk distance increased by 11.2 m with bosentan and decreased by 7.9 m with placebo, giving a non-significant mean treatment effect of 19.1 m (p=0.0758).[5] Significant benefits were seen, with reductions in pulmonary vascular resistance, in those patients who had haemodynamic assessments. More patients remained stable, without signs of clinical deterioration, in the bosentan group than in the placebo group (effect of bosentan on time to clinical worsening p=0.0114, log rank test). Exploratory end points in EARLY also included change from baseline to month six in N-terminal-prohormone brain natriuretic

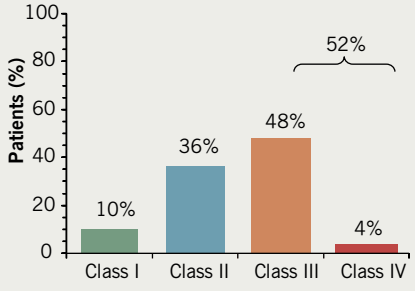
Figure 1: NYHA Functional Class at presentation in pulmonary arterial hypertension (PAH)



Adapted from AJRCCM 2006;**173**:1023–1030

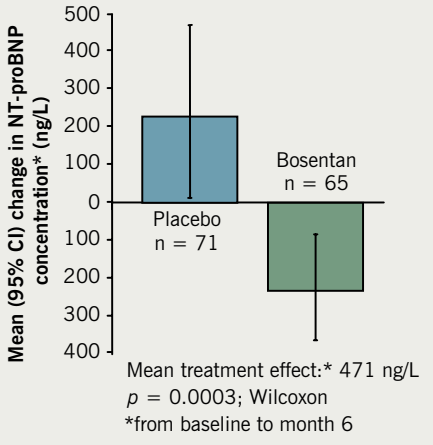
Key: NYHA=New York Heart Association

Figure 2: NYHA Functional Class of patients with pulmonary arterial hypertension (PAH) at the Pulmonary Vascular Diseases Center, University of Bologna (n=83)



Key: NYHA=New York Heart Association

Figure 3: EARLY: Effect of bosentan on NT-proBNP concentration



Adapted from Galiè N, *et al. Lancet* 2008;**371**: 2093–2100

Key: CI=confidence intervals; NT-proBNP=N-terminal pro brain-type natriuretic peptide; EARLY= Endothelin antagonist trial in mildly symptomatic pulmonary arterial hypertension patients

Figure 4: Ambrisentan is structurally different from bosentan and sitaxentan

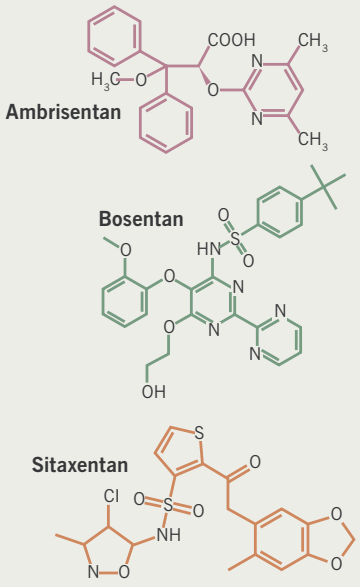


Table 1: Baseline characteristics of patients in the ARIES-1 and ARIES-2 studies

	ARIES-1 (n=202)	ARIES-2 (n=192)
IPAH	63%	65%
PAH associated with connective tissue disease, anorexigen use and HIV	37%	35%
WHO-FC		
I	2.5%	1.6%
II	32.3%	44.8%
III	58.2%	51.6%
IV	7%	2%
6-MWD (metres)	341±76	348±84

Key: IPAH=idiopathic pulmonary arterial hypertension; PAH=pulmonary arterial hypertension; ARIES= ambrisentan in pulmonary arterial hypertension, randomised, double-blind, placebo-controlled multicenter efficacy study; WHO-FC=World Health Organization functional class; 6MWD=six-minute walk distance
Data from Galie N *Lancet* 2008[6]

peptide (NT-proBNP). This too improved significantly, reflecting haemodynamic benefit, in the bosentan-treated patients (p=0.0003, Wilcoxon) **(figure 3).**[5]

Thirteen percent of patients in the bosentan group reported serious adverse effects (SAE), most commonly syncope; the SAE rate was 9% with placebo, the most common problem being right ventricular failure. Two deaths occurred during the study period, one in each patient group. Increases in aminotransferases >3x ULN occurred in 13% of bosentan-treated patients, compared to 2% in the placebo group.

