EDITORIAL

Long-term treprostinil in pulmonary arterial hypertension: is the glass half full or half empty?

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Pulmonary arterial hypertension (PAH) has traditionally been considered as an inevitably fatal disease. In the 1980s, a national registry funded by the National Institutes of Health (NIH) described the natural history of idiopathic PAH [1]. The median survival was <3 yrs and prognosis was mostly related to baseline functional capacity and pulmonary haemodynamics. In case series, the long-term outcome of patients with PAH associated with connective tissue disease, portal hypertension and HIV infection appeared to be even worse [2]. This was before the era of PAH-specific therapies. In the last decade, significant advances in the current understanding of the disease have led to the development of new specific treatments. In 1996, a placebo-controlled trial demonstrated significant survival benefit with *i.v.* epoprostenol in idiopathic PAH patients [3]. Several other therapies, including prostacyclin analogues, endothelin receptor antagonists and phosphodiesterase type-5 inhibitors, were subsequently evaluated in short-term randomised placebo-controlled trials. These studies demonstrated improvements in pulmonary haemodynamics, exercise capacity and quality of life [4–6]. This new era of therapy has clearly brought enthusiasm among physicians. From a clinician's perspective, the glass has been half filled.

Treprostinil *s.c.* was evaluated in a large randomised placebo-controlled trial involving 470 PAH patients randomised to either *s.c.* treprostinil or placebo [7]. Over a 12-week period, *s.c.* treprostinil improved patients' exercise capacity, PAH-related symptoms and haemodynamics. The median placebo-corrected increase in 6-min walking distance was 16 m, with greater improvements in severely ill patients at baseline and in those who could tolerate the highest doses. Unfortunately, this short-term trial, as with others, was underpowered and not designed to detect survival benefit. Indeed, the most ill patients are no longer entered into placebo-controlled trials and patients who deteriorate whilst under study are rapidly transitioned to rescue therapy.

Improvement in exercise capacity after 12–16 weeks of therapy does not necessarily translate into a better long-term outcome. In the only long-term randomised placebo-controlled trial ever performed in PAH [8], the initial improvement in exercise capacity was no longer significant at 12 months. This fact

emphasises the need for large observational studies to evaluate the long-term outcome with these therapies.

In the current issue of the *European Respiratory Journal*, BARST *et al.* [9] describe the long-term outcome of a large cohort of World Health Organization (WHO) functional class II–IV PAH patients treated with first-line *s.c.* treprostinil for up to 4 yrs. These patients either entered the open-label extension of a previous randomised controlled trial [7] or were enrolled as *de novo* patients. This resulted in the largest multicentre long-term observational study of PAH patients treated with novel therapies ever published. A wide variety of associated conditions were included, such as connective tissue disease, congenital heart disease, portal hypertension and HIV infection. Moreover, a significant number of WHO functional class II and IV were reported. These subpopulations have generally been under-represented in previous studies. Overall, the survival rates were 87, 78, 71 and 68% at 1, 2, 3 and 4 yrs, respectively. These estimates are fairly consistent with the recently published observational study by LANG *et al.* [10] of 122 patients with PAH and distal chronic thromboembolic pulmonary hypertension treated with first-line *s.c.* treprostinil. As previously reported in other series [2], baseline pulmonary haemodynamics (mixed venous oxygen saturation and pulmonary vascular resistance) and WHO functional class (in idiopathic PAH) were related to long-term prognosis.

These survival estimates do not represent the prognosis on *s.c.* treprostinil alone, but rather the results of a treatment approach consisting of first-line treprostinil, with additional PAH treatments if necessary. As a matter of fact, a majority of patients in the study by BARST *et al.* [9] discontinued *s.c.* treprostinil or had concomitant therapy added during follow-up because of clinical deterioration or adverse events. This is consistent with recent evidence-based guidelines, suggesting that combination therapy or transition to *i.v.* epoprostenol might be considered for patients who failed to improve or deteriorated following first-line treatment [4–6].

