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REVIEW

Selexipag in the management of pulmonary arterial hypertension: an update

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Abstract: Selexipag is a compound that was designed to overcome the issues associated with oral administration of prostanoid compounds, beraprost and treprostinil in the treatment of pulmonary hypertension (PAH). As a selective IP agonist, it was designed to avoid the off-target prostanoid effects especially in the gastrointestinal system. To place this compound in context, this paper briefly reviews the efficacy, tolerability, and safety of subcutaneous, inhaled, and oral prostanoid preparations and comparesthemto selexipag. Selexipag is the first agent targeting a prostanoid receptor where a reduction in the primary efficacy morbidity/mortality composite end-point has been demonstrated. While safety outcomes favor selexipag over placebo, tolerability issues remain. Efficacy in terms of improvement in effort tolerance, hemodynamic and mortality benefit is less than seen with IV therapy. This is the first prostanoid demonstrated in a clinical trial to have added benefit in those on background double combination therapy and the first non IV prostanoid to demonstrate outcome benefit in the connective tissue disease (CTD) population in a randomized controlled trial.

Keywords: prostacyclin, prostaglandin, safety, tolerability, adverse events, efficacy

Pulmonary arterial hypertension (PAH)

PAH is a rare disorder and is characterized by the progressive obliteration of the small (50–200 μm) pulmonary arterioles due to the abnormal proliferation of all cell types within the vessel wall. This leads to an inexorable increase in the resistance to pulmonary blood flow, thereby increasing right ventricular workload and ultimately causing right heart failure and death.[1] The natural history of the untreated condition is short, with median survival varying from 1 year in scleroderma-associated PAH,[2] to 2.8 years for idiopathic PAH (IPAH),[3] but rather longer for congenital heart disease (CHD)-associated PAH.[1] Nonetheless, survival has more than doubled in recent cohorts, now being three or more years for SSc PAH[4,5] and more than 6 years for IPAH.[6] It is expected to increase further when early combination therapy is adopted.

Multiple drug therapies have been developed to combat three of the dysfunctional pathways that contribute to the pathogenesis of PAH, culminating in the reduced production of prostacyclin (PGI_2) and nitric oxide (NO) and the increased production of endothelin production (ET-1).[1]

PAH pathobiology and pharmacology

The etiology of PAH is believed to be driven by endothelial cell dysfunction. In addition, there is a clear genetic contribution in a significant proportion of those with IPAH, with single gene mutations, mainly autosomal dominant, being identified in

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approximately 25% patients in this subgroup.[7] In hereditary PAH (HPAH), the identified genetic abnormalities dominantly involve the transforming growth factor β pathway, while others include the two-pore domain potassium channel, TASK-1 (KCNK3) and genes involved in cellular osmotic control and in angiogenesis (AQP1 and SOX17).[7] While genetic abnormalities are clearly central, the reduced penetrance and relatively low prevalence observed, means that these must form part of a complex series of drivers leading to PAH. Guignabert and colleagues have proposed that genetic, epigenetic, and environmental factors can all contribute to the altered ion channel, growth factor, hormonal, and cytokine abnormalities required to drive PAH,[8] with a secondary reduction in NO and PGI_2 production and increased ET-1 production.[9] If correct, current therapeutic efforts must be regarded as purely palliative, targeting downstream consequences of the underlying pathobiological causative factors. There is abundant evidence that the immune system plays at least a contributory pathogenic role with altered cytokine production increasing inflammatory cell activation.[10,11] Furthermore, there is clear evidence of altered mitochondrial function increasing energy inefficiency while promoting resistance to apoptosis.[12]

Thus, there are many potential avenues to move treatment forward. To date, however, we continue to rely on the original 3 pathways identified over 20 years ago.[13] While it is clear that using these agents in a stepped fashion (adding additional therapies if the clinical and hemodynamic response is inadequate) has improved outcomes somewhat, the data are less than impressive. In the French registry, a 5.9 year 50% survival was reported.[14] In the COMPERA population, a 5.6-year survival among IPAH patients was reported.[15] In the UK national registry, average survival is less than 4 years for IPAH,[16] for reasons that have yet to be determined. In any event, it is clear that a reactive approach to managing deterioration is associated with poor outcomes in PAH.