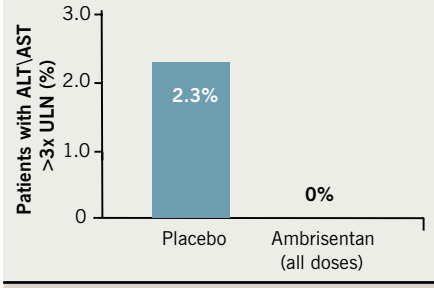
…ARIES studies reviewed

Professor Galiè then presented results from the ARIES studies with ambrisentan.[6] This compound is structurally different to the other ERAs, bosentan and sitaxentan – it is a propanoic acid class molecule rather than a sulfonamide **(figure 4).**[7] Ambrisentan is a selective endothelin A receptor antagonist which is administered orally once daily for treatment of PAH. The drug has been investigated in the recently reported ARIES-1 and ARIES-2 studies. ARIES-1 was conducted predominantly in North America, and ARIES-2 conducted mainly in Europe. The studies were concurrent, double-blind, and placebo-controlled. They randomised 202 and 192 PAH patients, respectively, to ambrisentan 5 or 10 mg (ARIES-1) or ambrisentan 2.5 or 5 mg (ARIES-2) orally once daily for 12 weeks. (Only the 5mg and 10mg doses are licensed for treatment of PAH.) The primary end point for each study was change in six-minute walk distance from baseline to week 12. Clinical worsening, WHO FC, Short Form-36 Health Survey score, Borg dyspnoea score and B-type natriuretic peptide (BNP) concentrations were also assessed. In addition, a long-term observational extension study was also performed. **Table 1** shows the baseline characteristics of patients in the studies: the majority of patients had idiopathic PAH and about 40% of patients were in the early symptomatic stages, FC I or II.[6]

Results showed that the six-minute walk distance increased significantly in all ambrisentan-treated groups.[6] The mean placebo-adjusted treatment effects were 31 m and 51 m in ARIES-1 for ambrisentan 5 and 10 mg, respectively; and 32 m and 59 m in ARIES-2 for ambrisentan 2.5 and 5 mg, respectively. In patients completing 48 weeks of ambrisentan monotherapy (n=280), the improvement from baseline was 39 m. Time to clinical worsening did not improve significantly in ARIES-1 but a statistically significant improvement was observed in ARIES-2. Professor Galiè explained that, in his view, this difference was exclusively related to the difference in clinical worsening among the placebo groups of ARIES-1 and ARIES-2, which had different rates of hospitalisations at 3% and 14%, respectively. He believes that there is a geographical difference in attitude towards hospitalisations in Europe and the US, and in his view it is easier to hospitalise patients in Europe compared to the United States. There was a significant improvement in WHO FC in the ARIES-1 patients receiving ambrisentan (p=0.036), while a similar but non-significant trend was seen in ARIES-2 (p=0.117). Also in ARIES-1 and ARIES-2, there was a reduction in BNP compared to placebo for all doses of the drug (p=0.003) and there was a significant improvement in quality of life in ARIES-2.

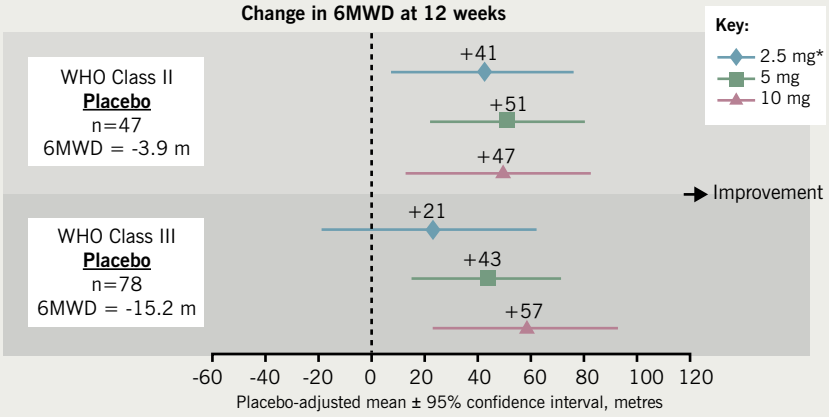
Interestingly, in the three months of this study no increases in liver enzymes more than three times the upper limit of normal were observed in the ambrisentan groups, but there was an increase in 2.3% of placebo patients **(figure 5)**[6]. Peripheral oedema, headache and nasal congestion are all peripheral effects which may be related to vasodilatation;[8] they tended to be more frequent in the ambrisentan-treated patients **(table 2)**[6]. Twenty-two patients (16.7%) in the placebo groups and 25 patients (9.6%) in the combined

