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Key Points of"Treatment Algorithm for Pulmonary Arterial Hypertension" from the 7th World Symposium on Pulmonary Hypertension and Its Impact on PAH Treatment in China

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Abstract: Following the 7th World Symposium on Pulmonary Hypertension (WSPH)in 2024, the European Respiratory Journal published an updated treatment algorithm for pulmonary arterial hypertension (PAH)highlighting the emerging role of the activin signalling inhibitor (ASI) sotatercept, as a key therapeutic advancement. The updated plan underscores the importance of indicators such as World Health Organization functional class (WHO-FC)and 6-minute walk distance (6MWD) in risk assessment. It advocates for a personalized treatment approach based on risk stratification, encompassing both initial therapy selection and escalation strategies during follow-up. The anticipated introduction of the novel ASI sotatercept in China is expected to expand the therapeutic landscape for PAH management in the country.

Keywords: PAH; ASI; Sotatercept; WSPH; China

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1. Introduction

Following the 7th World Symposium on Pulmonary Hypertension (WSPH) in 2024, the European Respiratory Journal published an updated "Treatment algorithm for pulmonary arterial hypertension," presenting revised treatment strategies informed by global expert consensus [1] . Among these updates, the introduction of activin signalling inhibitors (ASI) marks a major therapeutic breakthrough, offering new directions for the global management of pulmonary arterial hypertension (PAH). This article summarizes the key points of the updated algorithm and seeks to encourage reflection among Chinese clinicians regarding the current landscape of PAH diagnosis and treatment in China.

2. Key points of "Treatment algorithm for pulmonary arterial hypertension"

2.1. Treatment goals and risk stratification

The updated treatment algorithm emphasizes that, among the various prognostic indicators for PAH, the World Health Organization functional class (WHO-FC), 6-minute walk distance (6MWD), and N-terminal pro-B-type natriuretic peptide (NT- proBNP), right ventricular imaging parameters, and hemodynamic measures possess the strongest prognostic value [2]. The core indicators and typically employed in PAH treatment guidelines to guide therapy selection, with the primary goal of achieving and maintaining a low-risk status. The current consensus continues to advocate for a treatment strategy guided by comprehensive risk assessment.

For initial treatment, the updated treatment algorithm recommends stratifying patients into high-risk and non-high-risk categories. At the first and subsequent follow-up evaluation, it endorses the use of the four-strata risk assessment model outlined in the 2022 ESC/ERS PH guidelines [3] . In addition to WHO-FC, 6MWD, and NT-proBNP, the algorithm emphasizes the importance of incorporating serial cardiac imaging and hemodynamic assessment for comprehensive risk reassessment, particularly when considering major therapeutic modifications.

The algorithm highlights that although the 6th WSPH recommended lowering the diagnostic threshold for mean pulmonary arterial pressure (mPAP) from ≥ 25 mmHg to > 20 mmHg [4], and the 2022 ESC/ERS guidelines proposed reducing the upper limit for abnormal pulmonary vascular resistance (PVR) from > 3 Wood Unit (WU) to > 2 WU [3], no approved therapies currently exist for patients either with mPAP in the range of 21–24 mmHg or PVR 2-3WU. Therefore, even when treatment is considered based on individual clinical scenarios, initial mono-therapy is generally advised over combination therapy.

In terms of initiating treatment, the algorithm recommends tailoring therapy according to risk stratification at the time of diagnosis, dividing patients into high-risk and non- high-risk categories. For patients categorized as non-high-risk at baseline, initial combination therapy with an endothelin-1 receptor antagonist (ERA) and a phosphodiesterase-5 inhibitor (PDE-5i) is recommended. And patients classified as high-risk should receive initial therapy that includes parenteral prostacyclin pathway agents (PPA) in combination with ERA and PDE-5i. Additionally, early evaluation for lung transplantation and timely referral should be considered for high-risk patients, depending on patient-specific factors, institutional expertise, and regional accessibility. Importantly, based on findings from the TRITON trial, initial triple oral therapy with selexipag, PDE-5i, and ERA is not recommended [1] .

