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Advances in treatment of pulmonary arterial hypertension

Evidence for new therapies to treat pulmonary arterial hypertension were discussed at a recent meeting of the American College of Chest Physicians. Steve Dawber reports

Additional therapies for treating pulmonary arterial hypertension (PAH) will soon be available, according to experts speaking at the American College of Chest Physicians' annual meeting held in Montreal, Canada, recently.

Several classes of compound are being investigated, including selective endothelin-A (ET-A) receptor antagonists, phosphodiesterase-5 inhibitors, and inhaled prostaglandins. Therapies which target molecular and genetic mechanisms may also prove beneficial.

Addressing the meeting Robert Schilz, assistant professor of medicine, Case Western Reserve University, Cleveland, Ohio, said: "The pathogenesis of pulmonary arterial hypertension is characterised by three interactive mechanisms: vasoconstriction, cellular proliferation, and thrombosis. Within the pulmonary microcirculation, there are several pathways which can be targeted to prevent the condition. These include pathways involving endothelin, nitric oxide and prostacyclin.

"The recent explosion in PAH knowledge means that we have now identified several genetic and molecular abnormalities. Genetic abnormalities include bone morphogenic protein receptor-II, activin receptor-like kinase-1, and the serotonin transport protein 5HTT, while at the molecular level there are changes in vascular endothelial growth factor, platelet-derived growth factor, interleukin-1, interleukin-6 and plasminogen-activator inhibitor-1."

— Sitaxsentan vs bosentan

Compared with bosentan, sitaxsentan is associated with significantly fewer liver function abnormalities (abLFTs), according to an 18-week, phase III analysis presented at the meeting. This long-term, open-label extension to the STRIDE-2 (sitaxsentan to

relieve impaired exercise) study is the first direct randomised comparison of these two agents' effects on abLFTs.

Two-hundred and twenty-nine patients were recruited to the study. All had a confirmed diagnosis of either idiopathic PAH, PAH associated with congenital heart defects, or PAH associated with connective tissue disease.

At the time of analysis, 65 per cent of patients had either completed one year of therapy or discontinued treatment. The investigators found that compared with bosentan, sitaxsentan was associated with a significantly reduced risk of developing over three times elevated levels of alanine transaminase or aspartate aminotransferase (4.4 per cent versus 15 per cent; $P=0.014$).

Terrance Coyne, chief medical officer, Encysive Pharmaceuticals, Houston, Texas, who presented the data, said: "In both groups, most abLFT occurrences were observed in the first three to six months of therapy. This suggests that this 120-day analysis is largely mature and is likely to be predictive of the full one-year data."

— Sitaxsentan for PAH-CTD

Sitaxsentan, an ET-A receptor antagonist over 300 times more selective than the current gold standard therapy bosentan, has become the first agent to demonstrate high efficacy levels in difficult-to-manage patients with pulmonary arterial hypertension associated with connective tissue disease (PAH-CTD).

Pooled multicentre, randomised, placebo-controlled data involving 512 PAH patients (World Health Organization function class II-IV) were presented. The studies were of 12-18 weeks' duration and each used the six-minute walk distance as its primary or secondary outcome measure. Of the 110 patients who presented with PAH-CTD, 28 received placebo, 26 received sitaxsentan 50mg/day, 39 received sitaxsentan 100mg/day, and 17 received 300mg/day respectively. The most significant results were achieved with sitaxsentan 100mg/day. Compared with placebo, sitaxsentan 100mg/day significantly increased six-

minute-walk distance by 38m ($P=0.042$). Importantly, there were no reported incidences of elevated liver enzymes.

Presenting these data, James Seibold, chair of the International Scleroderma Network's medical advisory board, said: "PAH is a leading cause of death and late disease morbidity in connective tissue disease, and is generally less responsive to therapy than other forms of PAH, particularly in the setting of systemic sclerosis (SSc). Endothelin levels are increased in SSc-PAH and have vasoconstrictive effects mediated predominantly via the ET-A receptor. These data show that selective ET-A antagonism with sitaxsentan appears to be an effective and well tolerated therapy for this syndrome."

— Intravenous treprostinil

Intravenous treprostinil sodium can provide sustained improvements in exercise capacity and haemodynamics, according to data presented by Vallerie McLaughlin, associate professor of medicine and director of the pulmonary hypertension programme, University of Michigan.