Figure 5: In the ARIES-1 and ARIES-2 studies, ambrisentan was associated with a low incidence of LFT abnormalities at 12 weeks



Key: ARIES=ambrisentan in pulmonary arterial hypertension, randomised, double-blind, placebo-controlled multicenter efficacy study; LFT=liver function test; ULN=upper limits of normal; ALT=alanine aminotransferase; AST=aspartate aminotransferase
Adapted from Galie N *Lancet* 2008[6]

Figure 6: In ARIES-C, ambrisentan improved exercise capacity at 12 weeks



Adapted from: Olschewski H *et al* American Thoracic Society International Conference 2007 Poster 2873
* ambrisentan 2.5mg is not a licensed dose

Key: CI=confidence intervals; ARIES=ambrisentan in pulmonary arterial hypertension, randomised, double-blind, placebo-controlled multicenter efficacy study; 6MWD=Six-minute walk distance

Table 2: Common adverse events in the ARIES-1 and ARIES-2 studies

Adverse event	ARIES-1 (12 wks)			ARIES-2 (12 wks)		
	placebo n=67 (%)	5 mg n=67 (%)	10 mg n=67 (%)	placebo n=65 (%)	2.5 mg n=64 (%)	5 mg n=63 (%)
Peripheral oedema	10.4	26.9	28.4	10.8	3.1	9.5
Nasal congestion	3.0	6.0	10.4	0.0	1.6	4.8
Headache	20.9	17.9	19.4	6.2	7.8	12.7

Key: ARIES=ambrisentan in pulmonary arterial hypertension, randomised, double-blind, placebo-controlled multicenter efficacy study
Adapted from Galie N *Lancet* 2008[6]

ambrisentan group had at least one serious side effect. There were six deaths (4.5%) on placebo and four (1.5%) in the combined ambrisentan groups, none of them judged to be causally related to the study drug by the investigators.[6]

Professor Galiè then described a pre-specified combined analysis of the ARIES-1 and -2 studies.[9] He said this confirmed that there is a dose response improvement in exercise capacity at 12 weeks with ambrisentan. The combined analysis also showed a statistically significant improvement in time to clinical worsening (71% relative risk reduction) for the three doses of ambrisentan (2.5, 5 and 10 mg once daily) relative to placebo: this distinction in time to clinical worsening between the treatment groups was not dose-related.[9] Sub-group analysis also showed that the improvement in exercise capacity was very similar in both FC II and III patients, with improvements in 6MWD at 12 weeks of between 43% and 57% for ambrisentan 5mg and 10mg doses (**figure 6**).[10] He presented open-label data on one-year incidence of aminotransferase abnormalities showing >3 x ULN rates of 2.8% and > 5 x ULN of 0.5%.

Summarising, Professor Galiè said that the evidence is now sufficient to justify the treatment of early symptomatic (class II) patients, thereby preserving functional capacity.

Treatment delays, even of a few months, may decrease the potential benefit patients can derive from drugs. "We have to start treating these patients with pulmonary hypertension as soon as we have a reliable diagnosis," Professor Galiè concluded

Conflict of interest

NG has participated in advisory board activities for Actelion, Pfizer, United Therapeutics, Eli-Lilly, Bayer-Schering, Encysive and GSK.

References

1. Galie N, Manes A, Palazzini M *et al*. Pharmacological impact on right ventricular remodelling in pulmonary arterial hypertension. *Eur Heart J* 2007; **9**: H68-H74.

2. Sitbon O. ERS 2007: abstract 1593 (manuscript submitted).

3. Humbert M, Sitbon O, Chaouat A *et al*. Pulmonary arterial hypertension in France : results from a national registry. *Am J Resp Crit Care Med* 2006; **173**: 1023-30.

