New therapies in the treatment of pulmonary hypertension
[bilingual text]

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Abstract

Besides all progress in the therapy of pulmonary arterial hypertension over the past years, there is still no cure for this devastating disease. By introducing effective and nonparenteral medications (e.g., oral endothelin receptor antagonists [ERAs], inhaled prostanoids), quality of life, exercise tolerance and prognosis of patients have substantially improved. However, applicability of these therapies can be hampered by serious side effects and/or the necessity for elaborate application techniques. Whether selective ERAs – due to their specificity for the A-type receptor – have potential benefits over the nonselective ERA bosentan remains to be answered by the analysis of pivotal trials recently carried out with ambrisentan and sitaxsentan. Inhaled treprostinil can potentially have benefits over the already approved inhaled iloprost, related to its higher pulmonary selectivity as well as to the longer biological half-life. However, this has yet to be proven in long-term randomized controlled trials. In comparison to the previously mentioned substances, the selective phosphodiesterase-5 (PDE_5) inhibitor sildenafil approached approval closest as new therapy for pulmonary arterial hypertension. Oral sildenafil has proven its efficacy as a selective pulmonary vasodilator in various forms of pulmonary hypertension. The results of the pivotal phase III trial have confirmed the

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strong efficacy and excellent tolerability of this substance. Combination therapies, despite all progress seen for single agents, can be regarded as the most promising therapeutic approach for the future. However, controlled randomized trials that are currently under consideration have to confirm this notion.

Key Words: Pulmonary hypertension · Vasodilative therapy · Nitric oxide · Prostacyclin · Endothelin antagonist · Phosphodiesterase inhibitors · Combination therapies

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Introduction

The therapy pursuant to the guidelines for pulmonary arterial hypertension (PAH) was already discussed extensively in the contribution from Hoeper in this issue. In this case, pursuant to the guidelines means referencing approved medications or substances that have found their way into evidence-based therapy recommendations due to clear status in publications. The content of this contribution is the presentation of new therapy approaches, which are partially still under development, and that can find their way into the therapy guidelines in the near future or that are already being employed in so-called "off label use" due to clear evidence of efficacy. Specifically, we will discuss therapy with inhaled prostanoids, selective endothelin A receptor antagonists (sitaxsentan and ambrisentan) and phosphodiesterase-5-(PDE5-) inhibitors (especially sildenafil). Furthermore, combination therapies will be discussed as a possible future therapy standard.

Vasoactive therapy

The points of attack for a vasoactive therapy are the potentially reversible components of vascular obstruction. In principle, there are two possibilities to expand the vessel diameter with pharmacological intervention:

- Elimination of permanently increased vasotone by relaxing the smooth vessel musculature (direct effect of vasodilators);
- Influence of the vessel structure (vascular remodeling) by using anti-inflammatory and anti-proliferative substances.

A number of vasodilating agents have been clinically tested in the treatment of chronic pulmonary hypertension. With respect to the application of calcium antagonists, prostanoids and non-selective endothelin antagonists, we refer once again to the article by Hoeper in this issue. Although inhaled iloprost (Ventavis®) was also discussed in this article, this therapy form will be briefly mentioned here again since it provides the theoretical and clinical background for explaining the new inhaled treprostinil therapy.

Inhaled iloprost

The inhalation of aerosolized prostanoids avoids a large part of the disadvantages of infusion therapy while providing efficacy: due to the alveolar deposition of the active substance, pulmonary and intrapulmonary selective action is achieved. Therapy for pulmonary hypertension with repeated inhalations of the long-acting prostacyclin analog iloprost has proven its efficacy with simultaneous good safety in a multi-centric, randomized, placebo-controlled study [1]. In the group that was treated with iloprost, there was both a significant improvement in the 6-min. walk test (as a benchmark for stamina) and in the NYHA class (New York Heart Association) in comparison to the group treated with placebo. This study that is relevant for approval of the drug was already preceded by several, non-controlled studies in patients with various forms of pulmonary hypertension [2-4]. The phase III study was predominately able to confirm the earlier positive experiences. However, in addition to the expensive aerosol technology, a disadvantage of this therapy is the relatively short duration of action for a single dose (60-90 min.), which makes frequent inhalations necessary (six to nine times per day) and there is a therapeutic pause during the night.