For obvious ethical reasons, long-term placebo-controlled trials to assess the effect of PAH therapies on long-term survival are no longer possible. To overcome this blind alley, the long-term outcome of treated idiopathic PAH patients has been repeatedly compared with historical controls or the expected survival based on the NIH survival equation [10–15]. Indeed, the NIH registry validated an equation predicting survival, according to baseline haemodynamic severity. The outcome of patients with other types of PAH has been less well described. BARST

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et al. [9] also described the long-term outcome on first-line *s.c.* treprostinil in a subset of idiopathic PAH patients in whom baseline haemodynamics were available. Their long-term survival was improved compared with the expected survival based on the formula from the NIH registry [1]. These results are certainly reassuring and encouraging. However, background practice has dramatically changed since the NIH registry was described in the 1980s. Due to the lack of a proper control group and randomisation procedures, any improvement in the observed long-term outcome with therapy cannot be unambiguously attributed to *s.c.* treprostinil. Comparing the long-term outcome of patients with various PAH-specific therapies from previous observational studies also carries major limitations. As stated by BARST *et al.* [9], this approach is similarly hazardous because baseline characteristics of patients substantially differed from one study to another.

Finally, the study by BARST *et al.* [9] also provides substantial information about the safety profile of long-term *s.c.* treprostinil. The average dose observed in this study was substantially higher than in the pivotal trial (median dose $8 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) [7]. In the 1,419 patient-years of follow-up, therapy was generally well tolerated. Infusion site pain remained a prominent drawback of *s.c.* treprostinil, and was reported by 92% of patients. Despite significant improvement in pain management in recent years with gels and appropriate analgesia, 23% of patients still discontinued therapy because of infusion site pain and/or reaction. Apart from the prostacyclin-related effects, other adverse events were rare.

The pivotal placebo-controlled randomised trial on *s.c.* treprostinil [7] clearly documented the potential role of *s.c.* treprostinil in the current therapeutic "arsenal" for PAH patients, and the study by BARST *et al.* [9], which is the largest long-term observational study ever published in PAH, is further supportive. Treprostinil *s.c.* has now received approval for the treatment of PAH in Europe, North America and some South American countries. While PAH patients benefit from this therapy, one question remains: what is the precise role of *s.c.* treprostinil in the current treatment algorithm? As there is no head-to-head comparison between *s.c.* treprostinil and other treatment options, we still have to make somewhat arbitrary decisions about the therapy of choice for a given patient. The final choice will depend on a variety of factors, including PAH severity, route of administration, side-effects and available data on efficacy. Recent clinical guidelines suggest that specific therapy for PAH should be based on disease severity as assessed by the functional capacity [4–6]. Treprostinil *s.c.* is currently indicated for WHO functional class III and IV PAH patients (approved for WHO II–IV in the USA). Given the growing number of available oral therapies also indicated for WHO functional class III patients, *s.c.* treprostinil is likely to be considered as a second-line therapy for these patients. Interestingly, the study by BARST *et al.* [9] also included 78 WHO functional class IV patients. The proportion of these who discontinued *s.c.* treprostinil during follow-up because of clinical deterioration is unknown. Nevertheless, their long-term survival appears similar to idiopathic WHO functional class IV patients treated with first-line *i.v.* epoprostenol [11, 12]. From a pharmacological standpoint, *s.c.* treprostinil has obvious advantages over *i.v.* epoprostenol, such as route of

administration and longer half-life. Although BARST *et al.* [9] confirmed that *s.c.* treprostinil may be a valuable option for some of these patients, it must be emphasised that most experts still recommend *i.v.* epoprostenol as first-line therapy for most WHO functional class IV patients because of the demonstrated survival benefit in this subset [3–6].

Taken together, these results on long-term survival of pulmonary arterial hypertension patients treated with first-line *s.c.* treprostinil are encouraging. This large observational study further suggests that pulmonary arterial hypertension is no longer an inevitably fatal disease. From a patient's perspective, however, these encouraging results may seem to be a "half-empty glass", as long-term survival and quality of life remain unsatisfactory for many patients.

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