4. Sitbon O, Humbert M, Nunes H *et al*. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol* 2002; **40**: 780-8.

5. Galie N, Rubin LJ, Hoeper MM *et al*. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet* 2008; **371**: 2093-100.

6. Galie N, Olschewski H, Oudiz RJ *et al*. Ambrisentan for the treatment of pulmonary arterial hypertension. Results of ARIES 1 and 2. *Circulation* 2008; **117**: 3010-19.

7. Barst RJ. A review of pulmonary arterial hypertension: role of ambrisentan. *Vasc Health Risk Manag* 2007; **3**: 11-22.

8. Cho S, Atwood JE. *Am J Med* 2002; **113**: 580-6.

9. Galie N. American Thoracic Society International Conference 2007, Poster 3192.

10. Olschewski H. American Thoracic Society International Conference 2007, Poster 2873.

Future of PAH: what does success look like?

Professor Jean-Luc Vachiéry, Université Libre de Bruxelles, Belgium, began by looking at progress in the management of PAH over the last 50 years. Current therapies are now based on experience with earlier treatments, including calcium channel blockers[1] and surgery,[2] and by more recent, evidence-based RCTs with newer drugs **(figure 1).**[3-5]

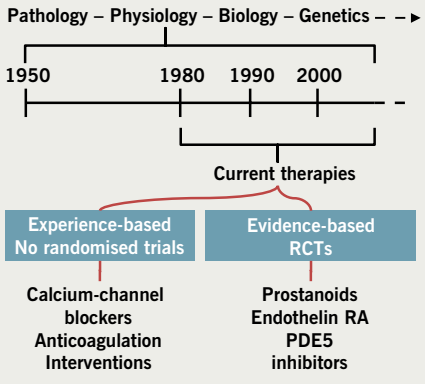
We are facing different needs in a rapidly evolving field, according to Professor Vachiéry. He outlined the many emerging issues in PAH **(table 1)**, which is an incurable disease.[6] Unequivocally, patients need a cure and better quality of life with enhanced survival, while clinicians need evidence to guide treatment strategies. This must be balanced by healthcare regulators, who will be under pressure to control the costs, and also by industry, which has a huge responsibility in this field, especially as PAH is considered to be an orphan disease.[7]

A likely first step might be to understand new targets. Evidence to guide clinical decision-making in how to measure success is coming from RCTs, but sometimes it can be difficult to translate this evidence into clinical experience. Professor Vachiéry discussed some of these new targets and investigational therapies,

'The future of PAH starts today… it's our responsibility to make it happen'

including vasoactive intestinal peptide (VIP)[8] and antiproliferative agents.[9] As cancer and PAH may share similar pathophysiology of aberrant cell proliferation, growth factor inhibition could play a role in the treatment of PAH, said Professor Vachiéry. But these new agents which target, for example, platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) are not yet fully proven in his view. Another concept is to transplant autologous endothelial progenitor cells which, one Chinese study suggests,[10] may be beneficial in patients with idiopathic PAH. The technique is being further assessed in a larger Canadian trial, the Pulmonary Hypertension: Assessment of Cell Therapy (PHACeT) trial.

Figure 1: Developments in treatment for pulmonary arterial hypertension (PAH)



Key: RCT=randomised controlled trial; RA=receptor antagonists; PDE5=phosophodiesterase 5

Adapted from: Sitbon[1], Klepetko[2], Rubin[3], Barst[4] and Galie[5]

Table 1: Emerging issues in pulmonary arterial hypertension (PAH)

Patients
• Need a cure – deserve best care
• Better QOL – maybe survival
• Facing different needs in a rapidly evolving field
Clinicians
• Elaborate new concept
• Need evidence to guide strategy
• Need experience for management
HC regulators
• Need to allocate ressources
• Quality control
Industry
• Drug development – operate RCT
• Need to invest in orphan diseases

Key: QOL=quality of life; RCT=randomised controlled trials

What evidence can be derived from RCTs and will success derive from combination therapy? These are important questions to assess as the impact of treatments on disease progression is not yet known. We will have to change and redefine success and update clinically relevant end points, in Professor Vachiéry's opinion, with robust demonstrations of safety and efficacy. Clinical trial end points over the past 15 years have included exercise capacity, haemodynamics, quality of life, time to clinical worsening, NYHA class, biomarkers and imaging.[3-5] Time to clinical worsening as assessed in clinical trials has evolved from event recording (death and transplantation) to more complex end points such as;

- refractory systolic hypertension
- worsening right ventricular failure
- rapidly progressing end-organ damage
- decrease in six-minute walk duration.