Inhaled treprostinil

Treprostinil is a long-acting prostacyclin analog, which offers potential benefits versus epoprostenol due to its long plasma half life and chemical stability in solution, and therefore was initially developed as a substitute for infusion treatment.

In order to avoid complications related to catheters, the treprostinil infusion is administered subcutaneously via a special cannula (taken from long-term insulin therapy). The study for this therapy concept that is relevant for approval of the drug showed efficacy in the treatment of patients with pulmonary arterial hypertension [5]. However, the downside of this form of treatment is that up to 80% of the patients have pain at the injection site, which makes a long-term therapy more difficult. Initial trials in Giessen have shown proof of efficacy of *inhaled* treprostinil for the effective reduction of the pulmonary vascular resistance (PVR) [6]. In this first study, 17 patients with severe pre-capillary pulmonary hypertension were administered inhaled treprostinil (15 mcg/inhalation). This led to a major reduction in pulmonary selective pressure and resistance with an overall duration of action of > 180 min. In direct comparison with inhaled iloprost, inhaled treprostinil showed a stronger pulmonary selectivity, so that it is possible to increase the dosage to up to 90 mcg (absolute inhaled dose per inhalation exercise) without adverse effects occurring [6]. Due to these unique properties (pronounced pulmonary selectivity and long duration of action after an individual inhalation), it is possible to reduce the number inhalations necessary to up to four per day; the inhalation period can be reduced to < 1 min. by selecting a suitable device. Additionally, the initial data shows that it is technically feasible for there to be only one to two breaths in an application. A multi-centric, placebo-controlled study shall now also study the efficacy of this new therapy during long-term use.

Selective endothelin A receptor antagonists

The activation of endothelin A (ET_A) receptors leads to vasoconstriction and vascular proliferation in the lung, while the ET_B receptor binds (and eliminates) circulating endothelin and leads to an increase in the endogenous prostacyclin and nitrogen monoxide (NO) production. In addition, it is assumed that the liver toxicity described for bosentan is mainly related to the ET_B-inhibiting effect. Against the backdrop of these presumably risky partial components of the non-selective endothelin receptor antagonist (ERA), selective ET_A antagonists have made their way into clinical testing. There are currently experiences with two substances in this regard, which are discussed in detail below.

Sitaxsentan. The selective ET_A receptor antagonist sitaxsentan (Thelin®) has a much higher binding affinity for the ET_A receptor than for the ET_B receptor. Preclinical data have already indicated a possible efficacy for PAH treatment. Published clinical phase II data show that at a comparable efficacy to bosentan, the incidence of liver toxicity in the group treated with 100 mg sitaxsentan (tablet taken once per day) is 0% and is 10% in the group treated with 300 mg [7]. In the phase III study that is relevant for drug approval, which is still being evaluated, both 50 mg and 100 mg sitaxsentan were used in comparison to a placebo or bosentan (125 mg twice a day). The data that has so far only been published by press release indicates again that 100 mg dose of sitaxsentan showed a trend of lower liver toxicity than bosentan (3% vs. 11%) while having comparable efficacy (improvement in walking distance in the 6-min. walk test by 31.4 m [sitaxsentan] vs. 29.5 m [bosentan]). It is currently not known when and for what patient cohort this medication will be approved. For sitaxsentan, an interaction with warfarin is described, which requires a dosage adjustment of the oral anti-coagulant.

Ambrisentan. Just as with sitaxsentan, ambrisentan is a selective ET_A antagonist [8]. A phase II study on this substance has already been completed, however, the results are currently not available in published form. The phase III study that is relevant for the drug approval is currently still recruiting patients and is expected to be completed at the end of 2005.