2.2. Follow-up and treatment escalation plans

The updated treatment algorithm recommends early reassessment to guide treatment escalation. A follow-up at 3–4 months is considered appropriate for most patients [3] , provided they are clinically stable or show signs of improvement. For those with clear clinical deterioration, immediate treatment intensification should be considered. In patients initially treated with mono-therapy, the addition of a second agent,particularly in those who have not achieved a low-risk profile,should be evaluated at this point or even earlier. Evidence suggests that patients who received early intensification of therapy demonstrating better long-term outcomes than those who underwent delayed escalation [5] .

Regarding the necessity of further treatment in patients classified as low risk during follow-up, the algorithm notes that many of these individuals continue to experience notable symptoms or reduced exercise capacity, and remain at risk for disease progression [6]. Although clinical trials have shown only modest short-term improvements in WHO-FC and 6MWD in this group [7], and a limited absolute reduction in clinical deterioration [8], individualized

treatment decisions are still encouraged. In this context, expanded therapeutic goals have been proposed, including achieving PVR < 5 WU [9], relative PVR reduction of > 50%–60% [10–12], improvement in stroke volume index (SVI) or other hemodynamic parameters [13], and normalization or near-normalization of right heart size and function on cardiac imaging [14] . However, further longitudinal studies are needed to determine whether these additional targets offer prognostic value beyond standard low-risk criteria.

For patients reassessed as intermediate-low risk or higher during follow-up, intensification of targeted therapy is warranted. Those receiving initial oral combination therapy who remain in the intermediate-low category based on the four-strata risk model may benefit from additional or alternative treatments. These include the addition of sotatercept, oral or inhaled PPAs, or transitioning from PDE-5i to riociguat. Patients stratified as intermediate-high or high risk at their first follow-up should be considered for parenteral PPA or be considered for add-on sotatercept, while those at highest risk should receive a parenteral PPA, if not already receiving. Persistent intermediate-high or high- risk status across multiple follow-ups should prompt escalation to maximal medical therapy and referral for lung transplantation. Currently, maximal therapy includes quadruple therapy, with sotatercept added to the conventional triple combination targeting the endothelin, nitric oxide, and prostacyclin pathways. Clinical trials have demonstrated that patients already receiving triple therapy experienced additional clinical benefit upon the addition of sotatercept. In all patients who demonstrate progression or sustained high-risk features, timely evaluation for lung transplantation is strongly recommended. [1] .

2.3. For patients with cardiopulmonary comorbidities and other PAH patients at higher risk of adverse drug reactions

Patients with PAH and concomitant cardiopulmonary comorbidities may experience a higher incidence of adverse events and demonstrate less stable responses to therapy, necessitating more cautious use of targeted treatment and closer clinical monitoring [15] . Therefore, monotherapy may be preferred in PAH patients with cardiopulmonary comorbidities.

2.4. Drug administration and adverse reactions

The updated treatment algorithm notes that although most adverse events associated with targeted therapies (such as peripheral edema, nasal congestion, anemia caused by ERA drugs; headache, flushing, indigestion, epistaxis caused by PDE-5i drugs; headache, indigestion, dizziness, hypotension caused by soluble guanylate cyclase stimulators; flushing, headache, jaw pain, nausea, diarrhea caused by PPA drugs; headache, diarrhea, epistaxis, bleeding events caused by sotatercept, etc.) can generally be managed with supportive care or dose adjustment, certain adverse effects warrant heightened attention. [1] .

For sotatercept, which is about to be approved in China, treatment is initiated at 0.3 $mg \cdot kg^{-1}$, and then increased to 0.7 $mg \cdot kg^{-1}$ for subsequent doses administered every 3 weeks. Downtitration to 0.3 $mg \cdot kg^{-1}$ can be considered when required for adverse events (particularly for elevated haemoglobin) or tolerability. Monitoring is recommended for increased haemoglobin, reduced platelets and the development of new telangiectasias, and an increased risk of bleeding events has been seen in trials. In addition, sotatercept carries a risk of fetal harm, and may have the potential to reduce future fertility and males and females, based on animal studies[16].

