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SOTATERCEPT AS A POTENTIAL DISEASE-MODIFYING THERAPY IN PULMONARY ARTERIAL HYPERTENSION: A NARRATIVE REVIEW

Aleksandra Kamińska[1] ✉, Maria Miller[2], Aleksandra Pakulska[2], Aleksandra Błoch[2], Natalia Rządzińska[2]

[1] Medical Center HCP in Poznan, Poland
[2] Jan Biziel University Hospital No. 2 in Bydgoszcz, Poland

✉ olakaminska2111@gmail.com

ABSTRACT

Background

Pulmonary arterial hypertension (PAH) is a progressive and potentially fatal disease characterized by increased pulmonary vascular resistance, pulmonary vascular remodeling, and right ventricular failure. To date, therapy has relied mainly on vasodilatory action and has not sufficiently improved patients' long-term prognosis. There is therefore a need for therapies targeting pathways involved in disease progression and pulmonary vascular remodeling.

Aims

To summarize current data on the mechanism of action, efficacy, safety profile, and therapeutic role of sotatercept in the treatment of PAH.

Methods

A literature review was conducted using the PubMed and Scopus databases. Publications concerning sotatercept and PAH were analyzed, with particular emphasis on clinical and preclinical studies, pooled analyses, systematic reviews, meta-analyses, and safety publications.

Results

Sotatercept is a first-in-class activin signaling inhibitor that acts on dysregulated pathways associated with pulmonary vascular remodeling. Preclinical studies have shown reductions in vascular remodeling, inflammation, and right ventricular dysfunction. In the PULSAR and STELLAR trials, the use of sotatercept in patients with PAH improved exercise capacity and hemodynamic parameters. In the STELLAR trial, sotatercept increased the six-minute walk distance by 40.8 m compared with placebo, and the risk of death or clinical worsening was reduced by 84%. Data from the SOTERIA study suggest that clinical benefits are maintained over longer follow-up. The most common adverse events included epistaxis, telangiectasia, and hematological abnormalities.

Conclusions

Sotatercept represents an important therapeutic innovation in the treatment of PAH as an add-on therapy that potentially affects the mechanisms of vascular remodeling. Further studies are needed to assess its long-term safety, impact on survival, and optimal place in treatment regimens.

Keywords: sotatercept; PAH; pulmonary arterial hypertension; activin signaling; TGF-β; ActRIIA-Fc; PULSAR trial; STELLAR trial; SOTERIA.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive and potentially fatal disease of the pulmonary circulation. It is characterized by increased pulmonary arterial pressure,

elevated vascular resistance, and pathological remodeling of the precapillary pulmonary arteries [1–4]. According to contemporary criteria, PAH is defined as elevated mean pulmonary arterial pressure at rest, with normal pulmonary arterial wedge pressure, as well as increased pulmonary vascular resistance, which is assessed during right heart catheterization [4–6]. The consequence of these changes is narrowing of the lumen of the pulmonary arteries, an increase in right ventricular afterload and its compensatory hypertrophy, and ultimately right ventricular heart failure and death [7–10].

PAH is a rare disease, with a prevalence in Western countries of approximately 15–50 cases per million inhabitants. Despite its rarity, it represents a considerable clinical burden because it is characterized by a progressive course, nonspecific symptoms, and high mortality [4,5,11]. PAH may present as exertional dyspnea, increasing fatigue, and syncope. The disease is diagnosed at various stages of life. It occurs more frequently in women, especially in the idiopathic form [4]. Despite advances in pharmacological treatment, the long-term prognosis is unsatisfactory, and the five-year mortality in patients with newly diagnosed disease is estimated at approximately 40% [11,12].

The pathophysiology of PAH includes vasoconstriction, endothelial dysfunction, thrombosis, inflammation, and progressive pulmonary vascular remodeling [4,11]. Endothelial dysfunction, regarded as a hallmark of PAH pathophysiology, is associated with an impaired balance between vasodilatory factors (nitric oxide and prostacyclin) and vasoconstrictive factors (endothelin 1, serotonin, and thromboxane A2) [4]. Progressive pulmonary vascular remodeling is associated with excessive proliferation and reduced apoptosis of pulmonary vascular cells, resulting in narrowing of their lumen [4,7,8]. A growing body of evidence indicates that an important role in this process is also played by disrupted signaling within the transforming growth factor β (TGF-β) superfamily, especially within pathways associated with activins, bone morphogenetic proteins (BMP), and the activin receptor type IIA (ActRIIA) [9,13].