Predicting outcomes

One major advance shown in analyses from the recent registries is in risk stratification. Individuals with multiple low-risk features clearly have an excellent survival, whether assessed at baseline or at follow-up.[14,15,17] The data clearly show that improvement from high or intermediate risk to low risk is associated with improved outcomes.[15] This provides a rational for targeting the early use of multiple therapies. In all three published registries, patients with IPAH have an excellent 5 years survival if low-risk features dominate, but poor survival if considered intermediate or at high risk.[14,15,17] It follows that we should maximize therapy even if clinical benefit is limited in patients that are not low risk on initial therapy.

Of the therapies based around promoting vasodilation, PGI_2 is considered the most important, and drug targeting of this pathway has been the subject of intense research, leading to a number of compounds together with different modes of administration. The first drug licensed for the treatment of PAH was epoprostenol (PGI_2), which remains the most efficacious therapy available and is the only drug that has been shown to improve survival in a randomized controlled trial1 It is, however, poorly tolerated and difficult to administer because of i.v. formulation.

Prostanoid synthesis and targets

Endogenous prostanoids are vasoactive lipid mediators derived from arachidonic acid that regulate the response of many homeostatic and stress response pathways such as vascular function, wound healing, and inflammation. The prostanoid family co-ordinates the responses of local cells to various physiological and pathological stimuli. This is achieved by co-ordinated synthesis and rapid metabolism of five different prostanoid family members, namely prostaglandin E_2, prostaglandin D_2, prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), prostaglandin I_2 (PGI_2), and thromboxane A_2 (TxA_2) that dominantly stimulate five equivalent receptor subtypes. Significant cross-talk is evident in these pathways. Thus, for example, epoprostenol (PGI_2) activates multiple cell surface receptors, the IP receptor causing vasodilation, EP_1, EP_3, and TP leading to vasoconstriction, while having almost no activity at other prostanoid receptors (EP_2, EP_4, DP_1, and FP receptor).[9,18] This complex system fine-tunes local responses to the prevailing conditions. The differential distribution of prostaglandin receptors facilitates different responses of particular vascular beds to various physiological and pathological stressors, with the dominance of the vasodilatory IP receptors and vasoconstrictive TP and EP_3 receptors in the lung arteries but vasodilatory IP, DP_1, and EP_4 receptors with vasoconstrictive TP and EP_1 receptors in the pulmonary veins. This allows for differential control of relaxation and vasoconstriction at each site depending on the dominant local paracrine prostaglandin environment.[19] Though the IP receptor is considered the most important target in the treatment of PAH, there is now data showing that EP_2 receptors are upregulated in PAH and may play an important role at inhibiting cell proliferation in human pulmonary arterial smooth

cells.[20] Selexipag as an IP agonist has no significant effect on the EP_2 receptor; treprostinil by contrast is a potent agonist of this receptor and also at the DP_1 receptor.[8]

Prostanoids and pulmonary arterial hypertension

Initial studies on the potential of epoprostenol as a pulmonary vasodilator were undertaken in the early 1980s[21] and evidence for a relative deficiency of PGI_2 in PAH was documented in the early 90s.[22] The pivotal trial published in 1996 demonstrated the substantial clinical and even mortality benefit with epoprostenol.[23] Tuder and colleagues subsequently reported in 1999 that PGI_2 synthase expression was reduced in PAH.[24] In the same year, initial descriptions of the prostanoid receptors were published.[25] The IP receptor (which is activated by PGI_2) has been the focus of the most recent efforts to improve the selectivity of prostanoid therapy in PAH. While epoprostenol remains the only therapy with a proven mortality benefit in PAH, the short half-life (3–5 mins) means that continuous ambulatory intravenous administration is necessary. This negatively affects the quality of life,[26] is associated with an ongoing risk of sepsis, and leaves patients vulnerable to rebound pulmonary hypertension if supply is interrupted even briefly. This has led to the search for more stable PGI_2 analogs that can be administered by less invasive routes. Iloprost and beraprost were among the first PGI_2 mimetics to be developed.

