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REVIEW

The Role of Intravenous Selexipag in Managing PAH and Bridging Gaps in Oral Treatment: A Narrative Review

Sienna Goren[1,*], Nermeen Kidwai[1,*], Wilbert S Aronow[2], Gregg M Lanier[2]

[1]New York Medical College, Valhalla, NY, USA; [2]Departments of Medicine and Cardiology, Westchester Medical Center and New York Medical College, Valhalla, NY, USA

*These authors contributed equally to this work

Correspondence: Wilbert S Aronow, Department of Cardiology, Westchester Medical Center, and Professor of Medicine, New York Medical College, Macy Pavilion, Room 141, Valhalla, NY, 10595, USA, Tel +1 914 493 5311, Fax +1 914 235 6274, Email Wilbert.Aronow@wmchealth.org

Abstract: Pulmonary arterial hypertension (PAH) is a rare and potentially fatal condition characterized by progressive increases in blood pressure in the arteries of the lungs. Oral selexipag, approved by the Food and Drug Administration (FDA) in 2015 for the treatment of PAH, targets prostacyclin receptors on pulmonary arterial vascular smooth muscle and endothelial cells to improve blood flow through the lungs and reduce pulmonary vascular resistance. Oral selexipag is effective, but may be discontinued due to factors like side effects, emergency conditions, or inability to take oral medication, potentially leading to severe adverse events, such as rebound pulmonary hypertension and right heart failure. To address treatment interruptions, intravenous (IV) selexipag was introduced as an alternative for patients who are temporarily unable to take oral medications. IV selexipag bypasses hepatic metabolism, requiring a 12.5% higher dose compared to the oral form to achieve similar therapeutic effects. It is administered via IV infusion twice daily over 80 minutes, typically for short-term use. However, caution is needed when prescribing selexipag to patients with hepatic or renal issues, and it is contraindicated with strong CYP2C8 inhibitors. A Phase III clinical trial confirmed that switching between oral and IV selexipag was safe, with comparable efficacy and tolerability, though it was limited by small sample size and short duration. Given the risks of treatment interruption and the complexity of managing PAH, this review provides essential insights into the practical use of IV selexipag as a bridging therapy. Furthermore, it calls for larger clinical trials to refine dosing strategies, explore long-term outcomes, and identify patient populations most likely to benefit from IV selexipag.

Plain Language Summary: Pulmonary arterial hypertension (PAH) is a rare and dangerous condition that causes high blood pressure in the arteries of the lungs, leading to right heart failure and potentially death. Selexipag is a medication used to treat patients with PAH by widening the blood vessels in the lungs. However, some patients may not be able to take oral selexipag as prescribed, which can worsen their condition. In 2021, an intravenous (IV) form of selexipag was approved as a temporary alternative for these patients. This review examines available literature to provide background and practical instruction for providers prescribing IV selexipag.

Unlike oral selexipag, which is processed by enzymes in the liver, the IV form bypasses liver metabolism and enters the bloodstream directly. As a result, the IV dose is typically 12.5% higher than the oral dose to achieve the same therapeutic effects. IV selexipag is administered twice daily through an infusion lasting about 80 minutes and is intended for temporary use. Healthcare providers should use caution when prescribing selexipag to patients with liver or kidney issues. Additionally, selexipag should not be used with medications that block CYP enzymes. A phase III clinical trial reports that common side effects of the IV form of selexipag include headaches and irritation at the injection site. While IV selexipag is considered safe and effective for short-term use, larger studies are needed to better understand how to manage transitions between oral and IV forms.