It has been used as a secondary end point in drug trials.[3-5, 11]

Composite end points in RCTs may have several components **(table 2).**[5, 12-14]

Table 2: Composite end points in RCTs

Patients

- 6MWD + principal reinforcing EP
- clinical events
- dyspnoea/fatigue rating
- signs/symptoms score

10% increase 6MWD + NYHA class + events

- no deterioration or death

> 25% drop peak VO_2 + disease progression

- Death, transplantation or other PGI_2 therapy

Early escape criteria

- Drop in 6MWD > 20% vs. base
- Increase by > 1 FC
- Worsening right heart failure
- Progressing end-organ failure
- SBP < 85 mmHg

At least 2

Key: RCT=randomised controlled trial; EP=end point; VO_2=pulmonary gas exchange; PGI_2=prostacyclin; 6MWD=six-minute walk distance; SBP=systolic blood pressure; FC=functional class
Data from Galie,[5] Simonnean,[12] Olschewski,[13] and Barst[14]

Composite end points have been used to evaluate treatments for heart failure, as seen in large trials such as SOLVD,[15] MERIT[16] and CHARM.[17] It is likely too in PAH that combinations of drugs will be assessed utilising composite end points.

How can the evidence gained translate into practice? Professor Vachiéry considered that clinical judgement was paramount. Clinical assessment may be derived from measures including NYHA FC, signs of right heart failure, aetiology and rate of progression; whereas the degree of exercise (in)tolerance can be assessed by six-minute walk duration.[18] Right ventricular (dys)function may be evaluated using biological surrogate markers and/or imaging (echocardiography, magnetic resonance imaging) and/or invasive techniques.[18] What is missing may come down to the definition of treatment failure, the type and timing of combination therapy, future targets and the definition of specialised centres. Clearly, more clinical trials are needed to provide evidence of significant, safe and clinically meaningful interventions. This will in the future be increasingly difficult as there are relatively few patients with this so-called orphan disease.

We have made such progress over the past 20 years that, when deciding on treatment, we have the luxury of choice, said Professor Vachiéry: we definitely need specialised centres. "The future of PAH starts today" and the bar has been raised very high. Now "it's our responsibility to make it happen" and to concentrate efforts on finding better tools to improve the quality of life and survival of these patients, said Professor Vachiéry

Conflict of interest

J-LV is consultant to GSK and Encysive Europe. He is an advisory board member to and has received speaker fees from Actelion, Encysive Europe, GSK, Pfizer and United Therapeutics.

References

1. Sitbon O, HymbertM, Ioos V *et al*. Who benefits from long-term calcium-channel blocker therapy in primary pulmonary hypertension? *Am J Respir Crit Care Med* 2003;**167**:A440.

2. Klepetko W, MayerE, Sandoval J *et al*. Interventional and surgical modalities of treatment for pulmonary arterial hypertension. *J Am Coll Cardiol* 2004;**34**:73S–80S.

3. Rubin LJ, Badesch DB, Barst RJ *et al*. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002; **346**:896–903.

4. Barst RJ, Langleben D, Badesch D *et al*. STRIDE Study Group. Treatment of pulmonary arterial hypertension with the selective endothelin-A receptor antagonist sitaxsentan. *J Am Coll Cardiol* 2006;**47**:2049–56.

5. Galie N, Olschewski H, Oudiz RJ *et al*. Ambrisentan for the treatment of pulmonary arterial hypertension. Results of the ARIES Study 1 and 2. *Circulation* 2008;**117**:3010–19.

6. Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med* 2004;**351**:1425–36.

7. Humbert M, Khaltaev N, Bousquet J *et al*. Pulmonary hypertension. From an orphan disease to a public health problem. *Chest* 2007;**132**:365–7.

8. Petkov V, Mosgoeller W, Ziesche R *et al*. Vasoactive intestinal peptide as a new drug for treatment of primary pulmonary hypertension. *J Clin Invest* 2003;**111**:1339–46.

9. Souza R, Sitbon O, Parent F *et al*. Long-term imatinib treatment in pulmonary arterial hypertension. *Thorax* 2006;**61**:736.