Iloprost administered by inhalation 6–9 times daily proved effective as monotherapy improving 6MWD by 36 m and doubled the frequency with which a reduction in functional class was observed.[27] Similar levels of benefit were demonstrated when inhaled iloprost was added to background bosentan therapy in one study,[28] but not in another.[29] The data suggest that the hemodynamic benefit is only seen at peak dose and is lost at trough levels. Long-term efficacy has been supported only by subgroup analysis (those remaining on therapy) in a monotherapy long-term extension trial but was absent when alternate advanced therapies like phosphodiesterase type 5 (PDE5) inhibitors or ET-1 receptor antagonists (ERAs) were permitted.[30,31]

The first oral prostanoid trial was undertaken using beraprost as a monotherapy which increased 6MWD by 25 m without an impact on functional class or time to clinical worsening.[32] Beraprost was also studied in a placebo-controlled trial of 12 months duration (the only controlled trial of this length among the early studies), unfortunately, this demonstrated that the early benefit was lost by 1 year;[33] thus, this agent has never been licensed in the United States or European Union, although it is licensed in Asia. A single isomer of beraprost (esuberaprost), in clinical development as an oral formulation, and assessed in the United States and Israel in a multi-center, double-blind, randomized, placebo-controlled, Phase 3 study with Tyvaso® (treprostinil inhalation solution) in PAH patients (BPS-314d-MR-PAH-302 or BEAT study),[34] has very recently been reported by United Therapeutics to fail to meet its primary endpoint of delayed time to first clinical worsening event.[34]

Treprostinil was first studied as a subcutaneous continuous infusion therapy, thus avoiding the risk of sepsis, and with the longer in vivo half-life (180–270 mins) of this agent, rebound pulmonary hypertension has proved less of an issue than with IV epoprostenol. While effective in terms of 6MWD (+16 m), the doses achieved in the pivotal trial were low because of the frequent occurrence of infusion site pain.[35] As centers have become experienced, escalation to more effective doses has been shown to be feasible, though the side effect burden remains high and it can take an average of 6 months to achieve a stable effective dose.[36] Treprostinil is also available as a 4 times daily inhalation therapy, with efficacy in terms of 6MWD (+19 m) and N-terminal pro-brain natriuretic peptide (NT-proBNP) in a population on background monotherapy with sildenafil or bosentan, although no improvement in time to clinical worsening was observed.[37] Treprostinil has also been studied as an oral preparation with significant benefit in terms of 6MWD (+23 m) shown in treatment-naive patients[38] but not when added to background therapy.[39] However, the recently completed Freedom-EV study has reported a 26% reduction in morbidity/mortality events in a large (690 patients) event-driven study in patients on background monotherapy.[40] Importantly, in this study, while mortality was equivalent during the randomized treatment phase, mortality is reported as being reduced by 37% up to end of study (including the open-label extension).[41] Details, in particular sensitivity analysis including the 11% in whom vital status was unknown at the end of the study and peer review of these data, are awaited.

The challenges faced in delivering equivalent doses of prostanoid orally compared to IV have been shown in a parenteral to oral transition study; the doses needed to achieve the required bioavailability (44 mg/d)[42] were substantially higher than achieved in the placebo-controlled studies (3.1 mg BID in the Freedom C study).[39] To achieve this, three times daily dosing of treprostinil was

required and almost all patients reported side effects, especially headaches and gastrointestinal upset.[42] Despite three times daily dosing, blood levels of treprostinil varied by more than two-fold at steady state. Treprostinil has subsequently been shown to be highly effective when administered via a totally implantable IV delivery system, although procedural complication rates still remain high.[43]

The issue for the easy administration of prostanoids therefore remains. Subcutaneous administration is associated with significant infusion site pain and inhaled administration cumbersome (15–20 mins, four to six times daily, between inhalation and device maintenance). Oral administration is dose-limited by side effects, assumed to be due in part to off-target effects,[44] though this view has recently been challenged,[45] and in part due to the short half-life resulting in a failure to achieve steady-state kinetics. This led to a search for a selective IP agonist with a longer half-life.

