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Original article

A disease looking for innovative drugs: The case of pulmonary arterial hypertension

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ABSTRACT

Background: Pulmonary arterial hypertension (PAH) is a life-threatening rare disease. Between 2001 and 2016 the European Medicines Agency (EMA) approved nine drugs to treat PAH. Considering the poor prognosis of patients with PAH it would be useful to understand whether the approved therapies can change the natural history of the disease. We assessed the therapeutic value and the quality of the evidence on medicines that have been authorized by the EMA in the 2000s.

Methods: Information about drug approval was obtained from the EMA website and the European Public Assessment Reports. MedLine, Embase, and Cochrane databases were systematically searched for published randomized clinical trials and meta-analyses of the selected drugs and their combinations.

Results: At the time of approval no medicine had been proved to reduce mortality or slow the progression of the disease or to improve patients' quality of life. Recent meta-analyses concluded that, compared to placebo, active treatments reduced mortality but there was no conclusion on any preferred therapeutic option. Approvals of monotherapies in the absence of best evidence of their efficacy, have prompted the search for better efficacy of their combinations. Three meta-analyses found no advantage in survival from combinations as opposed to monotherapies.

Conclusions: This model case confirms previous analyses that marketing authorizations granted in spite of low evidence of therapeutic efficacy not only expose patients to treatments with unknown benefit-risk profiles but also hamper post-marketing research aimed at filling the information gap.

1. Introduction

Pulmonary arterial hypertension (PAH) is a life-threatening disease and a rare form of pulmonary hypertension involving haemodynamic and pathophysiologic states of high mean pulmonary arterial pressure (> 25 mm Hg at rest) in the absence of any lung or left-sided cardiac abnormalities as a cause of the increase. [1]

PAH can be idiopathic, heritable, drug- or toxin-induced, or caused by associated conditions, such as HIV infection, congenital heart diseases, portal hypertension, schistosomiasis, and connective tissue diseases. Complications can include right ventricular dysfunction/right heart failure, peripheral oedema, ascites, and tachyarrhythmias [1].

The prevalence of PAH is around 15–60 per 1,000,000 adults overall and 5–10 per 1,000,000 adults for the idiopathic form. [2] The reported prevalence of disease-associated PAH is 5–10% in patients with congenital heart disease, 9% in patients with systemic sclerosis, 2–6% in patients with portal hypertension, and 0.5% in patients with HIV [3]. Most forms of PAH develop in adults; cases in children are rare; women are twice as likely as men to be affected. [4] Survival with treatment can range from about 80% at one year to about 50% at five years. [1]

In the past 20 years several specific drugs targeting the endothelial dysfunction associated with PAH have been licensed. [5] Considering the poor prognosis of patients with PAH it would be useful to understand whether the approved therapies can be defined as disease-modifying, meaning they actually change the natural history of PAH. We assessed the therapeutic value and the quality of the evidence on medicines that have been authorized by the European Medicines Agency (EMA) in the 2000s.

2. Methods

We searched the EMA website (http://www.ema.europa.eu/ema/) for drugs approved for the treatment of PAH and conducted a literature search for the pivotal trials of these drugs. Two reviewers independently extracted data from phase III pivotal trials from the European Public Assessment Report (EPAR) available in the EMA

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Table 1
Evidence from pivotal trials on drugs approved by the EMA for PAH.

Active principle, MA Date	Name of pivotal trial	Comparator	Primary Endpoint	Actual evidence from pivotal trials[a]	Duration of treatment
cGMP activators					
Nitric oxide 01/08/2001	CINRGI[19]	Placebo	ECMO rescue[b]	1 in 4 patients can avoid ECMO	71 h
Riociguat 27/03/2014	PATENT-1[20]	Placebo	6MWD[c]	Patients walk about 30 m longer which is < 10% more than they walked before	12 and 16 weeks
ETA/ETB antagonists					
Bosentan 15/05/2002	AC-052-352[16]	Placebo	6MWD[c]	Patients walk about 40 m longer which is about 10% longer than they walked before	16 weeks
Ambrisentan 21/04/2008	ARIES 1, ARIES 2[15]	Placebo	6MWD[c]	Patients walk about 40–50 m longer which is 12–15% longer than they walked before	12 weeks
Macitentan 20/12/2013	AC-055-302/ SERAPHIN[18]	Placebo	COMPOSITE[d]	1 in 8 patients does not get worse	3.6 years
PGI agonists					
Iloprost 16/09/2003	RR A02997[17]	Placebo	COMPOSITE[e]	1 in 8 patients improves his/her NYAH class; 1 in 8 patients walk at least 30 m longer over the 330 m than they walked before	12 weeks
Selexipag 12/05/2016	GRIPHON[21]	Placebo	COMPOSITE[f] HR:0.60 (99% CI 0.46–0.78)	1 in 20 patients avoids hospitalization; 1 in 10 patients has no progression	
PDE5 inhibitors					
Sildenafil 28/10/2005	A1481140[22]	Placebo	6MWD[b]	Patients walk about 40 m longer which is about 10% longer than they walked before	12 weeks
Tadalafil 01/10/2008	PHIRST-1, PHIRST-2[23]	Placebo	6MWD[b]	Patients walk at most 30 m longer which is < 10% longer than they walked before	16 weeks