10. Wang XX, Zhang FR, Shang YP *et al*. Transplantation of autologous endothelial progenitor cells may be beneficial in patients with idiopathic pulmonary arterial hypertension. *J Am Coll Cardiol* 2007;**47**:1566–71.

11. Galie N, Ghofrani HA, Torbicki A *et al*. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005;**353**:2148–57.

12. Simonnean. *Am J Respir Crit Care Med* 2002;**165**:800–04.

13. Olschewski H. *N Engl J Med* 2002;**347**:322–9.

14. Barst RJ. *J Am Coll Cardiol* 2003;**41**:2119–25.

15. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fraction and congestive heart failure. *N Engl J Med* 1991;**325**:293–302.

16. MERIT-HF Study Group. Effect of metoprolol CR/XL in congestive heart failure: Metoprolol CR/XL Randomized Intervention Trial (MERIT-HF). *Lancet* 1999;**353**:2001–07.

17. Pfeffer MA, Swedberg K, Granger CB *et al*. Effects of candesartan on mortality and morbidity in patients with congestive heart failure: the CHARM-Overall programme. Lancet 2003;**362**:759–66.

18. Galie N, Torbicki A, Barst R *et al*. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. *Eur Heart J* 2004;**25**:2243–78.

Volibris®▼ (Ambrisentan) Prescribing Information
Please refer to full Summary of Product Characteristics (SPC) before prescribing

Uses: For the treatment of patients with pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease. **Dosage and administration:** Treatment must be initiated by a physician experienced in the treatment of PAH. Tablet, to be taken orally only. Adults: 5mg is the normal effective dose for Functional Class II and III PAH. 10mg offers extra efficacy in Functional Class III or connective tissue disease (CTD) patients where required. **Contraindications:** Hypersensitivity to the active substance, to soya, or to any of the excipients. Pregnancy and lactation. Severe hepatic impairment. Baseline values of hepatic aminotransferases (aspartate aminotransferases (AST) and/or alanine aminotransferases (ALT)) >3xULN. **Precautions:** Initiation of ambrisentan is not recommended for patients with clinically significant anaemia – haemoglobin or haematocrit levels should be measured prior to initiating treatment and is recommended at regular intervals thereafter. If sustained, unexplained, clinically significant anaemia develops then discontinuation of ambrisentan should be considered. Peripheral oedema (fluid retention) may require further investigation. Ambrisentan should not be initiated in women of child-bearing potential unless the result of a pre-treatment pregnancy test is negative and reliable contraception is being practiced. Monthly pregnancy tests during treatment are recommended. Hepatic aminotransferases (ALT and AST) should be evaluated prior to initiation. Monthly monitoring of ALT and AST is recommended. If sustained, unexplained, clinically significant ALT and/or AST elevation develop, or if ALT and/or AST elevation is accompanied by signs or symptoms of hepatic injury (e.g. jaundice), ambrisentan should be discontinued. **Pregnancy and lactation:** Contraindicated. **Drug Interactions:** Use caution when co-administered with cyclosporin A. Caution is recommended when co-administering with other treatments for PAH (e.g. prostanoids and phosphodiesterase type V inhibitors) as efficacy and safety around this co-administration has yet to be specifically evaluated. **Side Effects:** ***Very Common:*** Headache (including sinus headache and migrane), peripheral oedema (fluid retention). ***Common:*** palpitations, anaemia, upper respiratory congestion, sinusitis, nasopharyngitis, rhinitis, abdominal pain, constipation, flushing. ***Uncommon:*** Hypersensitivity reactions. **Overdose:** Doses above the recommended regimen may result in headache, flushing, dizziness, nausea and nasal congestion, symptomatic or asymptomatic hypotension. Cardiovascular support may be required in severe hypotension. **Legal category:** POM. **Presentation and Basic NHS cost:** Film coated tablet in 5mg and 10mg doses. 5mg tablets x 30, £1,651.07; 10mg tablets x 30 - £1,651.07 **Product Licence (PL):** EU/1/08/451/002 (5mg – Blister pack x 30 tablets), EU/1/08/451/004 (10mg – Blister pack x 30 tablets) **PL Holder:** Glaxo Group Ltd, Greenford, Middlesex, UB6 0NN **Last date of revision:** 24th September 2008

VOL/PRI/08/37985/1

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to GlaxoSmithKline on 0800 221 441