Selexipag pharmacology and pharmacokinetics

The development of a selective oral IP agonist was first reported in 2007, and in contrast to PGI_2 and its stable analogs, it was shown to have no binding activity at any other prostanoid receptor, including the EP_3 receptor.[46] Selexipag is a nonprostanoid prodrug, that is metabolized by the liver to an active metabolite {4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}acetic acid (ACT-333679; MRE-269), which has a 13-fold higher affinity at the IP receptor and a half-life of around 8 hrs. ACT-333679 has limited binding affinity to EP_2, EP_4, and DP_1 receptors (Ki≥2.6 μM), but nonetheless, these receptors may contribute to immunomodulatory off-target effects.[47] With twice-daily oral administration, steady state is achieved within 3 days; thus, in principle, this should lead to reduced side effects and convenient twice-daily oral administration.

The active metabolite of selexipag was shown to induce full relaxation of rat pulmonary artery rings contracted with either ET-1 or phenylephrine, and human pulmonary arteries precontracted with $PGF_{2\alpha}$.[48,49] By contrast, ACT-333679 has been reported as less effective than other prostanoids in human pulmonary arteries precontracted using phenylephrine or U46619 (thromboxane mimetic).[50] ACT-333679 has also been shown to act as a partial agonist of the IP receptor in respect of "upstream" effects, which it has been suggested may reduce tachyphylaxis, but could also explain differences in efficacy in some models.[51]

In the phase 1 study, single ascending dose and multiple ascending dose administration were evaluated in 64 subjects.[52] Single doses were tolerated up to 400 mg, but side effects (headache, nausea, vomiting) became frequent at higher doses[45] With multiple ascending dosing, 600 mg BD was tolerated and steady state was observed after 8 days with no accumulation, with the half-life of the metabolite at steady state, being around 12 hrs. Finally, side effects (as well as peak active metabolite concentration) were lessened by taking the drug with food. Analysis of the pharmacokinetics of selexipag and its main metabolite undertaken in the Griphon trial shows that at steady state the concentration of the main metabolite varies by 3-fold being around 10 ng/mL at trough to 30 ng/mL at peak dose effect. The bioavailability is reduced by approximately 30% in the presence of background ERAs and PDE5 inhibitors.[53]

The safety of selexipag administration has been studied in patients with hepatic and renal impairment.[54] Selexipag metabolites are largely excreted by the hepato-biliary route, after glucuronidation by UGT1A3 and UGT2B7; thus impaired liver function, as anticipated, affects pharmacokinetics. In this study, selexipag levels were more affected by hepatic impairment than the active metabolite levels, being about twice normal in moderate hepatic impairment, while levels were 4–5 times normal with a significantly longer half-life in severe hepatic impairment. On the basis of PK modeling, once-daily dosage was recommended in severe hepatic impairment (Child-Pugh C), but the usual uptitration regime in other circumstances. By contrast, in severe renal impairment (eGFR 15–30 mL/min), only modest changes in serum levels were observed, and while no adjustment is required, caution with dose titration is recommended (if eGFR <30 mL/min/1.73 m^2.

Selexipag is an inhibitor of CYP2C8 and CYP2C9 and induces CYP3A4 and CYP2C9 in vitro. Also, selexipag inhibits the transporters OATP1B1, OATP1B3, OAT1, OAT3, and BCRP. However, due to its relatively low unbound exposure at clinically used doses, selexipag has a low potential for causing drug–drug interactions.[55] As expected, selexipag has no effect on warfarin levels[56] and no significant interaction with the CYP3A4 metabolized midazolam.[57] The impact of other drugs on selexipag exposure has also been investigated. Strong inhibitors of CYP2C8 (eg, Gemfibrozil) significantly extend the half-life of the active metabolite so their co-administration is contraindicated, while the strong inducer of CYP2C8 (eg, rifampicin) shortens the half-life and thus may require more frequent administration of selexipag.[58] A study of the

impact of moderate CYP2C8 inducers (eg, Clopidogrel) on selexipag has been completed and results are awaited (NCT03496506). In the meantime, the SmPC (summary of products characteristics) guidance recommends dose modification or avoidance of co-administration.[59]

Hemodynamic efficacy of selexipag: phase 2 study

The proof of principle study was published by Simmoneau and colleagues.[60] This involved 43 patients with a 3:1 randomization, with 33 patients receiving selexipag and 10 placebo. Importantly, all patients were on background PDE5 inhibitor or ERA and 30% were on combination oral therapy. The maximum treatment dose (800 mcg BID) was achieved in 42% of those on selexipag and 90% randomized to placebo and this indicates that tolerance was less than hoped for. Typical prostanoid side effects dominated (due to the small study size, an increase in likelihood, as determined by odds ratio, was only significant for headache [OR=8; 95% CI: 1.5, 44.2], although an increased trend was also seen for extremity pain, nausea, and diarrhea). The burden of "prostanoid type" side effect profile was almost identical to that reported in the 12-week trial of oral beraprost.