Current treatment of PAH is based mainly on pharmacological modulation of three vasoactive pathways and includes endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, soluble guanylate cyclase stimulators, prostacyclin analogues, and prostacyclin receptor agonists [5,9]. These therapies form the basis of modern PAH treatment, owing to symptom reduction, improvement of functional capacity and hemodynamic parameters, and delay of disease progression [5,11,14]. Most of the available drugs, although they may slow disease progression, only partially affect pulmonary vascular remodeling, do not fully reverse it, and do not reduce PAH-related mortality [9,13,15]. Therefore, there is a need for new therapies that target pathways

involved in pulmonary vascular remodeling and may influence the course of the disease, rather than acting primarily through the reduction of pulmonary vascular tone [4,11].

Over the past three decades, the treatment of PAH has evolved from supportive care, including oxygen therapy, diuretics, anticoagulation in selected patients, and lung transplantation in advanced cases, to targeted pharmacological therapy [38,44]. The introduction of prostacyclin analogues, endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, soluble guanylate cyclase stimulators, and prostacyclin receptor agonists has substantially improved symptoms, exercise capacity, hemodynamics, and time to clinical worsening [38,43,44]. Current treatment strategies are based on early risk stratification, initial combination therapy in many patients, sequential treatment escalation, and referral for lung transplantation in patients with insufficient response [38]. However, these therapies primarily target vasoconstriction and endothelial dysfunction, whereas their effect on established pulmonary vascular remodeling remains limited [4,9,13,15]. This therapeutic gap has stimulated the development of agents directed at molecular pathways involved in vascular remodeling, including activin signaling within the TGF-β superfamily [3,4,13,21].

Sotatercept is a new therapeutic option that may address the need for treatment directed at pulmonary vascular remodeling [16]. It is the first-in-class activin signaling inhibitor approved for the treatment of PAH. As an ActRIIA-Fc fusion protein, it acts on the dysregulated signaling pathways of the TGF-β superfamily that participate in pulmonary vascular remodeling [13,17]. Its mechanism of action therefore differs from the vasodilatory therapies available to date and may influence the process of vascular remodeling [7,11,18]. Preclinical studies have shown that sotatercept may also reduce right ventricular dysfunction, and clinical studies have demonstrated improvements in functional and hemodynamic parameters in patients with PAH [18,19]. The clinical efficacy of sotatercept was demonstrated in the phase 2 PULSAR trial and the phase 3 STELLAR trial [20]. Based on the results of the phase 2 PULSAR trial and the phase 3 STELLAR trial, sotatercept was approved in 2024 in the United States and Europe for use in adult patients with PAH as an add-on therapy [8,11,17].

Aims

This narrative review aims to summarize the available data on the mechanism of action, efficacy, safety profile, and therapeutic role of sotatercept in the treatment of PAH.

The review was guided by the following research questions: (1) What is the mechanism of action of sotatercept in PAH? (2) What evidence supports its efficacy in clinical and preclinical studies? (3) What is known about its safety profile? (4) What is its potential therapeutic role in current PAH treatment strategies?

MATERIALS AND METHODS

This article is a narrative review. A review of the available literature was conducted to present current data on the mechanism of action, clinical efficacy, safety, and potential place of sotatercept in the treatment of PAH. The final literature search was conducted on June 10, 2026. Articles in English were analyzed. The review primarily included publications from 2020–2026, supplemented by earlier studies that are key to understanding the mechanism of action of sotatercept, as well as the results of the registrational PULSAR and STELLAR trials. Owing to the narrative nature of the review, no meta-analysis of the results was performed, and no formal risk-of-bias assessment was conducted.

The database search identified 149 publications (82 in PubMed and 67 in Scopus). After removal of 31 duplicates, 118 publications were screened by title and abstract. Of these, 54 were excluded, and 64 full-text articles were assessed for eligibility. A further 20 publications were excluded because they did not meet the predefined eligibility criteria. Ultimately, 44 publications were included in the final narrative analysis.

The literature review was conducted using the PubMed and Scopus databases. Because this was a narrative review, the literature search was conducted iteratively using predefined keywords rather than a formal systematic review protocol.

