INVITED MANUSCRIPT

Tyrosine Kinase Inhibitors for Treatment of Pulmonary Arterial Hypertension

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Tyrosine kinase inhibitors are potentially exciting therapies for pulmonary arterial hypertension. However, pleiotropic and variable effects of multitargeted tyrosine kinase inhibitors have limited the ability to identify safe, well-tolerated, and effective agents. In this paper, a succinct description of the range of tyrosine kinase inhibitors that are relevant to pulmonary arterial hypertension (either treating or causing it) is provided. This includes a discussion of how the varied targeting of the agents impacts their therapeutic and adverse effects and how better understanding of the animal models is improving prediction of clinical effects. Proof of concept was obtained in the studies of oral imatinib, although excessive side effects and some cases of subdural hematoma in patients receiving imatinib who were on anticoagulation occurred. Alternative approaches include alteration of the dose, formulation or route of delivery of imatinib, and use of newer agents such as seralutinib that has potentially advantageous receptor targeting combined with inhaled delivery in an effort to reduce systemic effects. These approaches hold promise that ultimately effective new therapies for pulmonary arterial hypertension using tyrosine kinase inhibition will be forthcoming.

Tyrosine kinases are a family of enzymes that regulate critical processes involved in cellular proliferation. A large number of tyrosine kinase inhibitors (TKIs) have been developed and designed to target specific kinases felt to be important in disease states, particularly cancer. Targeting various tyrosine kinases involved in cancer has revolutionized the treatment and outcome of these conditions.

Pulmonary arterial hypertension (PAH) shares many features of a cancer-like state, including abnormal proliferation of pulmonary artery smooth muscle cells. Accordingly the potential for TKIs to treat PAH is logical. TKIs often target multiple tyrosine kinases to a variable extent, resulting in differing and pleiotropic effects. The effects of various TKIs can be tested in animal models of disease, providing additional proof of principle for use in humans. However, these models are imperfect in predicting both beneficial and harmful effects. As multiple TKIs have been studied and approved for use in humans, the understanding of how differences in target specificities translate to potential for both beneficial and adverse clinical effects is improving. TKIs relevant to PAH are shown in Table 1.

Sorafenib is a tyrosine and serine/threonine kinase inhibitor used to treat liver, renal, and thyroid cancers. In animal models, it had greater effect on right ventricular pressure and mass than imatinib. Limited open label studies in humans have shown variable effects with some signals of reduction in pulmonary artery pressure but also concern for fall in cardiac index. Nintedanib (Ofev) is a TKI with effects on platelet-derived growth factor, vascular endothelial growth factor, and fibroblast growth factor and is approved to treat several forms of pulmonary fibrosis. Animal studies have shown conflicting effects, varying from beneficial hemodynamic effects and improvement in pulmonary vascular lesions[1] and also some acute pulmonary arterial relaxation[2–4] to adverse pulmonary vascular effects.

Dasatinib, which is approved by the Food and Drug Administration for treating certain hematologic malignancies, has unfortunately been found sometimes to cause pleural effusions and pulmonary hypertension,[13,22,23] whereas the TKI imatinib, also approved by the Food and Drug Administration for the treatment of hematologic malignancies, has been shown to improve pulmonary hypertension. The adverse effects of dasatinib are believed to be potentially related to its targeting of the Src family of kinases, although more recent evidence suggests important effects on reactive oxygen species and vascular endothelial permeability.[12] Once such effects are recognized, animal studies may help predict the safety of other TKIs in this regard. For example, seralutinib does not have these effects on vascular permeability.[18]

Imatinib is a TKI that targets BCR-ABL and accordingly is highly effective for chronic myelogenous leukemia. It also targets platelet-derived growth factor receptor, which is upregulated in the pulmonary arteries in PAH.[24] Oral imatinib was shown initially in case series to result in improvement in hemodynamics, echocardiographic parameters of right ventricular function, and improvement in N-terminal prohormone of brain natriuretic peptide

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Table 1. Tyrosine kinase inhibitors relevant to pulmonary arterial hypertension

Drug	Characteristic	Animal studies	Human studies
Sorafenib	Tyrosine and serine/threonine KI	Reduced RV pressure, mass > imatiinib[5]	Small case series,[6,7] concern of fall in cardiac index
Nintedanib	PDGF, VEGF, and FGF	Conflicting data; no effect versus pulmonary artery vasodilation, reduced RV fibrosis, variable effects on hemodynamics[1,8,9]	Small case series suggests worsening in PAH[9]
Dasatinib	Src, BCR-ABL	Worsening PH, increased ROS, vascular endothelial permeability, reduced KCNK3 signaling[10–12]	Cases of PAH with pleural effusions[13,14]
Oral imatinib	PDGF, BCR-ABL	Improved hemodynamics, vascular pathology but potential for cardiotoxicity[15]	Improved PVR but fluid retention, GI intolerance, SDH in patients on A/C[16]
Inhaled imatinib	PDGF, BCR-ABL	Inhibited development of PH[17]	Phase 2/3 study terminated due to lack of reduction in PVR
Inhaled seralutinib	PDGRα/β, CSF1R, c-Kit[18]	Improved hemodynamics, lung pathology more than oral imatinib; absence of adverse effects on pulmonary endothelial permeability[18,19]	Phase 2 positive for reduction in PVR, NT-proBNP, preservation of RV function[20,21]; phase 3 enrolling