Only 31 or 33 patients randomized to selexipag and 9 of 10 randomized to placebo completed the study. However, analysis of all treated patients (32 selexipag, 10 placebo) showed a significant hemodynamic benefit at 17 weeks (relative reduction in PVR of 33%; 95% CI −15% to −47%). Among placebo patients, PVR increased by 224±355 d.s.cm^{-5}, while PVR fell by 130±310 d.s.cm^{-5} among selexipag-treated patients. In the per protocol analysis (the primary endpoint analysis of the trial), the net benefit of selexipag was a 30% (95% CI −12 to −45%) relative reduction in PVR. Cardiac output increased by 0.5 l/min/m^2 (CI 0.13–0.83) and SVR fell by just over 100 d.s.cm^{-5} in the treated group, without any reduction in blood pressure. In this relatively small study, no significant effects were observed on the secondary endpoints (FC, NTproBNP, and 6WMD), but appropriate trends were noted.

The Griphon trial: phase 3

The event-driven outcome Griphon trial[61] is the largest trial ever undertaken in pulmonary hypertension. A total of 1156 patients were randomized 1:1 to selexipag or placebo, uptitrated to a maximum of 1600 mcg BiD over 12 weeks, and then followed until 331 primary endpoint events occurred. Selexipag was started at 200 mcg BD and increased at 200 mcg twice-daily increments until side effects were unmanageable, whereby the dose was then reduced by 200 mg BD and continued at this dose until 26 weeks. Further dose increases were then permitted as tolerated to the maximum dose (1600 mcg BD).

The primary endpoint was a composite of all-cause mortality, hospitalization for worsening PAH, the need for lung transplantation or balloon septostomy, the need for parenteral prostanoid therapy, or long-term oxygen or disease progression. The latter was defined by a 15% reduction from baseline of the 6MWD plus a fall in FC if FC 2 or 3 or the need for additional therapy (if FC 3 or 4 at baseline). As many of these components are subjective, a blinded endpoint committee had to validate each event. No mortality benefit was observed during the trial, as reported in the primary manuscript, death from any cause occurred in 3.1% of the placebo patients compared to 4.9% of those randomized to selexipag. This of course reflects only death as a first event, a subsequent analysis by the European Medicines Agency reported that all deaths up to end of study occurred in 14.3% of the placebo patients compared to 12.2% of the selexipag patients.[62] This contrasts to the reported improved survival in the Freedom-EV trial with treprostinil (when the open-label extension is included). Unfortunately, since there was no open-label extension period in the Griphon trial, we cannot know how additional therapy administered after a primary endpoint event occurred may have influenced subsequent survival in either population.

While the absence of a clear signal on mortality will remain a concern, we can make limited inferences from other data. Disease progression or death accounted for 82% of all primary endpoint events, and these are strongly associated with worsening prognosis.[63–66] A subsequent landmark analysis has shown that the occurrence of any non-fatal primary endpoint events as described in the Griphon trial was associated with an increased risk of death up to the end of the trial HR 4.48 (95% CI 2.98–6.73) if the event occurred before 3 months and HR 3.52 (95% CI 2.34–5.31) when analyzed for events occurring before 12 months.[67] We can therefore have a very high degree of confidence in the value of the primary endpoint as a marker of disease progression.

A total of 155 patients (27%) in the selexipag group and 242 patients (41.6%) in the placebo group had a primary endpoint event HR 0.6 (99% CI 0.46–0.78). A prespecified dose-based analysis showed no evidence of a dose-dependent effect: those on the lowest maintenance dose (200–400 mcg BD) had a hazard ratio of 0.6, medium

dose (600–1000 mcg BD) HR 0.53, and high dose (1200–1600 mcg BD) an HR of 0.64. The net benefit in terms of 6MWD was modest (+12 m 99% CI 1–24) and N-NT-proBNP levels fell significantly in the active treatment group when compared to placebo (−123 ng/L (95% CI −175 to −78)). Subgroup analysis showed no difference in effect, whether patients were taking background therapy (20.4% of the study population), monotherapy (47.1%), or combination background therapy (32.5%), and this finding was the same regardless of disease subtype, functional class, geographic location, and/or sex.