In PubMed, the following search terms and their combinations were used: sotatercept; PAH; pulmonary arterial hypertension; activin signaling; TGF-β; ActRIIA-Fc; PULSAR trial; STELLAR trial; and SOTERIA. The search strings included: sotatercept AND PAH, sotatercept AND pulmonary arterial hypertension, sotatercept AND activin signaling, sotatercept AND PULSAR, STELLAR AND sotatercept, and SOTERIA AND pulmonary arterial hypertension.

In Scopus, searches were performed using the same core search terms and analogous Boolean combinations, including: sotatercept, sotatercept AND PAH, sotatercept AND pulmonary arterial hypertension, sotatercept AND activin signaling, sotatercept AND

PULSAR, STELLAR AND sotatercept, and SOTERIA AND pulmonary arterial hypertension.

The analysis included preclinical and clinical studies, pooled analyses of clinical trials, narrative reviews, systematic reviews, meta-analyses, and publications describing the mechanism of action of sotatercept, the TGF-β/BMPR2/activin pathways, and the clinical efficacy and safety of sotatercept.

Publications were excluded if they were not directly related to sotatercept, concerned forms of pulmonary hypertension other than PAH without separately reported data for PAH, or addressed the use of sotatercept in indications unrelated to pulmonary arterial hypertension. Duplicate publications, articles published in languages other than English, and conference abstracts without an available full text were also excluded. Editorials, letters, commentaries, and other publications that did not provide original data or a substantive synthesis relevant to the scope of the review were omitted. Articles were additionally excluded if they did not provide relevant information on at least one of the following areas: the mechanism of action of sotatercept, preclinical findings, clinical efficacy, safety profile, pharmacological characteristics, or its potential therapeutic role in PAH.

RESULTS

Mechanism of action of sotatercept

One of the causes of the development of pulmonary arterial hypertension is an imbalance within the transforming growth factor β superfamily. In this disease, the signaling branch of the SMAD family proteins type 2 and 3 (Suppressor of Mothers Against Decapentaplegic 2/3, SMAD2/3), which stimulates vascular cells to divide, is overactive. At the same time, the opposing SMAD1/5 branch, which under normal conditions inhibits this process, is weakened [21]. In contrast to the pro-proliferative activin-like ligands, bone morphogenetic proteins 9 and 10 are circulating, protective ligands of the bone morphogenetic protein receptor type 2 (BMPR2) axis. Produced mainly in the liver (BMP-9) and the right atrium (BMP-10), they bind in pulmonary endothelial cells to the ALK1–BMPR2 receptor complex and activate the antiproliferative, endothelium-stabilizing SMAD1/5 pathway [22]. BMPR2 plays a key role here: in patients with PAH its activity is reduced, which further intensifies TGF-β signaling and promotes pulmonary vascular remodeling [3]. A decrease in the activity of the BMPR2–SMAD1/5 pathway

leads to an increase in the concentration of activin-like ligands, such as activin A and the growth differentiation factors (GDF) GDF8 and GDF11, which stimulate the activin receptor type IIA and even more strongly drive the pro-proliferative SMAD2/3 pathway. As a result, the balance between the two branches is shifted toward excessive vascular remodeling [23]. Sotatercept represents a therapeutic response to the dysregulation described above. It is a fusion protein in which the extracellular domain of the human ActRIIA receptor has been combined with the Fc fragment of immunoglobulin G1 [24]. It acts as a so-called ligand trap, capturing activins and growth differentiation factors circulating in the blood before they can stimulate the ActRIIA receptor [25]. In this way, sotatercept inhibits excessive pro-proliferative signaling and may help restore the balance between pathways that promote and inhibit pulmonary vascular cell growth [26]. Preclinical studies and clinical changes in hemodynamic parameters suggest that this mechanism may affect processes associated with pulmonary vascular remodeling. However, direct clinical evidence of reversal of established vascular remodeling remains limited [27].