Every step counts

NEW Volibris™ ▼
ambrisentan

For most patients, being diagnosed with PAH is an extremely frightening experience. No longer being able to manage the everyday activities in life can be a particularly difficult prospect to cope with. Volibris is the first non-sulphonamide class ERA.[1] It has proven efficacy in PAH and is the first medicine approved for the treatment of both Functional Class II & III patients, to improve exercise capacity.[1-4]

Along with proven efficacy vs placebo and baseline, Volibris also has a low risk of drug-drug interactions affecting other drugs[1,5,6] and a low incidence of liver function test abnormalities, even with long-term use.[1-4]

So, for your Functional Class II and III patients, make once-daily Volibris your first choice.

Volibris® (Ambrisentan) Prescribing Information
Please refer to full Summary of Product Characteristics (SPCs) before prescribing
Uses: For the treatment of patients with pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease. **Dosage and administration:** Treatment must be initiated by a physician experienced in the treatment of PAH. Tablet, to be taken orally only. Adults: 5mg is the normal effective dose for Functional Class II and III PAH. 10mg offers extra efficacy in Functional Class III or connective tissue disease (CTD) patients where required. **Contraindications:** Hypersensitivity to the active substance, to soya, or to any of the excipients. Pregnancy and lactation. Severe hepatic impairment. Baseline values of hepatic aminotransferases (aspartate aminotransferases (AST) and/or alanine aminotransferases (ALT)) >3xULN. **Precautions:** Initiation of ambrisentan is not recommended for patients with clinically significant anaemia – haemoglobin or haematocrit levels should be measured prior to initiating treatment and is recommended at regular intervals thereafter. If sustained, unexplained, clinically significant anaemia develops then discontinuation of ambrisentan should be considered. Peripheral oedema (fluid retention) may require further investigation. Ambrisentan should not be initiated in women of child-bearing potential unless the result of a pre-treatment pregnancy test is negative and reliable contraception is being practiced. Monthly pregnancy tests during treatment are recommended. Hepatic aminotransferases (ALT and AST) should be evaluated prior to initiation. Monthly monitoring of ALT and AST is recommended. If sustained, unexplained, clinically significant ALT and/or AST elevation develop, or if ALT and/or AST elevation is accompanied by signs or symptoms of hepatic injury (e.g. jaundice), ambrisentan should be discontinued. **Pregnancy and lactation:** Contraindicated. **Drug Interactions:** Use caution when co-administered with cyclosporin A. Caution is recommended when co-administering with other treatments for PAH (e.g. prostanoids and phosphodiesterase type V inhibitors) as efficacy and safety around this co-administration has yet to be specifically evaluated. **Side Effects:** ***Very Common:*** Headache (including sinus headache and migraine), peripheral oedema (fluid retention). ***Common:*** palpitations, anaemia, upper respiratory congestion, sinusitis, nasopharyngitis, rhinitis, abdominal pain, constipation, flushing. ***Uncommon:*** Hypersensitivity reactions. **Overdose:** Doses above the recommended regimen may result in headache, flushing, dizziness, nausea and nasal congestion, symptomatic or asymptomatic hypotension. Cardiovascular support may be required in severe hypotension. **Legal category:** POM. **Presentation and Basic NHS cost:** Film coated tablet in 5mg and 10mg doses. 5mg tablets x 30, £1,651.07; 10mg tablets x 30 - £1,651.07 **Product Licence (PL):** EU/1/08/451/002 (5mg – Blister pack x 30 tablets), EU/1/08/451/004 (10mg – Blister pack x 30 tablets) **PL Holder:** Glaxo Group Ltd, Greenford, Middlesex, UB6 0NN **Last date of revision:** 12th June 2008.

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to GlaxoSmithKline on 0800 221 441

References: 1. Volibris SPC 2. Galiè N *et al J Am Coll Cardiol* 2005; **46**: 529-535 3. Galiè N *et al* Ambrisentan for the Treatment of Pulmonary Arterial Hypertension. *Circulation* 2008. 4. Oudiz RJ. ARIES-E: Long term safety and efficacy of ambrisentan in Pulmonary Arterial Hypertension; *ATS 2007* 5. Gerber MJ *et al CHEST* 2006; 256S 6. Dufton C *CHEST* 2006; 254S

VOL/FPA/08/37193/1
Date of preparation: July 2008

GlaxoSmithKline