Abbreviations
cGMP activator: Activators of Soluble Guanylate Cyclase.
ETA/ETB non-peptide antagonist of human endothelin receptors.
PDE5 inhibitor: phosphodiesterase type 5 inhibitor.
PGI agonist: prostacyclin receptor agonist.
[a] Details of data supporting these statements are provided in the Additional Table and published reports on pivotal trials.
[b] Number of patients receiving rescue Extra Corporeal Membrane Oxygenation (ECMO).
[c] Mean change in Six-Minute Walking Distance from baseline compared to placebo.
[d] Worsening of PAH or start of iv or sc prostanoids or lung transplantation or atrial septostomy or death;
[e] Improvement in 6MWD + at least one NYHA class + no deterioration of PAH or death before week 12;
[f] Death or complication related to PAH, i.e. disease progression or worsening of pulmonary arterial hypertension that required hospitalization, initiation of parenteral prostanoid or long-term oxygen therapy, lung transplantation or balloon atrial septostomy.

website (Box). Differences were solved by consensus. The publications of those trials were hand-searched on Pubmed library. We also systematically searched Pubmed, Embase and Cochrane library databases up to July 2017 to identify studies testing the efficacy and safety of combinations of drugs for PAH.

3. Results

Between August 2001 and May 2016 the EMA approved nine drugs for the treatment of PAH belonging to four therapeutic classes (Table 1). Six drugs (ambrisentan, bosentan, iloprost, macitentan, riociguat, and sildenafil) [6–12] received the designation of Orphan Medicinal Product. The companies concerned requested and received the EMA scientific advice for selexipag pertaining to non-clinical and clinical aspects of the dossier, and for riociguat on the use of systolic blood pressure as a surrogate for the dose titration endpoint, and the design of the chronic thromboembolic pulmonary hypertension and PAH pivotal clinical trials.

None of the drugs were authorized under exceptional circumstances or had conditional approval. For macitentan, riociguat and selexipag the EMA requested additional post-marketing monitoring measures in view of the limited long-term data available. [9,11,13] Sitaxentanthelin was withdrawn four years after approval because of two cases of fatal liver injury. [14]

Pivotal trials of all products were placebo-controlled. [15–23] Placebo might have been inappropriate for ambrisentan since bosentan, another human endothelin receptor antagonist, had been licensed in 2002. [8,15] The same holds true for macitentan, [18] since ambrisentan and bosentan, two drugs with the same mechanism of action, were already available, together with iloprost, a prostanoid licensed in 2003, [7,8,10] and two enzyme phosphodiesterase 5 (PDE5) inhibitors, sildenafil and tadalafil, approved in 2005 and 2008, respectively. [12,24] Placebo was also used unduly in a pivotal trial of selexipag (approved in 2016) which should have been compared with iloprost or one of the two endothelin receptor (ET_A) antagonists, or one of the two selective PDE5 inhibitors. [21]

The primary endpoint was surrogate in seven out of ten pivotal trials. [15,16,19,20,22,23] Improvement in walking distance was the primary endpoint in six trials, [15,16,20,22,23] reporting the range or mean of extra meters walked in six minutes, the so-called six-minute walking distance (6MWD). After 12 weeks of treatment (with ambrisentan, bosentan, riociguat, or sildenafil) patients walked about 30–50 m longer at most than before which means 10–15% more than before (Table 1 and Additional Table). [15,16,20,22]

The pivotal trials of three active principles (iloprost, macitentan, selexipag) adopted combined endpoints including items with heterogeneous clinical value. [17,18,21] Iloprost was assessed on the basis of a composite endpoint including at least 10% improvement in walking distance and at least one NYHA class and no deterioration of PAH, or death within 12 weeks. Success was only achieved in 16.8% of patients on iloprost. [17] Considering the 4.9% success rate in the placebo group, the net benefit only applies to a dozen patients out of 100 treated (absolute risk reduction, ARR, 11.9%). There was no advantage in terms of PAH progression or mortality. The difference in responders