Results of preclinical studies

The efficacy of sotatercept in PAH was initially demonstrated in a series of preclinical studies conducted in various animal models. In rat models of severe, angio-obliterative PAH induced by administration of a VEGF inhibitor (Sugen) and exposure to hypoxia, as well as in mouse models of the hereditary form of the disease with haploinsufficiency of the BMPR2 gene, the sotatercept analogue (ActRIIA-Fc) clearly corrected cardiopulmonary function [24]. In a vasoproliferative study of hemodynamically severe PAH, ActRIIA-Fc was shown to be more effective than a vasodilator drug in alleviating pulmonary hypertension and arteriolar remodeling. Prophylactic use of the recombinant fusion protein ActRIIA-Fc led to a significant improvement in hemodynamic parameters, a reduction in right ventricular hypertrophy, and a decrease in pulmonary arteriolar remodeling [28]. At the cellular level, the drug inhibited the proliferation of pulmonary artery smooth muscle cells and pulmonary microvascular endothelial cells by blocking activation of the SMAD2/3 pathway dependent on activin and the growth differentiation factors GDF8 and GDF11 [28]. Mechanistic studies provided additional justification for this strategy: it was shown that an excess of activin A produced by the pulmonary endothelium drives internalization and lysosomal degradation of the BMPR2 receptor, deepening the deficiency of protective signaling in endothelial cells [29]. In addition, an anti-inflammatory effect was demonstrated: treatment with ActRIIA-Fc reversed pro-inflammatory and proliferative gene expression profiles and

normalized macrophage infiltration in the diseased lungs of rodents [24]. Beneficial effects were observed not only within the pulmonary circulation; in mouse models of left ventricular failure, the murine analogue ActRIIA-Fc limited cardiac remodeling and improved cardiac function, demonstrating additional cardioprotective potential [23].

Results of clinical studies

Randomized controlled trials have demonstrated improvements in several clinical and hemodynamic endpoints. For the first time, they showed that targeting the TGF-β superfamily translates into significant improvement in hemodynamic, functional, and clinical parameters in patients receiving standard therapy [19,22]. The first of these was the phase II PULSAR trial, a multicenter, double-blind, placebo-controlled study. The study enrolled 106 adult patients, randomized in a 3:3:4 ratio to placebo, sotatercept 0.3 mg/kg, or 0.7 mg/kg subcutaneously every 21 days for 24 weeks, in combination with standard treatment. The primary endpoint was the change in pulmonary vascular resistance (PVR), which decreased significantly in both sotatercept groups compared with placebo. The six-minute walk distance (6MWD) also improved, and the concentration of N-terminal pro-brain natriuretic peptide (NT-proBNP) decreased [25]. The improvements were maintained during the open-label extension phase, which included 97 of the 106 patients. The placebo-crossed and delayed-start analyses confirmed maintenance of improvements in PVR, walk distance, and functional class [30,31]. A further analysis also showed that the efficacy and safety of sotatercept were consistent regardless of the presence of a BMPR2 gene mutation, suggesting that the drug is also effective in patients without this hereditary predisposition [32]. A proteomic sub-analysis demonstrated that the drug's action also includes a reduction in BMP-9 and BMP-10 and modification of metabolic and inflammatory factors. Importantly, bone morphogenetic proteins 9 and 10 are physiological agonists of the protective arm of the BMPR2 axis, and therefore the reduction in their concentrations observed after sotatercept is mechanistically non-obvious and remains the subject of further research [19]. The consistency of these observations was confirmed by a later systematic review with meta-analysis [11]. The results of PULSAR became the basis for the registrational phase III STELLAR trial [33]. It enrolled 323 patients in WHO functional class II–III, on stable dual or triple background therapy, randomized 1:1 to sotatercept (0.3 mg/kg, increased to 0.7 mg/kg every 21 days) or placebo. The primary endpoint, the change in 6MWD after 24 weeks, improved by a median of 40.8 m compared with placebo. The benefit also extended to 8 of 9 secondary endpoints, including a reduction in PVR and NT-proBNP, improvement in WHO class and quality of life, and a reduc-

