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Temporary treatment interruptions with oral selexipag in pulmonary arterial hypertension: Insights from the Prostacyclin (PGI_2) Receptor Agonist in Pulmonary Arterial Hypertension (GRIPHON) study

Ioana R. Preston, MD,[a] Richard N. Channick, MD,[b] Kelly Chin, MD,[c] Lilla Di Scala, PhD,[d] Harrison W. Farber, MD,[e] Sean Gaine, MD,[f] Nazzareno Galiè, MD,[g] Hossein-Ardeschir Ghofrani, MD,[h,i] Marius M. Hoeper, MD,[j] Irene M. Lang, MD,[k] Vallerie V. McLaughlin, MD,[l] Ralph Preiss, MD,[d] Gérald Simonneau, MD,[m] Olivier Sitbon, MD,[m] Victor F. Tapson, MD,[n] and Lewis J. Rubin, MD[o]

From the [a]Pulmonary, Critical Care, and Sleep Division, Tufts Medical Center, Boston, Massachusetts; [b]Pulmonary and Critical Care, Massachusetts General Hospital, Boston, Massachusetts; [c]Pulmonary and Critical Care Division, University of Texas Southwestern Medical Center, Dallas, Texas; [d]Actelion Pharmaceuticals Ltd, Allschwil, Switzerland; [e]The Pulmonary Center, Boston University School of Medicine, Boston, Massachusetts; [f]National Pulmonary Hypertension Unit, Mater Misericordiae Hospital, Dublin, Ireland; [g]Department of Experimental, Diagnostic and Specialty Medicine, Bologna University Hospital, Bologna, Italy; [h]Department of Internal Medicine, University of Giessen and Marburg Lung Center, Giessen, Germany, member of the German Center of Lung Research, Giessen, Germany; [i]Department of Medicine, Imperial College London, London, United Kingdom; [j]Department of Respiratory Medicine, Hannover Medical School, Hannover, member of the German Center of Lung Research, Giessen, Germany; [k]Department of Internal Medicine II, Medical University of Vienna, Vienna, Austria; [l]Division of Cardiovascular Medicine, University of Michigan Health System, Ann Arbor, Michigan; [m]Faculté de Médecine, Hôpital Universitaire de Bicêtre, Université Paris-Sud, Le Kremlin Bicêtre, France; [n]Center for Pulmonary Vascular Diseases and Venous Thromboembolism, Cedars-Sinai Medical Center, Los Angeles, California; and the [o]Department of Medicine, University of California, San Diego Medical School, San Diego, California.

KEYWORDS:
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BACKGROUND: Parenteral prostacyclin analogs that target the prostacyclin pathway have been used to treat pulmonary arterial hypertension (PAH) since the 1990s. Abrupt discontinuation of parenteral prostacyclin analogs can be associated with acute deterioration of PAH. Less is known about temporary interruption of oral therapies that target the prostacyclin pathway, such as selexipag.

METHODS: We evaluated the frequency, duration, reasons, and consequences of temporary selexipag interruptions among PAH patients enrolled in the Prostacyclin (PGI_2) Receptor Agonist in Pulmonary Arterial Hypertension (GRIPHON) study. In GRIPHON, patients were randomized to selexipag or placebo and titrated to an individualized highest tolerated dose (200 to 1,600 μg twice daily) over 12 weeks, after which patients entered the maintenance phase. Treatment interruptions were allowed; if the interruption was < 3 days,

Reprint requests: Ioana R. Preston, MD, Pulmonary, Critical Care and Sleep Division, Tufts Medical Center, 750 Washington St, Boston, MA, 02111, USA. Telephone: +1 617 636 7609.

E-mail address: ipreston@tuftsmedicalcenter.org

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treatment was restarted at the previous highest tolerated dose; if the interruption was ≥ 3 days, retitration from 200 μg twice daily was required. Descriptive analyses were performed.

RESULTS: At least 1 treatment interruption occurred in 111 of 574 patients (19.3%) in the selexipag group and in 58 of 582 (10.0%) in the placebo group. Baseline characteristics were similar between patients with and without an interruption. Of the 111 patients in whom selexipag was temporarily interrupted, 94 (85%) were receiving background PAH therapy. Adverse events were the most common reason for selexipag interruption. Selexipag interruptions and reinstitution of treatment were well tolerated. There were no episodes of acute deterioration during treatment interruption.

