What added value do these compounds bring?

New compounds for the treatment of pulmonary hypertension

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Summary

Survival with pulmonary arterial hypertension has significantly improved in the last two decades with the development and approval of different compounds. This review highlights the properties of molecules that more recently became available for specific treatment of pulmonary hypertension.

Key words: pulmonary arterial hypertension; endothelin receptor antagonist; soluble guanylate cyclase stimulator; prostacyclin receptor agonist



Introduction

Pulmonary hypertension (PH) was reported for the first time in 1891 when the autopsy of a patient with sudden death revealed right ventricular hypertrophy and pulmonary artery sclerosis without any apparent cause. PH is a progressive disease with elevated pulmonary vascular resistance (PVR) as the basic cause for increased right ventricular afterload and hypertrophy, which eventually proceeds to right ventricular dilatation and failure, and premature death [1]. The prevalence of PH is 97 cases per million, with a female to male ratio of 1.8:1 and an age-standardised annual mortality rate between 4.5 and 12.3 per 100,000 people in the population [1].

PH is clinically classified into five groups: pulmonary arterial hypertension (PAH) (group 1), PH related to left heart disease (group 2), PH due to lung disease and/or hypoxia (group 3), chronic thromboembolic PH and other pulmonary artery obstructions (group 4), and PH with unclear and/or multifactorial mechanisms (group 5).

The present review focuses on PAH, which is haemodynamically characterised by the presence of a mean pulmonary artery pressure (PAP) >25 mm Hg, a pulmonary artery wedge pressure (PWP) ≤15 mm Hg and a PVR of >3 Wood units.

The pathophysiology of PAH is characterised by an imbalance between molecules mediating vasoconstriction (e.g., endothelin or thromboxane) or vasodilation (e.g., prostacyclin). Furthermore, mitogenic effects of these molecules, with specific pathomorphological changes in the pulmonary circulation are involved in disease progression.

Currently available compounds approved for specific treatment of PAH are in three different groups: endothelin receptor antagonists, phosphodiesterase type 5 inhibitors (PDE-5is) and soluble guanylate cyclase stimulators, and molecules interfering with the prostacyclin pathway. Treatment with these compounds in combination with general measures has increased 3-year survival after first diagnosis of idiopathic PAH from 48% in the 1980s to 74% in the last two decades, as shown in the REVEAL registry [1].

Treatment of pulmonary arterial hypertension

Treatment of pulmonary hypertension is a three-step strategy starting with general measures, which is followed by supportive drug therapy and specific pharmacological treatment [2].

General measures are physical activity, birth control and post-menopausal hormonal therapy, infection prevention, psychosocial support, adherence to treatment, genetic counselling and counselling about travel. Only the specific pharmacological treatment of PAH is discussed here, because supportive drug treatment is extensively reviewed elsewhere [3–8].

Endothelin receptor antagonists

The endothelin system is activated both in the plasma and the lung tissue of PAH patients. Two distinct endothelin receptor isoforms (type A, type B) are expressed in pulmonary vascular smooth muscle cells, where they mediate the vasoconstriction and mitogenic effects of the peptide hormone endothelin-1. Three endothelin-1 antagonists are available in Switzerland: bosentan since 2002, ambrisentan since 2008, and macitentan since 2014.

Bosentan, ambrisentan

Bosentan (Tracleer®) was the first oral active antagonist of both endothelin receptor types, A and B, and is licensed for the treatment of PH patients presenting

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with World Health Organization (WHO) functional class II to IV. Several randomised controlled trials evaluated bosentan in different forms of PH (IPAH [idiopathic PAH] and PH secondary to connective tissue disease or Eisenmenger syndrome). Bosentan treatment consistently improved exercise capacity, functional class, haemodynamics and echocardiographic variables, and prolonged time to clinical worsening [9–13]. However, an increase in hepatic aminotransferases is reported in approximately 10% of treated patients. This increase is most often reversible with dose reduction or drug discontinuation, but nevertheless mandates liver function monitoring on a monthly base.