tion in the French risk index [12,33]. The risk of a composite event including death or clinical worsening was reduced by 84%, and unplanned hospitalizations due to worsening PAH occurred in 1.9% of patients treated with sotatercept versus 8.8% in the placebo group. Further analyses showed changes in right-heart structure and function consistent with reverse right-heart remodeling. Sotatercept reduced mean pulmonary arterial pressure (by 13.9 mm Hg), decreased the work, power, and dimensions of the right ventricle, and improved right ventricular–pulmonary arterial coupling [34]. The early nature of this response was confirmed by observations assessing the acute hemodynamic effects of sotatercept, indicating a measurable, rapid effect of the drug on pulmonary circulation parameters [35]. Data from the open-label extension of PULSAR indicate maintenance of improvement in pulmonary vascular resistance, six-minute walk distance, and functional class over follow-up exceeding 18–24 months [30]. Pooled analyses of data from the PULSAR and STELLAR trials additionally confirmed that the improvement in 6MWD, PVR, and NT-proBNP occurred regardless of the baseline cardiac index value [17]. Long-term data on the efficacy and safety of sotatercept are provided by the observational SOTERIA study, which includes patients continuing treatment after the completion of trials including PULSAR and STELLAR. Interim data from the ongoing SOTERIA follow-up study indicate maintenance of the clinical response. Although the observed number of deaths may provide a preliminary survival signal, the effect of sotatercept on long-term survival has not been established. Ongoing analyses will allow a better determination of the significance of these observations for the long-term prognosis of patients with PAH [2]. A summary of the key clinical trials and analyses evaluating the efficacy of sotatercept in PAH is presented in Table 1.

Table 1. Summary of clinical trials and analyses on the efficacy of sotatercept in PAH

STUDY / ANALYSIS	TYPE / PHASE	POPULATION	ENDPOINT / AIM	K
PULSAR	Phase 2, RCT, double-blind, placebo-controlled	106 adults with PAH on background therapy	Change in pulmonary vascular resistance (PVR) at week 24	S re ir s g 0 2 p ir 6 d p
PULSAR — extension	Open-label extension	97 of 106 PULSAR patients (placebo-crossed and delayed-start analyses)	Durability of effect	M ir P fu n s th p
PULSAR — analysis by BMPR2	Planned analysis by BMPR2 mutation status	PULSAR participants	Efficacy and safety by BMPR2 status	C e s o m d e p
Proteomic sub-analysis	Sub-analysis (PULSAR + STELLAR)	PULSAR and STELLAR participants	Effect on TGF-β superfamily proteins	A b re B 1(m m ir fa
STELLAR	Phase 3, RCT, double-blind,	323 patients with PAH (WHO FC II–III) on dual/triple	Change in 6-minute walk	Ir 6

	placebo-controlled	therapy	distance (6MWD) at week 24	m m ir o e N c li 8 ri d h 1.
STELLAR — haemodynamics and RV analysis	Exploratory analysis	STELLAR participants	Haemodynamics and right ventricular (RV) function	R m H R a ir R a (c h a c re re
PULSAR + STELLAR pooled analyses	Pooled analyses	PULSAR and STELLAR participants	Efficacy by baseline cardiac index; durability	Ir 6 N ir b ir m e 2
SOTERIA	Long-term observational study (open-label)	480 patients after PULSAR/SPECTRA/STELLAR (median exposure 2.5 years, max 6.2)	Long-term efficacy and safety	M c a s e te re u

Abbreviations: PAH – pulmonary arterial hypertension; RCT – randomized controlled trial; WHO FC – WHO functional class; PVR – pulmonary vascular resistance; 6MWD – 6-minute walk distance; NT-proBNP – N-terminal pro-brain natriuretic peptide; mPAP – mean pulmonary arterial pressure; RV – right ventricle; TAPSE/sPAP – ratio of tricuspid annular plane systolic excursion to systolic pulmonary arterial pressure; BMPR2 – bone morphogenetic protein receptor type 2; BMP – bone morphogenetic protein.

