


# ■ magazine Scrip

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Pharmaceutical issues in perspective

A person in climbing gear stands on a rocky peak, silhouetted against a bright, hazy sky. A large, semi-transparent chest X-ray is overlaid on the background, showing the lungs and heart. The person is holding a rope, suggesting they are a climber or mountaineer.

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# Breathing space for PAH patients?

**Newer, safer, less invasive drugs are helping to manage pulmonary arterial hypertension, a disease for which treatments were until recently so restricted that there was little incentive to diagnose the condition, says Bruce Goldman**

**T**he following story, in relation to pulmonary arterial hypertension, is a classic. “A young mother, so sick she faints walking across the room from her hospital bed, gets put on a drug, and 13 years later she’s driving an hour from home to visit me, she takes her kids to school, and she coaches a hockey team. She’s got most of her life back.”

This particular anecdote is related by Dr David Langleben, cardiologist-in-chief and director of the Center for Pulmonary Vascular Disease at the Jewish General Hospital in Montreal and a professor of medicine at McGill University. But numerous clinicians could tell similar tales, highlighting major steps forward in the treatment of a debilitating disease: pulmonary arterial hypertension (PAH).

While by no means common, PAH – a progressive increase in the blood pressure in the lung resulting from narrowing and stiffening of pulmonary arteries – is not nearly as rare as was once thought. Its prevalence is estimated at around 200,000 cases in North America and Europe, of which perhaps merely 10–20% are diagnosed. This is partly because of the vagueness of initial symptoms, chiefly shortness of breath, which can be accompanied by fatigue, lightheadedness, chest pain, or fainting.

Moreover, until recently the range of therapies was so restricted there was little incentive to diagnose PAH. A decade or so ago, the only available drug therapy was very high doses of calcium-channel blockers, says Dr Raymond Benza, director of the pulmonary vascular disease programme at the University of Alabama. This therapy succeeded only in a tiny fraction of patients. For those most ill, the remaining alternative was a heart-lung transplant, for which donors were often unavailable and which bought only four to five years of additional survival.

Left untreated, PAH progresses even more swiftly than most cancers. In the 1980s, before drug therapies were widely available, the US National Institutes of Health (NIH) compiled a registry allowing for calculation of survival times from diagnosis for patients suffering from ‘idiopathic’ PAH – the most common form – whose derivation is unknown rather than secondary to other syndromes, notably scleroderma. The numbers were bleak: so-called Class IV PAH patients, who exhibit symptoms even at rest, could expect to live just six months; Class III patients, symptomatic on mild activity, 2.6 years; and Class II patients, whose symptoms manifest themselves on exertion, six years. (Class I patients are asymptomatic.)

## Changing times

But newer, safer, less invasive treatments are triggering an increased number of referrals to pulmonary-hypertension specialists. This era of dramatic change dates from the mid-1990s with the launch of GlaxoSmithKline’s Flolan (epoprostenol). Commercially available throughout North America, Europe, and Japan, Flolan profoundly altered the course of PAH. A study by Dr Vallerie McLaughlin, director of the pulmonary-hypertension programme at the University of Michigan, and her colleagues showed marked improvement in the survival rates of Classes III and IV idiopathic PAH patients on Flolan at one, two, and three years of treatment.

Flolan is notoriously difficult to use, though. It must be infused intravenously, 24 hours a day, through a surgical catheter placed under the patient’s clavicle, via a four-pound pump that patients, like the example in Langleben’s story, carry wherever they go. There’s a risk of dying should the flow be interrupted for even several seconds, and constant risk of infection by the catheter.

Flolan must be kept refrigerated at all times and remixed daily. It doesn’t work for everybody, nor does it typically work miracles or work forever, even though it has been considered the gold standard for PAH drug therapy.

In the past few years, a cornucopia of new drugs for PAH has emerged. The first oral agent, approved in the US in late 2001, was Tracleer (bosentan), whose mechanism of action is quite different from Flolan’s. Manufactured by Actelion, Tracleer is sold in North America and Europe and was just recently approved in Japan. Tracleer prescriptions, typically for Classes II or III patients, far outnumber those for Flolan, which is typically reserved for the sickest.

Flolan’s proven survival benefit makes conducting placebo-controlled trials of other agents unethical. But analysis by McLaughlin and her colleagues of idiopathic PAH patients given Tracleer as a first-line therapy showed median survival times exceeding those in the Flolan monotherapy studies or the NIH registry. (Because a significant fraction of study patients either switched to or added Flolan, the study cannot be said to prove Tracleer by itself improves survival rates.)

Tracleer patients experience high rates of liver-function abnormalities – raised blood levels of enzymes that can indicate liver damage. Clinicians say these abnormalities are often resolved by themselves or can be reversed with dosage reductions, or by temporarily withholding the drug. But patients must be monitored frequently, and permanent discontinuation is sometimes felt necessary.

May 2002 saw FDA approval of a subcutaneous formulation of Remodulin (treprostinil), marketed by United Therapeutics in the US. Like Flolan, with which it shares a common mechanism of action, Remodulin must be infused around the clock via a catheter hooked up to a pump. But it’s more stable and has a longer half-life, so it doesn’t need to be replaced as often as Flolan or refrigerated, and interrupted flow is not as life-threatening. Still, many clinicians don’t feel its efficacy is as great as Flolan’s, and frequent

injection-site pain has limited its use. In November 2004, the FDA extended Remodulin's label to include intravenous, as opposed to subcutaneous, delivery, which may address the injection-site pain issue.