Abbreviations: A/C, anticoagulation; CSF1R, colony-stimulating factor 1R; FGF, fibroblast growth factor; GI, gastrointestinal; KI, kinase inhibitor; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PAH, pulmonary arterial hypertension; PDGF, platelet-derived growth factor; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; ROS, reactive oxygen species; RV, right ventricular; SDH, subdural hematoma; VEGF, vascular endothelial growth factor.

and functional class.[25] However, in that series, 2 patients who were on warfarin sustained subdural hematomas. A subsequent placebo-controlled study in 59 patients demonstrated improvement in pulmonary vascular resistance.[26] In the randomized placebo-controlled study Imatinib in Pulmonary Arterial Hypertension, a Randomized, Efficacy Study (IMPRES), imatinib improved the placebo-corrected 6-minute walk by 32 m (95% confidence interval, 12–52; $P = .002$) and reduced placebo-corrected pulmonary vascular resistance by 379 dyne·s·cm^{-5} (95% confidence interval, −502 to − 255; $P < .001$).[16] However, serious adverse events were more common with imatinib than with placebo (44% versus 30%), and discontinuations were also more common (33% versus 18%). In addition, 8 patients developed subdural hematomas on imatinib therapy, all of whom were on warfarin. There were also frequent gastrointestinal side effects and peripheral swelling.

Accordingly, although oral imatinib was effective in lowering pulmonary artery pressure and resistance and improving 6-minute walk distance in patients with PAH, including patients on maximal therapy with phosphodiesterase-5 inhibitors, endothelin receptor antagonists, and parenteral prostanoids, it was never approved by regulatory agencies for the treatment of PAH. The exact mechanism of the subdural hematoma risk is unclear but may reflect some effect of the drug on the cerebral vasculature that was permissive for bleeding. However, the signals of beneficial effects on the pulmonary vasculature set the stage for exploration of alternative strategies of using TKIs in PAH. There are also concerns about potential cardiotoxicity of oral imatinib mediated via ABL-related gene (c-Abl).[15] Efforts to establish a safe and effective lower dose of imatinib have also been proposed.[27]

ALTERNATIVE FORMULATION OF ORAL IMATINIB

An alternative formulation of imatinib has been developed (TNX-201, oral enteric-coated imatinib, Tenax Therapeutics, Chapel Hill, SC). It is hoped that this formulation may mitigate some of the gastrointestinal intolerance issues of imatinib. Thus far, no tolerability and efficacy studies in PAH have been conducted.

INHALED ROUTE OF ADMINISTRATION OF TKIS

Delivery of drugs impacting the pulmonary vasculature by inhalation is intrinsically attractive as a method to more selectively target the organ of interest. Absorption of the drug across the alveolar septal membrane into the blood can result in activity on the resistance vessels of the lungs. Systemic absorption does occur, but the blood levels tend to be much lower than those achieved with systemic administration, so off-target effects may be reduced although not necessarily fully avoided.

Inhaled Imatinib

Inhaled imatinib was shown to be reasonably tolerated in healthy adults.[28] The Inhaled Imatinib in PAH Clinical Trial (IMPAHCT, NCT05036135) was an innovative phase 2/3 study of inhaled imatinib, seeking to take advantage of the known effects of imatinib on pulmonary artery pressure and resistance but hoping to lessen systemic risks and side effects by virtue of the inhaled route of administration. Unfortunately the study failed to meet its primary endpoint of reduction in pulmonary vascular resistance, so the study was terminated. Full publication of the findings are awaited.

Inhaled Seralutinib

Seralutinib is a small-molecule inhibitor specifically designed with the goal of targeting multiple pathways believed to be important in the pathophysiology of pulmonary vascular disease. In animal models of PAH, including the monocrotaline rat and the Sugen hypoxia model, seralutinib reverses the pathological findings in the pulmonary vasculature and improves hemodynamics and right ventricular function. It targets platelet-derived growth factor receptors A and B, c-Kit, and colony-stimulating

factor 1R (CSF1R).[18,19] CSF1R is a receptor on activated macrophages that may play a role in perivascular inflammation in PAH. It is more potent than imatinib against c-Kit and CSF1R kinases. It does not target BCR-ABL, so it is not anticipated to have cardiotoxicity, and does not impact pulmonary endothelial permeability in animal studies, so it is not anticipated to have the potential for pleural effusions/development of pulmonary hypertension in contradistinction to dasatinib.[18] In phase 1 and phase 2 studies (TORREY, NCT04456998), it appears to be well tolerated, with the most common side effect being cough, which is common with inhaled therapies.[20] Serious adverse effects were uncommon. The phase 2 (TORREY) study of inhaled seralutinib met its primary endpoint of a reduction in pulmonary vascular resistance. It also reduced N-terminal prohormone of brain natriuretic peptide and was associated with preservation of right ventricular function compared with placebo.[21] A pivotal phase 3 study (PROSERA) is currently recruiting (NCT05934526), with a primary endpoint of a 6-minute walk.

CONCLUSIONS

The promise of tyrosine kinase inhibition in the therapy of PAH has been more difficult to achieve than anticipated, reflecting the complexity of the effect of multitargeted TKIs and issues of tolerability. The key is to deliver an adequate dose of an effective drug to the pulmonary vasculature with an acceptable tolerability and safety profile. Enhanced understanding of receptor targeting of the various TKIs and the association of that targeting with either beneficial or adverse effects has expanded the ability of animal models to predict efficacy and safety. In this light, ongoing research holds great promise for identifying tyrosine kinase inhibitors that are safe and effective in the treatment of pulmonary arterial hypertension.

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