Safety

The safety profile of sotatercept has been evaluated both in randomized clinical trials and in long-term extension observations and post-marketing data analyses. In the STELLAR trial, adverse events occurring more frequently in the sotatercept group than in the placebo group included epistaxis, dizziness, telangiectasia, increased hemoglobin concentration, thrombocytopenia, and increased blood pressure [33]. A pooled analysis of the PULSAR and STELLAR trials confirmed that the most frequently reported treatment-related adverse events were epistaxis (22.1%) and telangiectasia (16.9%); the overall adverse event profile was similar between the sotatercept and placebo groups, but events related to the drug's mechanism of action as a class, namely bleeding and hematological abnormalities, occurred more frequently in the active treatment group [17]. Although telangiectasia, epistaxis, and gingival bleeding are usually mild, self-limiting, and rarely require treatment discontinuation, the authors emphasize that their presence indicates the action of sotatercept beyond the pulmonary circulation, and that long-term use of the drug may be associated with an increased risk of internal bleeding [13]. Serious adverse events were rare. In the long-term SOTERIA observation, which included 480 patients with a median exposure of 2.5 years (maximum 6.2 years), adverse events occurred in 96% of patients, but most were mild or moderate in severity. Serious treatment-related adverse events were found in 6% of patients, including serious bleeding in 4%; dose reduction was required in 10% of patients, and 7% discontinued treatment because of adverse events [2]. Importantly, in the STELLAR trial the rate of treatment discontinuation due to adverse events was even lower in the sotatercept group than in the placebo group (3.7% vs 6.9%), which confirms the good overall tolerability of the drug [33]. Analysis of post-marketing data confirmed the previously known hematological and vascular risks but also identified new threats, including intracerebral hemorrhages and ascites, that were not observed in the original clinical trials and require further observation under real-world clinical practice conditions [36]. Pooled data from meta-analyses of randomized controlled trials confirm that, despite the increased risk of bleeding and

hematological abnormalities characteristic of the mechanism of action, the overall safety profile of sotatercept remains acceptable [37].

DISCUSSION

Despite progress in the treatment of pulmonary arterial hypertension, this disease is still associated with an unfavorable prognosis. Exercise capacity, as well as the hemodynamic and survival parameters of patients, have improved thanks to the introduction of endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, soluble guanylate cyclase stimulators, and drugs acting on the prostacyclin pathway. Such therapeutic management did not eliminate the mechanisms underlying pulmonary vascular remodeling [4,38].

In recent years, increasing attention has been paid to the importance of disturbances in TGF-β signaling in the pathogenesis of PAH. Genetic studies have indicated that mutations in the BMPR2 gene occur in some patients with sporadic PAH and are the most common cause of the hereditary form of this disease [3,39]. A meta-analysis indicates that the presence of a BMPR2 mutation is associated with earlier onset of symptoms, a more severe course of the disease, and a worse prognosis [40]. The results of these studies led to the development of a therapeutic strategy aimed at restoring the balance between the protective BMPR2-SMAD1/5/8 pathway and the overactive activin-dependent SMAD2/3 pathway [3,21,39]. Sotatercept is the first drug developed on the basis of this concept and represents a therapeutic approach aimed at modulating pathways implicated in pulmonary vascular remodeling [1,26].

Disturbances in BMPR2 signaling extend beyond vascular cell proliferation itself. BMP9 and BMP10 play an important protective role toward the vascular endothelium by limiting the inflammatory process and the expression of chemotactic mediators [22]. One of the key elements of pulmonary vascular remodeling is impaired communication between endothelial cells, smooth muscle cells, and fibroblasts [41]. The action of sotatercept observed in preclinical studies, extending beyond hemodynamic effects, may suggest a potential influence on biological processes associated with disease progression [18,21].

A growing number of studies emphasize the role of inflammation in the development of PAH. Numerous immunological abnormalities present in patients with PAH have been described in the literature, including activation of macrophages and lymphocytes and

increased production of pro-inflammatory cytokines [42]. The sotatercept analogue leads to normalization of inflammatory infiltration in the lungs and to reversal of the expression of genes associated with inflammatory processes [24]. The PULSAR and STELLAR clinical trials demonstrated significant improvements in clinical outcomes with this therapeutic strategy [25,33]. Therapeutic benefits were also observed in patients already receiving optimal background therapy. The improvement in NT-proBNP concentration, exercise capacity, and pulmonary vascular resistance is consistent with a mechanism of action complementary to that of existing therapies, although the precise effects on pulmonary vascular remodeling require further investigation [12,17,25]. The results are consistent with the concept that effective PAH treatment may require dilation of the pulmonary vessels together with inhibition of the processes that lead to their remodeling [43].

It is worth noting the data indicating a potential effect of sotatercept on the clinical course of the disease. The STELLAR trial showed an 84% reduction in the risk of the composite endpoint of death or clinical worsening [33]. Similarly, the ZENITH trial demonstrated a significant reduction in the frequency of severe clinical events in patients with advanced PAH [1]. These observations suggest a potential effect beyond symptomatic improvement; however, their impact on long-term disease progression and survival has not yet been established. Longer follow-up studies are needed to determine whether these clinical benefits translate into sustained improvements in prognosis. In this context, sotatercept may represent an important development in the treatment of PAH [12].