3. The impact of “Treatment algorithm for pulmonary arterial hypertension” on

future PAH therapeutic approaches in China

The updated treatment algorithm outlines four major pathways targeted by pharmacologic therapy: (1) the endothelin receptor pathway; (2) the nitric oxide pathway; (3) the prostacyclin pathway; and (4) the activin signalling pathway. To date, only the first three classes of targeted therapies have been approved for clinical use in China. However, these therapy primarily exert their effects through vasodilation to alleviate symptoms; do not reverse pulmonary vascular remodeling. As a result, many patients continue to experience disease progression despite ongoing treatment. A 2022 national prospective multicenter registry study on PAH in China reported [17] that the proportion of patients at intermediate/ high risk during follow-up reached 40.8%, and the 10-year survival rate for PAH patients was only about 63.2%, highlighting the urgent need for more effective therapies that can improve long-term outcomes. Sotatercept, a first- in-class ASI , effectively reduces pulmonary artery pressure and improves symptoms in PAH patients by rebalancing proliferative and antiproliferative signalling to modulate vascular proliferation. Currently, sotatercept has been approved for use in over 40 countries and regions, including the United States and the European Union. Although it has not yet received full regulatory approval in mainland China, it was approved for import as a clinically urgent drug in the Hainan Boao Lecheng Pilot Zone in January , 2025. Multiple clinical studies, including the PULSAR [18], STELLAR [19], and ZENITH [20] studies, have evaluated the safety and efficacy of sotatercept in PAH patients across different risk levels (WHO-FC II, III, IV) receiving adequate background therapy. These studies demonstrated improvements in short-term indicators such as WHO-FC, 6MWD, and NT- proBNP, as well as hemodynamic parameters like PVR and mPAP. Additionally, sotatercept reduced the incidence of long-term events such as all-cause death, lung transplantation, and PAH-related hospitalizations of ≥ 24 hours. The ZENITH study [20], a phase III, multicenter, randomized, double-blind, placebo-controlled trial, evaluated the efficacy and safety of sotatercept in patients with PAH (WHO-FC III or IV) receiving maximum tolerated background therapy and at high risk of death within 1 year. In the second half of 2024, the ZENITH study was terminated early due to significant efficacy observed in the interim analysis. The results, published on March 31, 2025, in the New England Journal of Medicine , showed that sotatercept reduced the composite risk of all-cause death, lung transplantation, or hospitalization for at least 24 hours due to worsening PAH by 76% compared to the placebo group. The Kaplan-Meier curves demonstrated early and significant separation. In the safety analysis of the ZENITH study, similar to the STELLAR study, the percentage of patients experiencing severe adverse events, adverse events leading to drug discontinuation, and adverse events resulting in death was lower in the sotatercept group compared to the placebo group. Additionally, the HYPERION study, which included newly diagnosed (less than 12 months) PAH patients, was also terminated early based on the positive interim results of the ZENITH study. In June 2025, positive results from the HYPERION study were announced, achieving its primary endpoint of time to clinical worsening (TTCW) as measured by a composite endpoint of all-cause death, the need for non-planned PAH-related hospitalization > 24 hours, atrial septostomy, lung transplantation, or PAH deterioration. To date, the strong clinical profile of sotatercept had been primarily established through previous studies in a prevalent patient population comprised of patients that were several years into their treatment journey. These positive results from HYPERION expand on the body of clinical evidence now including recently diagnosed adults, supporting the practice-changing potential of sotatercept in a broad spectrum of PAH patients, including those earlier in their treatment journey.

The 7th WSPH emphasized the translation of modern pulmonary vascular research, introduced novel therapeutic approaches targeting pulmonary vascular remodeling, and updated evidence-based treatment algorithms, highlighting the complementarity between different therapeutic methods [1] . Regarding

updates to PAH treatment strategies, recommendations were primarily based on comprehensive analyses according to risk stratification [1] . The updated treatment algorithm specifically highlight that sotatercept, an activin signalling inhibitor, is the first targeted PAH therapy to act on a new pathway in nearly two decades and the addition of sotatercept to the treatment of PAH patients who are already receiving adequate background therapy with traditional vasodilator targeted drugs can still demonstrate further significant clinical benefits for them [1,18–20] . The recommendation of this drug in "Treatment algorithm for pulmonary arterial hypertension" brings optimistic expectations for the future treatment of PAH patients in China. The introduction of novel targeted therapies like sotatercept to China is expected to provide new strategies for the treatment of PAH, potentially breaking through current therapeutic bottlenecks and improving long-term patient outcomes as clinical experience and localized research accumulate.

Disclosure statement

The authors declare no conflict of interest.

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