Phosphodiesterase inhibitors

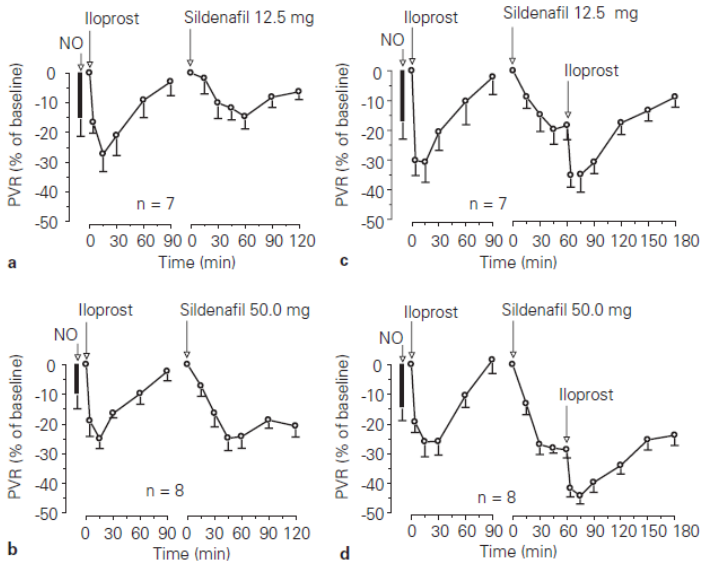
The mutual end segment in the sequence of action of the endogenous vasodilating mediators (e.g. NO, prostanoids and atrial natriuretic peptide [ANP]) is the intracellular release of cyclic nucleotides (cyclic adenosine monophosphate [cAMP], cyclic guanosine monophosphate [cGMP]. These so-called second messengers are mainly formed by an activation of adenylate and guanylate cyclase [9]. The decomposition of cyclic nucleotides by phosphodiesterase (PDE) limits the intensity and duration of action of the vasodilating agonists [9, 10]. PDEs partially show organ-specific or cell-specific distribution patterns [10, 11]. Thus, PDE5 is highly expressed in both the corpus cavernosum in

males and the lungs under physiological conditions [10]. In addition, PDEs are overexpressed in the case of various proliferative and constrictive vascular diseases. PDE inhibitors can interfere with the decomposition of cAMP or cGMP or both systems simultaneously, depending on their selectivity profile.

Therefore, therapeutic approaches are seen in two respects in the context of these pathophysiological considerations:
1. PDE inhibitors can inhibit the basal decomposition of cyclic nucleotides and therefore achieve vasodilating effects per se, and
2. PDE inhibitors can extend the effects of vasodilators such as NO and prostanoids.

Sildenafil. Sildenafil is a selective PDE5 inhibitor and has been approved for erectile dysfunction therapy. In this indication, the medication has shown an extraordinarily good safety profile so far, especially without detection of a relevant decrease in systemic blood pressure [12]. In patients that are treated with nitro preparations due to a cardiovascular disease, however, a combined application with sildenafil should be avoided in order to prevent undesired severe hypotension.

Based on experimental preliminary results, it was obvious to employ PDE inhibitors for the prolongation and/or increase in the action of prostanoids. Two clinical studies have been able to impressively prove that sildenafil is a potent vasodilator per se, which exhibits a surprising pulmonary selectivity despite systemic application [13, 14]. In addition, a clear synergistic action of oral sildenafil with inhaled iloprost was able to be documented. A comparison of the efficacy with the known pulmonary selective vasodilator inhaled NO was performed on 30 patients with severe pulmonary hypertension [14]. This showed that 50 mg of oral sildenafil caused significantly stronger pulmonary vasodilation than inhaled NO (PVR reduction: ~25% [50 mg sildenafil] vs. ~15% [~20 ppm NO]; Figure 1). With respect to possible combined applications of PDE inhibitors and prostanoids, both substances in this study showed an impressive synergism of efficacy (>45% PVR reduction), with preserved pulmonary selective method of action, and therefore very good tolerability. Also in the case of pulmonary hypertension as a secondary disease of an interstitial lung disease, sildenafil showed an excellent action profile. Although patients with pulmonary fibrosis and pulmonary hypertension have a predisposition for oxygenation disorders while being administered non-selective vasodilators, sildenafil not only showed selectivity in these patients (despite oral administration)



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Figures 1a to 1d. Comparison of pulmonary vasodilative potency of oral sildenafil, inhaled nitric oxide (NO) and inhaled iloprost (adapted from [14]). Comparative vasodilator testing was performed in 30 patients with precapillary pulmonary hypertension. The relative reduction (in %) of PVR subsequent to inhaled NO, inhaled iloprost, and oral sildenafil is presented. a, b) Investigation of the effects of each single substance. c, d) Combinations of inhaled iloprost with 12.5 mg (c) and 50 mg (d) oral sildenafil are displayed.