It is also worth noting the effect of sotatercept on right ventricular function. The main cause of death in patients with PAH is right ventricular heart failure [43]. The results of the STELLAR trial indicate improvement in right ventricular function parameters together with reductions in indices of structural remodeling [34]. The results of these studies are consistent with earlier experimental observations in which the sotatercept analogue reduced myocardial remodeling and improved ventricular function [23].

Despite the available evidence, several important issues requiring further research remain. First of all, most studies included patients who were receiving advanced combination therapy, and therefore it is not known whether comparable benefits would occur if sotatercept were implemented earlier [33,38]. In addition, it has not yet been determined which patient groups derive the greatest benefit from the therapy. Analyses of the PULSAR trial indicate that the efficacy of the therapy is independent of BMPR2 mutation status [32]. However, further studies are necessary to enable the identification of potential biomarkers of response to therapy.

The safety of the therapy also remains an important issue. Despite the favorable safety profile demonstrated in clinical trials and the SOTERIA observation [2,17], this therapy is associated with the possibility of characteristic adverse events, such as telangiectasia, epistaxis, increased hemoglobin concentration, and thrombocytopenia [13,33]. The results of post-registration studies, indicating the possibility of rare but potentially serious complications, including intracerebral hemorrhages, are of significant importance [36]. Therefore, it is necessary to continue observation regarding the safety of the therapy in everyday clinical practice.

In a broader perspective, the introduction of sotatercept represents another stage in the evolution of PAH treatment observed over the last decade or so. In the 2009 ACCF/AHA expert documents, PAH treatment was based almost exclusively on drugs targeting the three classic vasoactive pathways [44]. The 2022 ESC/ERS guidelines draw attention to the importance of combination therapy and individualization of therapeutic management [38]. The introduction of sotatercept represents a new stage in the development of therapies targeting molecular pathways involved in pulmonary vascular remodeling and may contribute to the development of further therapeutic approaches aimed at targeting pathways associated with disease progression.

LIMITATIONS

This review is narrative in nature, which entails several limitations. The work does not meet the criteria of a systematic review, which increases the risk of publication selection and potential interpretive bias. The literature was limited to selected databases and to publications in English, mainly from 2020–2026, which may have led to the exclusion of important studies published in other databases. These limitations should be taken into account when interpreting the results of this review.

CONCLUSIONS

Sotatercept is a first-in-class therapy in the treatment of PAH that is directly targeted at disturbances in the signaling pathways of the TGF-β superfamily, which play a significant role in pulmonary vascular remodeling. The results of studies indicate that the drug has a beneficial effect on hemodynamic parameters and the exercise capacity of patients. In addition, sotatercept may affect pathways involved in pulmonary vascular

remodeling and right ventricular function. Data from the STELLAR and PULSAR trials, together with findings from the ongoing SOTERIA follow-up study, support the efficacy of sotatercept as an add-on therapy to standard PAH treatment and suggest that it may reduce the risk of clinical worsening. However, an effect on long-term survival has not yet been demonstrated. Despite the demonstrated clinical benefits, further studies are necessary to analyze the long-term safety of the therapy, its effect on survival, and its optimal position in the treatment regimen of different groups of patients with PAH. Currently available scientific evidence indicates that sotatercept may represent an important add-on therapeutic option in the treatment of PAH.

DISCLOSURE

Author Contributions

Conceptualization: Aleksandra Kamińska, Maria Miller.

Methodology: Maria Miller, Aleksandra Pakulska.

Literature search: Aleksandra Kamińska, Maria Miller.

Study selection: Aleksandra Pakulska, Natalia Rządzińska.

Data extraction: Aleksandra Błoch, Aleksandra Pakulska.

Data interpretation: Aleksandra Pakulska, Natalia Rządzińska.

Writing: original draft preparation: Aleksandra Pakulska, Aleksandra Kamińska, Aleksandra Błoch.

Writing: review and editing: Natalia Rządzińska, Maria Miller, Aleksandra Kamińska.

Supervision: Aleksandra Błoch.

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Conflict of Interest

The authors declare no conflict of interest.

Use of Artificial Intelligence

Artificial Intelligence was used only for language editing and stylistic correction. All scientific content was verified and approved by the authors.

Ethics

Ethical approval was not required because this article is a narrative review.

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