Keywords: prostacyclin, right heart failure, treatment interruption, intravenous selexipag, IP agonist

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Introduction

Pulmonary arterial hypertension (PAH) is a rare, life-threatening disorder caused by progressive small vessel remodeling and narrowing in the pulmonary circulation, resulting in an increased right ventricular afterload and eventual right heart failure and possibly death.[1,2] It is defined by a mean pulmonary arterial pressure of greater than or equal to 20 mmHg at rest, pulmonary capillary wedge pressure less than 15 mmHg, and pulmonary vascular resistance greater than 2 Wood units.[3] PAH is thought to be caused by a relative reduction in vasodilators, including endogenous prostacyclins and nitric oxide, in comparison to vasoconstrictors such as endothelin 1.[4,5] Studies have also shown that vascular cell growth and inflammation play a role in PAH, and that PAH is associated with increased thrombosis and vasoconstriction.[5,6] Several pharmaceutical classes of medications are approved for the treatment of PAH, and include endothelin receptor antagonists (ERA), phosphodiesterase 5 inhibitors (PDE5i), soluble guanylate cyclase (sGC) stimulators, activin signaling inhibitors, and prostacyclin analogs and stimulators. Since prostacyclins are vasodilators with anti-proliferative, antithrombotic, and anti-inflammatory effects, they act as an effective treatment option for PAH.[6]

Oral selexipag was approved by the FDA in 2015 for the treatment of adult patients with PAH based on the results of the Prostacyclin (PGI2) Receptor Agonist In Pulmonary Arterial Hypertension (GRIPHON) trial, which demonstrated its efficacy in reducing the risk of disease progression and hospitalization of adult patients with PAH.[7,8] The Efficacy and Safety of Initial Triple Versus Initial Dual Oral Combination Therapy in Patients With Newly Diagnosed Pulmonary Arterial Hypertension (TRITON) trial then explored the role of oral selexipag in initial triple therapy for patients with PAH.[9] This study formed the basis of the guidelines created by the European Society of Cardiology (ESC) and European Respiratory Society (ERS), which recommend adding oral selexipag to dual ERA/PDE5i therapy for patients at intermediate-low risk of clinical worsening.[3,9]

Since PAH is a progressive disease, uninterrupted treatment is crucial for maintaining the therapeutic effects of PAH medications.[10,11] Patients may not adhere to their medications due to a number of reasons, such as difficulty in obtaining their prescription, forgetfulness, experiencing AEs, inability to swallow, or inability to have any oral intake because of emergency conditions like appendicitis.[10,11] Given these barriers, intravenous (IV) selexipag was developed as a short-term alternative therapy for patients with PAH who are temporarily unable to take oral selexipag, aiming to bridge the gap in therapy, delay disease progression, and reduce the risk of hospitalization.[10,12] Abrupt discontinuation of prostanoid therapy, including oral selexipag, can cause rebound pulmonary hypertension, a dangerous, rapid increase in pulmonary arterial pressure, as well as clinical worsening and increased risk of right heart failure.[13,14] Changes to prostanoid therapy should therefore be done gradually and under close monitoring of patient symptoms and hemodynamics. Despite these issues, there is limited information available on the effects of treatment interruptions or discontinuations, as well as on the best practices for reintroducing PAH treatment after an interruption.[11] This gap in knowledge underscores the need for a review of IV selexipag in PAH management. This review will evaluate the efficacy and safety of IV selexipag, explore the optimal dosing strategies, and highlight special considerations for patient populations, offering important insights into how to manage treatment interruptions and ensure continuous, effective care for this patient population.

Literature Search and Inclusion Criteria

This narrative review examines the use of IV selexipag in the treatment of adult patients with PAH. A targeted literature search was conducted using the PubMed database, FDA-approved prescribing information, and the Janssen Pharmaceuticals website.[12] Search terms included “IV selexipag”, “selexipag”, “intravenous selexipag”, “selexipag for adults”, and “selexipag AND pulmonary arterial hypertension (PAH).” The review primarily focused on studies evaluating intravenous selexipag but also considered oral selexipag, including the phase III GRIPHON and TRITON trials.

Inclusion criteria for the review were studies involving adults (≥18 years) with PAH who were receiving selexipag therapy. Exclusion criteria were studies involving children (≤18 years) or those evaluating selexipag for conditions other than PAH. This review is constrained by the limited availability of published studies on IV selexipag.