Ambrisentan (Volibris®) attaches preferentially to the type A endothelin receptor. Ambrisentan is approved for treatment of patients with PH associated to connective tissue or IPAH in functional class WHO II or III [14]. In the US, there is no recommendation for monthly liver function testing [15] because of the low incidence of abnormal liver function tests even when patients had received bosentan beforehand (0.8–3%, respectively). This low incidence was confirmed by the Volibris Tracking (VOLT) study, which was an open-label, prospective observational, multicentre, post marketing study including 999 patients [16].

Macitentan

Macitentan (Opsumit®) is approved for treatment of PAH patients with WHO functional class II or III. This dual endothelin receptor antagonist was tested in the SERAPHIN trial [17], which showed in the group receiving 10 mg macitentan a 45% reduction of the incidence of the combined endpoint all-cause mortality, atrial septostomy, lung transplantation, initiation of therapy with intravenous or subcutaneous prostanoids or worsening PAH. In addition, macitentan 10 mg increased exercise capacity and decreased the risk of all-cause hospitalisation and PAH-related hospitalisation. In a prespecified haemodynamic substudy of the SERAPHIN trial, 6 months of macitentan treatment increased cardiac index and decreased mean PAP and PVR as well as levels of N-terminal prohormone of brain natriuretic peptide (NT-proBNP). These changes were irrespective of the baseline WHO functional class and PAH-specific therapy, which was sildenafil in the majority of patients participating in this substudy [18]. Of note, macitentan treatment was likewise beneficial in patients without previous treatment for PAH. Significant liver toxicity was not observed, but a haemoglobin level of ≤8 g/dl was noted in 4.3% (10/242) of patients in the macitentan 10 mg group, compared with 0.4% (1/249) in the placebo group [17].

Phosphodiesterase type 5 inhibition and soluble guanylate cyclase stimulation

PAH is associated with impaired synthesis of nitric oxide, resulting in insufficient stimulation of the nitric oxide / soluble guanylate cyclase (sGC) / cyclic guanosine monophosphate (cGMP) pathway. Inhibition of the catalytic activity of PDE-5 increases cGMP in the vascular smooth muscle cell. Cyclic GMP is involved in various regulatory processes such as maintenance of vascular tone, smooth muscle cell proliferation, fibrosis and inflammation, suggesting that a cGMP increase should have favourable effects on haemodynamics and vascular remodelling in PAH. Indeed, PDE-5 inhibition with sildenafil or tadalafil results in significant pulmonary vasodilation with a maximum effect observed after 40 to 90 minutes [19]. Furthermore, these two molecules and their metabolites have antiproliferative effects [20] (fig. 1). Sidenafil has been available on the Swiss market since 1998, tadalafil since 2004; the sGC activator riocyguat (see below) became available on the Swiss market in 2013.

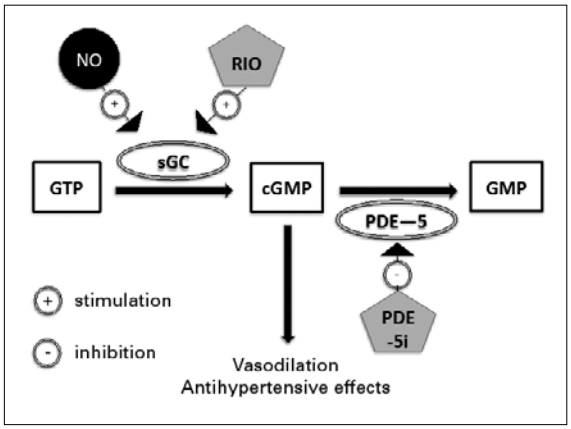


Figure 1: Pharmacologic stimulation and inhibition of the nitric oxide-soluble guanylate cyclase-cyclic guanosine monophosphate cGMP pathway. NO = nitric oxide; RIO = riociguat; sGC = soluble guanylate cyclase; GTP = guanosine triphosphate; cGMP = cyclic guanosine monophosphate; PDE-5 = phosphodiesterase type 5; PDE-5i = PDE-5 inhibitor.

Sildenafil, tadalafil

The first orally active, potent and selective PDE-5i, sildenafil, is sold under the name of Viagra® or Revatio®. Randomised controlled trials in PAH patients treated with sildenafil 20 mg three times per day showed favourable effects on exercise capacity, clinical symptoms and/or haemodynamics [21]. Sildenafil in combination with epoprostenol improved 6-minute walking distance and prolonged time to clinical worsening, suggesting synergistic effects [22].