In this open-label, multi-centre study, 47 PAH patients were treated with intravenous treprostinil either as initial therapy (*de novo*; $n=16$) or as a replacement for epoprostenol (transition; $n=31$). At one year, data were available for 16 patients (five *de novo* and 11 transition).

In the *de novo* group, six-minute walk distance increased from 323 ± 35 m at baseline to 454 ± 43 m at one year (mean increase 131m; $P=0.06$). Distances were unchanged in the transition group (482 ± 18 m to 482 ± 12 m; $P=0.96$).

The *de novo* group also experienced significant improvements in mean pulmonary artery pressure (66 ± 9 mmHg at baseline to 48 ± 7 mmHg at one year; $P=0.006$), cardiac index (1.5 ± 0.1 L/min/m² to 2.5 ± 0.2 L/min/m²; $P=0.04$), and pulmonary vascular resistance (37 ± 5 Wood units.m² to 16 ± 4 Wood units.m²; $P=0.01$). Dr McLaughlin concluded that the clinical efficacy of intravenous treprostinil appears to be maintained at one year and that it may be an effective alternative to intravenous epoprostenol in selected PAH patients.

The 71st annual meeting of the American College of Chest Physicians was held in Montreal, Canada, on 29 October-3 November 2005. **Steve Dawber** is a freelance journalist. He attended the meeting courtesy of Encysive Pharmaceuticals.

— Combination treatment

A phase II double-blind, placebo-controlled trial has shown that combination therapy with inhaled iloprost and oral bosentan is more efficacious than bosentan alone.

The 12-week study involved PAH patients who had been receiving stable doses of bosentan for at least 16 weeks. The results showed that compared with bosentan alone (125mg/day; n=33), a combination of iloprost (5mg six times daily) and bosentan (125mg/day; n=32) resulted in a mean increase in six-minute walk distance of 30m ($P=0.051$) and a reduced incidence of clinical deterioration (nil versus 15 per cent; $P=0.022$). For the purposes of the study, clinical deterioration was defined as death due to worsening PAH, receipt of lung transplant or atrial septostomy, admission to hospital for worsening PAH, or any early discontinuation from the study drug due to worsening PAH.

Presenting the results, Dr McLaughlin, said: "Combination therapy has become an area of increased interest for the PAH community, and patients in this study who received inhaled iloprost on top of oral bosentan not only tolerated the combination, but experienced enhanced treatment efficacy. Of particular note, combination patients had a statistically significant

improvement in their delay in time to clinical worsening when compared with those treated with bosentan alone. This important result suggests that this combination treatment strategy may slow the rate of disease progression."

— Clinical worsening

Sitaxsentan can significantly prevent clinical worsening in patients with idiopathic PAH, PAH associated with connective tissue disease, and PAH associated with congenital heart defects, new results showed.

David Badesch, professor of medicine, division of pulmonary sciences and critical care medicine, University of Colorado Health Sciences Centre, presented a pooled analysis involving 424 patients showing that, compared with placebo, sitaxsentan 100mg/day significantly reduced the time to clinical worsening after 18-weeks in patients in WHO functional class II–IV (96 per cent versus 89 per cent event-free patients; $P=0.0464$).

For the purposes of the analysis, clinical worsening was defined as death, transplantation, addition of new chronic PAH treatment, atrial septostomy, admission to hospital for worsening PAH, a combined deterioration in WHO functional class and ≥ 15 per cent decrease from baseline six-minute walk distance.

— Sildenafil and bosentan

An uncontrolled study has suggested that combining sildenafil with bosentan may improve exercise capacity in idiopathic PAH patients (New York Heart Association functional class II–IV). However, no benefits are seen in patients with scleroderma-associated PAH.

The 26-patient study, presented by Stephen Mathai, Johns Hopkins University, Baltimore, Maryland, showed that idiopathic PAH patients who received this combination (n=14) demonstrated improvements in six-minute walk distances, while patients with scleroderma-associated PAH (n=12) did not. There were two deaths in the scleroderma-associated PAH cohort.

According to Dr Mathai, the study had several limitations. These included the small number of patients, the lack of haemodynamic data before the addition of sildenafil, the presence of selection bias and the absence of a control group.

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