Selexipag Pharmacokinetics and Metabolism

Selexipag is a non-prostanoid IP prostacyclin receptor agonist (Figure 1).[6] Selexipag exerts its therapeutic effects by selectively targeting prostacyclin receptors on vascular smooth muscle cells and endothelial cells in the pulmonary arteries.[4,7,15] The prostacyclin receptor is a G-protein coupled receptor that stimulates cAMP production, leading to vasodilation and anti-proliferative effects.[4] By stimulating this pathway, selexipag improves blood flow in the lungs and reduces pulmonary vascular resistance (Figure 1).[15]

When administered orally, selexipag is rapidly absorbed and hydrolyzed in the liver and gastrointestinal tract by carboxylesterase 1 to its active metabolite, ACT-333679.[6,10,12,16,17] The majority of the hydroxylation of oral selexipag occurs in the liver via carboxylesterase 1, while a smaller portion is facilitated by carboxylesterase 2 in human intestinal microsomes.[16,18] The active metabolite ACT-333679 is approximately 37 times more potent than selexipag and is present at concentrations 3 to 4 times higher following oral administration.[10,17]

In contrast, intravenous selexipag is administered directly into the bloodstream, bypassing efficient hepatic and gastrointestinal metabolism.[17] Consequently, the levels of ACT-333679 increase more slowly with IV administration.[17] The ratio of ACT-333679: selexipag is 3.45 in the oral form, compared to 1.33 in the IV form, indicating that oral selexipag yields higher levels of active metabolite.[17] As a result, higher intravenous doses are required to achieve similar therapeutic effects.[17]

The elimination of selexipag and its active metabolite, ACT-333679, primarily occurs through biliary excretion. The inactivation of selexipag is mediated by oxidation and dealkylation reactions facilitated by cytochrome p450 enzymes, specifically CYP3A4 and CYP2C8.[16] Additionally, glucuronidation via UDP-glucuronosyltransferase 1A3 and UGT2B7 further prepares selexipag and its metabolites for excretion.[16]