Tadalafil (Cialis®) is a once daily selective PDE-5i. A randomised controlled trial in 406 PAH patients (of whom

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53% were on background bosentan therapy) tested tadalafil at low, medium, and high doses. Only patients in the high-dose (40 mg per day) group showed favourable changes in exercise capacity, symptoms, haemodynamics and time to clinical worsening [23]. Similar results were reported more recently for vardenafil (Levitra®), from a randomised controlled trial including 66 treatment-naïve PAH patients [24]. However, this drug is not approved for PAH treatment in Switzerland.

Riociguat

The sGC activator riociguat (Adempas®), the first molecule of its class, is approved for the treatment of patients with IPAH presenting in WHO functional class II or III, as well as patients with chronic thromboembolic PH (CTEPH). Riociguat directly activates GC; in addition, it sensitises sGC to endogenous nitric oxide.

Riociguat treatment with up to 2.5 mg three times per day improved exercise capacity, haemodynamics and WHO functional class, and increased time to clinical worsening, as shown by a randomised controlled trial including 443 PH patients. The study patients were either without specific PAH therapy at baseline (50%), or on background therapy with an endothelin receptor antagonist (44%) or prostanoids (6%); altogether, the study indicates benefit from riociguat treatment independent of the presence or absence of complementary treatment [25]. However, riocoguat did not decrease mortality of patients with IPAH or CTEPH in this study, and also no mortality benefit was demonstrated when data from 962 PH patients in five randomised trials were pooled [26].

The drug is well tolerated overall, and adverse events most commonly reported include headache, dyspepsia and gastritis, dizziness, nausea and diarrhoea. The most frequent serious adverse event reported was syncope, which occurred more often in the placebo group than in the 2.5-mg group (4 and 1%, respectively). Of note, the combination of riociguat and a PDE-5i is contraindicated because of the risk of hypotension and other relevant side effects detected in the open-label phase of a randomised controlled trial study [5]. Likewise, riociguat is contraindicated in patients with PH due to interstitial lung disease, since mortality was increased in the verum group of the RISE-IIP trial. Lastly, riociguat is contraindicated in pregnant women because of fetal harm.

Prostacyclin analogues and prostacyclin receptor agonists

Prostacyclin is produced by endothelial cells and acts as both a potent vasodilator and an endogenous inhibitor of platelet aggregation; in addition, cytoprotective and antiproliferative activities are reported. PAH is associated with dysregulation of the prostacyclin metabolic pathways and decreased expression of prostacyclin synthase. Synthetic prostacyclin analogues with similar pharmacodynamic effects but more favorable pharmakokinetic properties provided a dramatic therapeutic breakthrough in the last years in particular when PH is more severe. Eprostenol was made available in Switzerland in 2000, teprostinil in 2004, and iloprost in 2005; the prostacyclin receptor antagonist selexipag was approved in Switzerland in 2016.

Epoprostenol

This intravenous synthetic prostacyclin is approved for treatment of IPAH and associated PAH (APAH) in WHO functional classes III and IV. A limitation of epoprostenol treatment is the short half-life (3–5 minutes), which requires application by means of an infusion pump and a permanent tunnelled catheter. Epoprostenol was tested in three nonblinded randomised controlled trials in patients with IPAH or the scleroderma spectrum of diseases and in WHO functional classes III and IV [27, 28]. Epoprostenol always improved symptoms and haemodynamics, increased exercise capacity in both entities and up to now is the only treatment reducing mortality in IPAH [28]. Long-term persistence of efficacy was also shown in APAH and in non-operable CTEPH.

Iloprost

Iloprost is a chemically stable prostacyclin analogue for intravenous or aerosol administration. Inhaled iloprost has been tested in one randomised controlled trial, which compared daily repeated iloprost inhalations with placebo in patients with IPAH or CTEPH [29]. This study showed an increase in exercise capacity, improvement in clinical symptoms, and a decrease of the PVR and clinical events. Similar results were observed in another randomised controlled trial including 60 patients on bosentan background treatment.