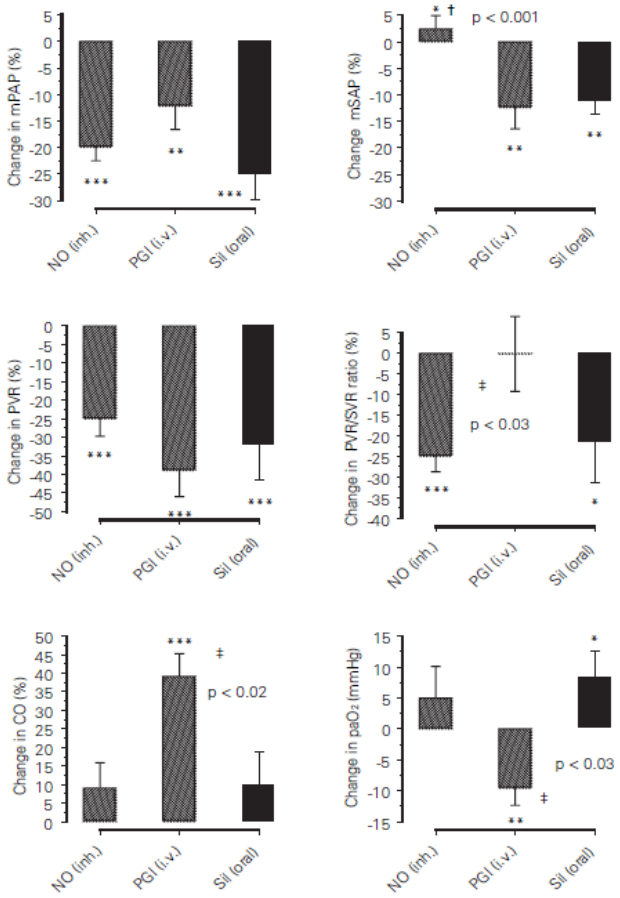

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Figure 2. Hemodynamic and gas exchange response to inhaled nitric oxide [NO (inh.)], infused prostacyclin [PGI (i.v.)], and oral sildenafil [Sil (oral)] in patients with lung fibrosis and pulmonary hypertension (adapted from [15]).
Deviations from pre-intervention baseline are displayed for inhaled NO, infused prostacyclin, and oral sildenafil. CO: cardiac output; mPAP: mean pulmonary arterial pressure; mSAP: mean systemic arterial pressure; paO_2: partial pressure of arterial oxygen (changes given in mm Hg); PVR: pulmonary vascular resistance index; PVR/SVR ratio: ratio of pulmonary to systemic vascular resistance.

in the sense of preferred reduction of the PVR, but also in the sense of intrapulmonary selectivity, which was expressed in improvement in the gas exchange [15] (Figure 2).

In a recently published study, it was able to be documented for the first time that sildenafil increased performance in the case of hypoxia-induced pulmonary hypertension, which was not only associated with a reduction in pressure in the lesser circulation, but also with an improvement in oxygenation [16].

In the meantime, the phase III study for the treatment of PAH with sildenafil that is relevant for drug approval has been completed. The results were presented in 2004 at the ACCP (American College of Chest Physicians) conference in Seattle, WA, USA. This showed that sildenafil is more effective at attaining the primary endpoint (improvement in the 6-min. walk test; up to 50 m in the 80 mg group) than the placebo with a high degree of significance at all three tested doses of 20 mg, 40 mg and 80 mg (each administered three times per day). Secondary parameters such as improvement in pulmonary hemodynamics and life quality parameters were significantly improved as well. The approval of the medication has been requested from the US and European authorities in the meantime.

Combination therapies

Unfortunately, the clinical reality of patients with severe chronic pulmonary hypertension is often the situation that there is a progressive deterioration of the clinical condition of the patient despite chronic therapy with prostanoids or endothelin antagonists.

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