Adverse events in the Griphon trial

Typical prostanoid side effects were common in those randomized to selexipag,[61] with more than twice as many of those on active therapy reporting headache [OR=3.9; 95% CI: 3.0, 4.9], nausea [OR=2.2; 95% CI: 1.7, 2.9], vomiting [OR=2.4; 95% CI: 1.7, 3.4], extremity pain [OR=2.9; 95% CI: 1.6, 3.4], and myalgia and flushing [OR=2.6; 95% CI: 1.7, 4.1] when compared to those receiving placebo over the 12-month study period. Although of low frequency there was also an excess of hyperthyroidism (1.4% vs 0%, p=0.004) and anemia (8.3% vs 5.4%, p=0.05) in those receiving selexipag. Hyperthyroidism is also reported with epoprostenol[68] and may be due to action on membrane-bound prostanoid receptors in the thyroid gland. The reason for anemia is unclear but was unrelated to iron deficiency and was rarely serious (0.9%). Patients randomized to selexipag were also twice as likely as placebo patients to discontinue therapy because of adverse events (14.3% v 7.1%). However, serious adverse events were not more common, 43.8% of those taking selexipag and 47.1% of those randomized to placebo, and adverse events likely related to PAH were more common among placebo versus selexipag patients: worsening of PAH 35.7% vs 21.9%, dyspnea 21% vs 16%, and peripheral edema 18% vs 13.9%. This demonstrates that despite the selectivity of selexipag for the IP receptor, there has been little benefit in terms of reducing "off target" prostanoid adverse events as demonstrated in a recent meta-analysis.[45]

As a long-term outcome trial, it was possible to assess the differential rate of adverse events between the titration and maintenance phases of the Griphon trial; this showed that typical prostanoid side effects were much more common during the titration phase, but remained common even during the maintenance phase (when over 72% of the selexipag patients reported prostanoid-associated side effects compared to 46.9% of the placebo patients).

Subgroups of special interest

Background double combination therapy

There are two subgroups in whom the benefit of prostanoid therapy requires special attention. Those on background combination therapy and connective tissue disease (CTD)-associated PAH – where both oral and inhaled prostanoid therapies have failed to show added benefit in these populations.

Given the results of the Seraphin and Ambition trials, standard therapy is now a combination of a PDE5 inhibitor and either ambrisentan or macitentan[1] The results of the Freedom-EV trial[40,41] will now need to be put in context. Of note, similar post hoc analysis of the Ambition trial has also shown a mortality benefit of combination therapy with an ERA and PDE5 inhibitor,[69] and a similar but non-significant trend in the Seraphin trial[67] More detail from the Freedom-EV trial will obviously inform our choice of second-line therapy, but issues of tolerability and complex dose escalation regimes may also influence clinical behavior. As outlined earlier for both inhaled and oral prostanoid therapy, it has not to date been possible to demonstrate benefit when studied in populations on background double combination therapy.

In the Griphon trial, 376 patients were receiving background ERA and PDE5 inhibitor therapy, 179 in the selexipag arm, and 197 in the placebo arm.[70] These populations were well-matched approximately 80% female, mean age 51, dominantly IPAH (approximately 60% in each treatment arm). In this sub-study, patients receiving placebo were somewhat more likely to be enrolled in Western countries (54.1% vs 51.4%), had a shorter time from diagnosis (3.6 vs 4 years), and were more likely to have CTD-associated PAH (28.2% vs 22.3%). In this population on background double combination therapy, subgroup analysis revealed that selexipag reduced the risk of the primary endpoint by 37% (HR 0.63; 95% CI 0.44–0.90). As in the overall trial, the occurrence of death or hospitalization was reduced by 39% for selexipag versus placebo (HR 0.61; 95% CI 0.39–0.96). The proportion of patients reporting serious adverse events was numerically lower among those randomized to selexipag (44.7% vs 52.8%) when compared to those on placebo. While this is a retrospective analysis, this is the first time that an IP agonist has been associated with an improved outcome when added to background combination therapy.