Teprostinil

Teprostinil is available for intravenous and subcutaneous application in Switzerland (Remodulin®); furthermore, it is available as aerosol (Tavyso®) or extended-release oral tablet (Orenitram®). Each formulation improves dyspnoea, and every administration route apart from oral increase 6-minute walking distance. Of note, the different routes of administration produce distinct adverse events, such as infusion-site pain for subcutaneous use (85%), cough and throat irritation with inhalation (54 and 25%, respectively), or abdominal discomfort with the oral preparation (6%) [30]. Each

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form was tested in large randomised, controlled, multicentre studies, but with different background therapy: intravenous and oral application was tested against placebo in recently diagnosed PAH patients without specific background therapy (470 and 349 patients, respectively) [31, 32], whereas inhalation was investigated in 235 clinically stable patients mostly in New York Heart Association (NYHA) class III, who were on PAH specific background therapy with either bosentan (70%) or sildenafil (30%) for at least 3 months prior to study initiation [33]. The difference in the pharmacological background may explain in part the disparate results observed with three formulations of teprostinil. Irrespective of this discussion, Chakinala et al. showed recently that transition from parenteral to oral teprostinil preserves the 6-minute walking distance and is safe in low risk PAH patients [34].

Selexipag

Selexipag (Uptravi®) is an orally available, selective prostacyclin receptor agonist and approved in Switzerland since 2016 for treatment of PAH patients in functional classes III and IV. Selexipag and its metabolite have modes of action similar to that of endogenous prostacyclin, but they are chemically and pharmacologically distinct. This dissimilarity is physiologically evident in the observation that vasorelaxation resulting from selexipag treatment is not attenuated by the presence of prostacyclin receptor antagonists [35].

In a phase II study, 17 weeks of selexipag treatment reduced the mean PVR by 30.3% from baseline in PAH patients presenting with a baseline PVR that had remained ≥400 dynes*sec*cm^{-5} despite of endothelin receptor antagonist and/or PDE-5i therapy [36]. The event-driven, phase III, Prostaglandin I_2 Receptor Agonist in PAH (GRIPHON) study enrolled 1156 patients and showed that selexipag treatment with individual symptom-guided up-titration (maximum dose 1600 µg twice daily) reduced the incidence of the composite endpoint by 40%. The composite endpoint consisted of all-cause mortality, PAH-related complications, hospitalisation for worsening of PAH, worsening of PAH resulting in the need for lung transplantation or atrial septostomy, initiation of parenteral prostacyclin analogues, chronic O_2 for worsening of PAH, or disease progression. The reduction in the incidence of the composite endpoint was independent of concomitant specific PAH treatment, which consisted of mono- or double therapy with an endothelin receptor antagonist and/or PDE-5i [37]. Of note, the effect of selexipag on the primary outcome was consistent across all dose levels. However, all-cause mortality alone was not different between the verum and the placebo groups. In the selexipag group, premature discontinuation occurred in 14.3%, whereas 7.1% patients in the placebo group discontinued treatment. Discontinuation was related to adverse effects such as nausea, diarrhoea, headache and jaw pain, and the majority of adverse events with selexipag occurred in the dose-adjustment phase.

The GRIPHON study has its share of limitations. First, a total of 18.9% of patients discontinued placebo or selexipag prematurely but early discontinuation had been anticipated and accounted for in the study design acknowledging discontinuation rates reported from previous randomised controlled trials. Another point of criticism is the limited follow-up data available on patients who had stopped the drugs. The second limitation lays in the fixation of the primary endpoints similar to earlier randomised controlled trial in PH, which are in part subjective.

Altogether, the results of the GRIPHON trial are promising. Furthermore, selexipag is the sole drug directed towards the prostaglandin I_2 receptor pathway, and is recommended for sequential double and triple combination therapy in PAH patients with WHO functional class II (table 1).

Table 1: Class of recommendation and level of evidence for the efficacy of macitentan, riociguat and selexipag monotherapy or sequential drug combination therapy in pulmonary artery hypertension, according to WHO functional class.