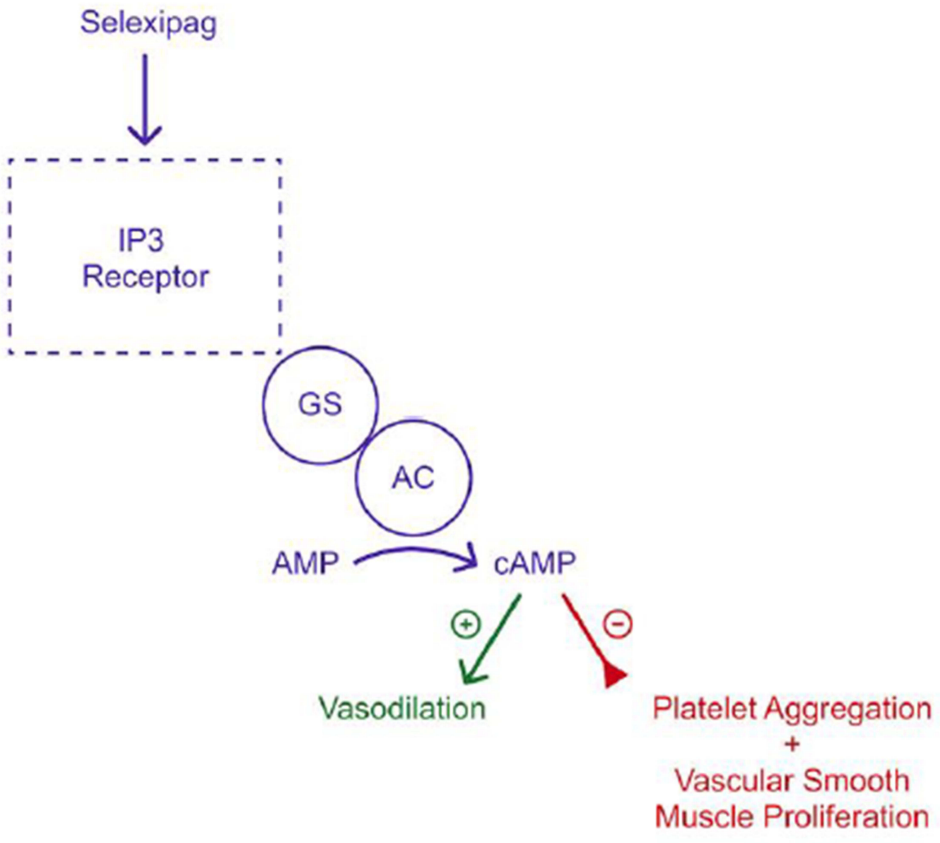

Figure 1 Mechanism of action of selexipag.
Abbreviations: IP3 Receptor, Inositol 1,4,5-trisphosphate receptor; GS, G alpha subunit of G protein-coupled receptor; AC, Adenylyl cyclase; AMP, Adenosine monophosphate; cAMP, Cyclic adenosine monophosphate; +, stimulatory; -, inhibitory.

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The half-life of selexipag is approximately 0.8 to 2.5 hours, while the active metabolite ACT-333679 has a half-life of 6.2 to 13.5 hours, reflecting its more prolonged activity in the body.[12] In a study of healthy male subjects, selexipag itself was not detectable in urine, but ACT-333679 was observed approximately 12 hours after administration.[6] Notably, the active metabolite was only detected in urine at doses of selexipag above 200 μg, with the amount of excreted ACT-333679 increasing proportionally with higher doses of the drug.[6]

Intravenous Selexipag Administration and Dosing

IV selexipag is safe to be administered via peripheral IV access for short-term administration.[10] IV infusions should be administered twice daily over a period of 80 minutes, using tubing that is protected from light and no filters.[12] Flushing the line may lead to accidental bolus of IV selexipag and may result in significant hypotension and side effects and should be avoided.[12] Once the selexipag vial has been completed, the infusion should be continued at the same rate with a 0.9% saline to ensure any remaining selexipag in the IV line is administered.[12]

IV selexipag dosage is determined by the patient's current oral selexipag dose.[12] According to a study on selexipag's bioavailability in healthy adult males, IV doses should be 12.5% higher than oral doses to achieve similar exposure to the active metabolite.[17] For example, a patient taking selexipag 1400 mcg twice a day should be transitioned to IV selexipag 1575 mcg starting 12 hours after the last oral dose, and then continued every 12 hours while unable to take oral selexipag.[12] Once the patient is able to resume oral therapy, IV selexipag use should be discontinued, and patients should return to oral tablets.[12]

The half-life of selexipag is 3–4 hours.[12] If a patient has not taken selexipag for under 12–20 hours (less than 4–5 half-lives), they may resume oral selexipag at their previous dose.[11] If it has been greater than 12–20 hours (greater than 4–5 half-lives), it is recommended to resume oral selexipag at a lower dose with re-titration up to the previously tolerated dose.[11] If selexipag has been withheld for more than one week, re-titration should begin at 200 μg BID and titrated up weekly to the previously tolerated maximal dose.[11] In transitioning between intravenous and oral selexipag, it is safe for patients to bypass re-titration and renew oral administration at the originally prescribed dose.[10,12] Commonly reported side effects of IV selexipag include headache, nausea, vomiting, infusion-site erythema, swelling, and pain.[12,17]

Clinical Trial Insights

In a Phase III clinical trial examining the safety and tolerability of transitioning between oral and IV selexipag, 20 patients with PAH received three IV selexipag infusions before returning to oral selexipag treatment.[10] The study included 16 females and 4 males, with an average age of 56.5 years. Among them, thirteen patients (65%) were classified as WHO functional class II, one patient as WHO functional class I, and six patients (30%) as WHO functional class III. Prior to study enrollment, these patients had been on stable oral selexipag doses, which were matched with corresponding IV dosages during the trial. The study confirmed that the IV and oral administrations provided comparable exposure to selexipag's active metabolite, indicating equivalent efficacy of the drug. All patients were also receiving at least one other oral PAH-specific therapy in addition to oral selexipag. The additional therapeutic methods used for these patients included 1 patient on a PDE5 inhibitor, 1 receiving sGC stimulation, 13 on an ERA/PDE-5 inhibitor, and 5 receiving both an ERA and a sGC stimulator.