A study to further explore the role of selexipag when added to background double combination therapy is underway.[71] The

TRITON (NCT02558231) evaluates the relative merits of initial combination therapy (macitentan and tadalafil + placebo) compared to upfront triple therapy (macitentan, tadalafil, and selexipag). The recruitment target of 238 patients has been reached and the primary endpoint is 6-month change in pulmonary vascular resistance. The trial will also provide further insights into safety, tolerability, disease progression, and impact on 6-min walk testing.

Connective tissue disease-associated PAH

The response of CTD PAH to specific therapies is notably worse in terms of clinical efficacy and outcome.[72] A meta-analysis of all phase 3 trials submitted to the FDA suggested that the benefit in CTD patients was significantly lower in terms of 6MWD than observed in the IPAH population, but the impact in terms of clinical worsening and mortality was non-significant.[73] Furthermore, the same authors reported that among the CTD population drug-associated side effects were significantly higher when compared to IPAH.[74]

The Griphon trial included 334 patients with CTD PAH, of whom 170 had scleroderma-associated PAH, with half were randomized to selexipag and half to placebo.[75] As expected, CTD patients were older, more likely to be female, and had a shorter history of PAH when compared to the overall trial population. SScPAH was associated with a worse baseline function and higher event rate compared to the overall population. Dosing achieved was identical to that in the overall population with 24% on the low dose (400 mcg BD or less), 27% on the medium dose, and 45% on the high dose (1,200 mcg BD or more).[61]

While there were no significant differences between the populations, those receiving selexipag were numerically more likely to be female (93% vs 87%), had a longer baseline 6MWD (354 m vs 334 m) and fewer were on background double combination therapy (24% vs 33%). In addition, fewer patients randomized to selexipag had a diagnosis of SScPAH (77 vs 93). Although the groups were not entirely comparable, nevertheless, the net benefit for the CTD population was a 41% reduction in events (HR 0.59; 95% CI 0.41–0.85), with a similar level of net benefit among those with SScPAH (HR 0.56; 95% CI 0.34–0.91)[75] As in the overall population, disease progression and hospitalization accounted for the majority of events (80.2%). The impact on 6MWD and NT-proBNP was the same as in the overall population (+12 m and −140 ng/L, respectively).

Tolerability might be expected to be a problem in this population especially as most patients were on background therapy; however, the reporting of serious adverse events was numerically lower among those randomized to selexipag (48% vs 52%). Though discontinuations were more common in this population 19.2% compared to 14.3% in the overall population randomized to selexipag, this was driven by standard prostanoid side effects (headache, nausea, and vomiting) to which CTD patients are more sensitive. The difference in discontinuation rates between those on active treatment compared to placebo was similar to the whole population (9.1% CTD vs 7.2% whole study population), indicating equivalent tolerance of added therapy[75]

Conclusion

Selexipag represents a major step forward in terms of designing a molecule to target a specific aspect of the prostacyclin pathway, namely the IP receptor, whether the is the only receptor that should be targeted is as yet unresolved. Furthermore, the Griphon trial provides clear evidence of the ability of this agent to reduce disease progression at each tolerated dose, in all population subgroups and in the presence of optimal background therapy. Nevertheless, this has not sorted the issue of tolerability seen with prostanoids, though the pharmacodynamic data may suggest that more frequent drug dosing could help smooth the dose–response curve and lessen side effect burden. Finally, the recent long-term outcome data with treprostinil will need to be compared carefully with the results of the Griphon trial to determine the precise clinical role of IP agonists versus other PG mimetics in the clinical armamentarium.

Disclosure

Dr JG Coghlan has received grants from Actelion Ltd; honoraria and consultancy fees from GSK, United Therapeutics, Pfizer and Actelion Ltd. Professor LH Clapp has received grants from United Therapeutics and Lung Biotechnology and received consultancy fees from United Therapeutics and Arena Pharmaceuticals. Professor LH Clapp has a patent WO2018089804 issued. The authors report no other conflicts of interest in this work.

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