Treatment	WHO functional class II recommendation/ evidence	WHO functional class III recommendation/ evidence	WHO functional class IV recommendation/ evidence
Macitentan	I B	I B	IIb C
Riociguat	I B	I B	IIb C
Selexipag	I B	I B	
Macitentan added to siledenafil	I B	I B	IIa C
Riociguat added to bosentan	I B	I B	IIa C
Selexipag added to ERA or PDE-5i	I B	I B	IIa C
Riociguat added to sildenafil or other PDE-5i	III B	III B	III B

ERA = endothelin receptor antagonist; PDE-5i = phosphodiesterase type 5 inhibitor. Class of recommendation: I, IIa, III; evidence: A, B, C

Future compounds

The last years have seen the testing of drugs such as imatinib mesylate (Glivec®), which inhibits platelet-derived growth factor signalling. The IMPRES study investigated imatinib mesylate as add-on treatment in PAH patients in WHO class III or IV in spite of specific therapy. In the treatment group, exercise capacity and haemodynamics improved significantly (6-minute walking test +32 meters, PVR –397 dynes*sec^{-1}*cm^{-5}; respectively). However, functional class, time to clinical

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worsening and mortality were not different from controls after 24 weeks. In addition, severe side effects (44 vs 30%) and study discontinuation (33 vs 18%) were more common in the treatment group [38]. Altogether, this interesting pharmacological approach needs further investigation.

Another compound is sorafenib (Nexavar®), which inhibits multiple kinases, including tyrosine and serine/threonine kinases. This molecule was tested as add-on therapy in nine patients with treatment-refractory PH. Treatment was started with an initial dose of 50 or 100 mg per day and increased to 100–400 mg per day. The WHO functional class improved in eight of the nine patients and the mean PAP decreased by 14 to 28% in six of eight patients. The main adverse effects were skin reactions on the hands and the feet, which were observed in five of nine patients [39]. Altogether, this pilot study suggested sorafenib could be an additional therapeutic strategy in patients with refractory PAH. However, testing in a larger clinical study is mandatory.

Combination therapy

Most trials in PAH have tested the therapeutic efficacy of drugs in an add-on design, which is close to the clinical setting where drugs with different mechanisms of action are applied in a sequential manner. However, COMPASS-2, which investigated the effect of bosentan added to sildenafil treatment, failed to show a significant decrease in the delay to first morbidity and mortality [40], and oral teprostinil when added to background endothelin receptor antagonist or PDE-5i treatment failed to show a clinically significant increase in distance in the 6-minute walking test [31, 33]. Nevertheless, SERAPHIN and GRIPHON showed that time to the combined morbidity and mortality endpoint was increased when macitentan or selexipag were added to specific PAH background therapy with one or two other drugs.

The AMBITION trial assessed up-front combination therapy vs monotherapy in a head to head comparison. The 500 study patients were randomly assigned in a 2:1:1 ratio to receive ambrisentan and tadalafil or either alone. The up-front combination therapy was associated with a 50% reduction in the primary endpoint, mostly driven by a lower risk of clinical failure and an increase in exercise capacity [40]. However, substitution of the combination tested in the AMBITION trial by other members of the same family failed to show similar outcomes. One reason may be that bosentan induces CYP3A4 activity, which results in a decrease in the plasma levels of sildenafil and its active metabolite [41].

At the moment, sequential combination therapy is recommended for the PAH patient with clinical deterioration while on specific PAH monotherapy. This class I recommendation is based on the add-on study design in those studies that tested more recently developed compounds. Based on the results of the AMBITION trial, initial combination therapy with a recommendation class is limited to the combination of ambrisentan with tadalafil.

Conclusion

The emergence of specific treatments for PAH has improved functional status, exercise capacity and time to clinical worsening over the last two decades. The recently developed compounds macitentan, riociguat, and selexipag provide additional benefit when given either as monotherapy or in combination with compounds interacting with other pathways active in PAH. The absence of an effect on PAH-associated mortality remains a drop of bitterness. However, a post-hoc analysis of the SERAPHIN study showed that the incidence of a morbidity events <3 months after study inclusion was associated with increased mortality [42], suggesting that reduced morbidity may be associated with improved prognosis.

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