During the study, there were 8 mild AEs, 5 moderate AEs, and 1 severe AE experienced by participants. Eight of those patients experienced at least one AE attributed to IV selexipag, primarily prostacyclin-associated effects or infusion site reactions. The most commonly reported AEs included headache (4 patients), infusion site erythema (2 patients), and peripheral edema (2 patients). However, both cases of peripheral edema were determined by the investigators to be unrelated to IV selexipag. Although there were no discontinuations of selexipag due to AEs, after re-initiation of oral selexipag, one patient with type II diabetes and cataracts developed retinal detachment and unilateral blindness. The authors of this study concluded the complication was related to the administration of selexipag. Additionally, another patient experienced right ventricular failure attributed to a respiratory infection. Throughout the study, there were no reported symptomatic blood pressure changes or adverse events related to hypotension. Moreover, there were no changes in the WHO functional class status for any of the patients, and there were no reports of mortality or treatment discontinuations.[10]

Safety and Contraindications to Selexipag

Regarding safety considerations, hepatic and renal function should also be considered prior to treatment with oral or IV selexipag.[4,19] For patients with mild-moderate hepatic impairment (Child-Pugh score A and B) or severe renal insufficiency (GFR 15–30 mL/min/m2), there is increased exposure to selexipag and its active metabolite, ACT-333,670.[16] For patients with moderate hepatic impairment, the recommended oral dose is 200 mcg once daily, with increases at weekly intervals by 200 mcg daily.[19] The highest tolerable dose for these patients is 1600 mcg.[4,19] Selexipag should be avoided in patients with severe liver impairment (Child-Pugh score C).[6,16]

Selexipag is contraindicated for use with strong CYP2C8 inhibitors, such as gemfibrozil, clopidogrel, deferasirox, and teriflunomide.[19] Studies of strong CYP2C8 inhibitors have been found to increase the concentration of selexipag's active metabolite and cause AEs with administration.[16,19] While concurrent use of selexipag with strong CYP2C8 inhibitors is not recommended, less potent inhibitors (such as clopidogrel) may be used if the selexipag dose is adjusted or reduced to once daily.[16,19]

In contrast, strong CYP2C8 inducers (such as rifampicin) decrease exposure to selexipag's active metabolite, and thus patients taking strong CYP2C8 inducers and selexipag are recommended to increase their twice daily dose of selexipag.[19] IV selexipag is not recommended for treatment escalation, long-term use, self-administration, or patients who have not previously used oral selexipag.[20]

Conclusion

For adult patients with PAH, intravenous (IV) selexipag offers a safe and tolerable temporary alternative to oral treatment.[10,12] Dosing for IV selexipag should be calculated in alignment with the patient's current oral dose, with the typical IV infusion involving twice daily administrations over an 80-minute period.[12] The most common AEs of IV selexipag usage are headache and infusion site reactions.[10] Results from the Phase III clinical trial indicate that the switch from oral to IV selexipag and back is well tolerated and safe for patients with PAH, although patients with underlying comorbidities should be monitored for more serious AEs upon re-initiation of oral selexipag.[10] The study was limited by a small sample size, with a study population of predominantly female patients (80%), limiting the generalizability of the study to a broader population of patients with PAH. Additionally, the short treatment duration of 12 days restricts the ability to assess the long-term safety and efficacy of IV selexipag, though it is primarily intended for short-term use. The study's open-label design also introduces the risk of reporting bias, as both patients and investigators were aware of the treatment being administered.[10]

Further research with larger clinical trials is needed to refine best practices for transitioning between oral and IV selexipag, ensuring safe and effective dosing protocols, and identifying which patient populations would benefit most from this temporary treatment option. Long-term studies may also be needed to monitor the safety of repeated transitions between oral and IV forms of selexipag. With these considerations, IV selexipag offers a valuable tool for maintaining therapeutic continuity in PAH management, particularly in situations where oral medication adherence is disrupted.

Disclosure

Dr. Lanier is on the speakers' bureau for Janssen Pharmaceuticals, the maker of selexipag and United Therapeutics. All other authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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