In December 2004, the FDA approved yet another Flolan-like drug, Ventavis (iloprost), marketed in the US by CoTherix. Available since September 2003 in Europe, where it was developed by Schering AG, Ventavis is inhaled, rather than infused, from a 'smart' seven-pound plug-in nebuliser that senses the midpoint of a patient's inhalation and only then releases the compound. Although non-invasive, Ventavis must be inhaled for about ten minutes straight, six to nine times daily.

Meanwhile, Pfizer's Viagra (sildenafil) is seeing heavy off-label use to treat PAH and late last year, solid results were reported for a Phase III trial of sildenafil in PAH patients. FDA approval of sildenafil for PAH, under the trade name Revatio, is expected this June or thereabouts.

To date, PAH drugs fall into three classes, distinguished by their mechanisms of action. Sildenafil's efficacy in PAH, as in erectile dysfunction, stems from its inhibition of PDE-5, an enzyme that breaks down a smooth-muscle-relaxing downstream product of the nitric-oxide pathway. Flolan, Remodulin, and Ventavis restore an endogenous substance, prostacyclin, which acts as a vasodilator in pulmonary blood vessels. Both Tracleer and

another drug, Thelin (sitaxsentan), expected to be approved by the FDA late this year or early next year, block receptors for a substance called endothelin, a powerful vasoconstrictor that is overexpressed in blood vessels of PAH patients' lungs. Endothelin also elicits cell division and proliferation of smooth muscle, causing pathological vascular remodelling.

The pharmacological and, possibly, clinically relevant distinctions between Thelin, developed by Encysive, and Tracleer are best understood if one considers the physiology of the pulmonary blood vessel, whose inner lining of endothelial cells is ringed by smooth muscle cells. When smooth muscle contracts, the blood vessel narrows; when it relaxes, the vessel widens. Pulmonary vessels host two types of receptors for endothelin: ET-A and ET-B. ET-A, found only on smooth-muscle cells, mediates vasoconstriction. ET-B shows up on both smooth-muscle and endothelial cells. On smooth-muscle cells, ET-B causes vasoconstriction, too. But on endothelial cells, its role is radically different: it not only clears endothelin from the circulatory system but triggers production of two substances – nitric oxide and prostacyclin – that relax smooth-muscle cells, causing vasodilation.

Tracleer blocks both receptor types, whereas Thelin is strongly selective for ET-A. There is much debate about which approach is superior. Some animal studies have suggested

that in diseased tissue ET-B's function becomes transformed to resemble that of ET-A. However, Langleben's work, announced at the American Thoracic Society's annual meeting in Seattle in 2003, showed conclusively that ET-B's crucial endothelin-clearing role is retained in advanced PAH patients. Blocking this receptor could thus be counterproductive. ET-B is also found in many other tissues such as the kidneys, notes Alabama University's Benza, who suggests this may account for water retention observed in some PAH patients using Tracleer.

### Tracleer versus Thelin

So far, the clinical data demonstrate no vast difference in efficacy between the two compounds. But trial designs vary, so it's difficult to compare one with another. The closest Thelin and Tracleer have come to going head-to-head in the same patient population is in Encysive's pivotal Phase III trial, STRIDE-2, concluded early this year. In that study, some patients were given placebo, others Thelin, and others still Tracleer. Placebo and Thelin recipients and their handlers were blinded, while the Tracleer arm was open-label, a condition often considered to bias results in a positive direction because patients know their pill contains an active agent. Nonetheless, in this trial Thelin edged ahead of Tracleer in patient improvements in exercise capacity and class designation. Thelin also inclined towards

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superiority over placebo ( $p=0.08$ ) in clinical worsening, whereas Tracleer patients, despite Tracleer's open-label advantage (and the claim on its label to reduce clinical worsening), suffered slightly more clinical-worsening events than placebo. Liver-function abnormality levels at 12 weeks for Thelin (3%) and Tracleer (11%) reflected levels typical of earlier trials of both drugs. Furthermore, Thelin's discontinuation rate was lower.

Thelin is known to boost levels of another drug, the blood thinner warfarin, commonly used in PAH patients. But no significant bleeding events occurred with Thelin in STRIDE-2. According to Benza, warfarin levels are impacted by about 200 drugs as well as by food and other environmental factors, so all patients on warfarin must be carefully monitored in any case. Dropping a patient's warfarin dose by 80% before starting on Thelin, then adjusting that dose to optimal levels later, prevents trouble, he says.

Demonstrating the advantage of having more than one agent available in a class, a subset analysis of 48 patients in an earlier trial showed that of 13 patients discontinuing Tracleer because of liver-function abnormalities, only one incurred them with Thelin, and of 35 patients who had dropped Tracleer for lack of efficacy a full one-third responded well to Thelin.

There is no perfect PAH drug yet. But the existence of oral or inhaled agents representing at least three mechanisms of action has

clinicians wondering: will combining compounds from different classes yield treatment synergies?

Well-designed combination studies make inherent sense, says McLaughlin. "We need to see which ones work – and whether they're cost-effective, because many of the therapies are quite expensive." She observes that the combination of an endothelin-receptor antagonist and a PDE-5 inhibitor could be given orally.

Here, says Langleben, the ET-B receptor's function in stimulating nitric-oxide production may pose problems for Tracleer, which has been found to interact with sildenafil in a way that raises Tracleer concentrations in the blood by 50% and lowers sildenafil levels by 50%. That could, in theory, double the dosage (and cost) of sildenafil and boost the already high rates of liver-function abnormalities caused by Tracleer. (Interactions of Thelin and sildenafil appear to be clinically insignificant.)

More companies offering a greater number of active agents means a bigger market as more-aggressive diagnostic efforts are encouraged, with early treatment favouring the newer, non-invasive drugs. As Benza points out: "We didn't have options before. Now we do. And the more options you arm doctors with, the better they're going to be able to treat disease."



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