CONCLUSIONS: Based on observations from GRIPHON, selexipag interruptions can be expected in clinical practice. However, temporarily interrupting selexipag was well tolerated and manageable.

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The prostacyclin pathway plays an important role in the pathogenesis of pulmonary arterial hypertension (PAH).[1] Prostacyclin levels are reduced in PAH,[1] and deficient prostacyclin signaling contributes to vasoconstriction and cell proliferation in the lung vasculature.[2] As a consequence, several PAH therapies that aim to restore the prostacyclin pathway have been developed.[3] These include replacement therapies that are administered via continuous intravenous or subcutaneous infusion,[4] inhalation,[3] or oral route.[3]

Although parenteral prostacyclin analogs are important in PAH management, they are associated with limitations, including the risk for acute deterioration of PAH symptoms, leading to rapid decompensation if therapy is interrupted.[5–7] Treatment interruptions can occur as a result of problems with the drug delivery system, such as pump malfunctions, or dislocation of the central venous catheter used for intravenous administration.[7–9] Even short interruptions of intravenous therapy can place patients at risk for rapid decompensation,[10] and on rare occasions, treatment interruption has resulted in death from acute pulmonary hypertensive crisis.[11,12]

To circumvent the disadvantages associated with parenteral therapies and the short half-life of prostacyclin analogs, a new oral, selective prostacyclin receptor (IP receptor) agonist, selexipag, has been developed.[13] In the long-term Phase III study Prostacyclin (PGI_2) Receptor Agonist in Pulmonary Arterial Hypertension (GRIPHON),[13] selexipag reduced the risk for the primary composite end point of morbidity/mortality by 40% compared with placebo (hazard ratio, 0.60; 99% confidence interval, 0.46–0.78; $p < 0.001$).[13] However, experience with temporary discontinuation of selexipag is limited, and there are no published data on the effect of such interruptions on the safety of patients with PAH. Nevertheless, it is important that the possible risks associated with selexipag interruptions are recognized. We addressed this by investigating the frequency, duration, reasons, and consequences of interruption in selexipag treatment during GRIPHON.

Methods

Study Design

GRIPHON was a global, double-blind, randomized, event-driven, Phase III study and has previously been described.[13] The study was registered on the www.clinicaltrials.gov website (NCT01106014). The primary composite end point was the time from randomization to first morbidity/mortality event up to the end of double-blind treatment. All primary end point events were adjudicated by a blinded independent critical event committee.

Patients were randomized (1:1) to receive placebo or selexipag.[13] During a 12-week titration phase, the study drug was initiated at 200 μg twice daily and titrated weekly in increments of 200 μg twice daily up to the highest tolerated dose or to a maximum of 1,600 μg twice daily.[13] The dose was increased until unmanageable adverse events associated with prostacyclin use developed and was then decreased by 200 μg twice daily to reach the highest tolerated dose for that patient.[13] After 12 weeks, patients entered the maintenance phase and continued treatment until the end of study (for patients who did not have a primary end point event), occurrence of a primary end point event, or premature discontinuation.[13] End of study was achieved when 331 primary end point events had occurred.[13] Study treatment could be interrupted or permanently discontinued if it was in the patient's best interests or for administrative reasons. If treatment was interrupted for < 3 days, selexipag could be reintroduced at the highest tolerated dose achieved before the interruption. If treatment was interrupted for ≥ 3 days, subsequent retitration from 200 μg twice daily was required.

The study was conducted in accordance with the amended Declaration of Helsinki, and local Institutional Review Boards or independent Ethics Committees approved the protocol.

Study patients

Patients were aged 18 to 75 years with PAH diagnosed by right heart catheterization.[13] Patients were required to have a pulmonary vascular resistance of at least 5 Wood units (400 dyn · sec · cm^{-5}) and a 6-minute walk distance of 50 to 450 m.[13] Patients were treatment naïve or were receiving an endothelin receptor antagonist, a phosphodiesterase type 5 inhibitor, or both, at a dose that had been stable for at least 3 months.[13] All patients provided written informed consent.

Outcome measures and statistical analyses

Exploratory post hoc analyses were performed to determine the frequency and duration of treatment interruptions, with the primary source of information being the study drug log. The reason for treatment interruptions and, when reported, the corresponding adverse events leading to an interruption are summarized. The safety of treatment interruptions was studied by assessing adverse events that occurred during the interruption (defined as adverse events that started from the day after the last day of treatment up to 14 days or up to 1 day before restart for interruptions ≤ 14 days).