A team-based patient engagement approach to selexipag initiation and maintenance in pulmonary arterial hypertension (TEAM PAH): Interim analysis of a real-world retrospective study

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Introduction

- Pulmonary arterial hypertension (PAH) is a complex disease that leads to progressive right ventricular failure[1]
- Selexipag is an oral prostacyclin receptor agonist that delays disease progression and reduces the risk of hospitalization for PAH (GRIPHON trial)[2,3]
- Selexipag is initiated at 200 µg twice daily and titrated in 200 µg dose increments, usually weekly, to an individualized maintenance dose (IMD)[3]
  - Side effects associated with the prostacyclin pathway occur more frequently during the dose adjustment phase when the incremental dose increase is the highest
- Drug titration and maintenance can be hindered by side effects common to prostacyclin pathway agents, highlighting the need for multidisciplinary collaboration, frequent patient contact, and individualized dosing[4]

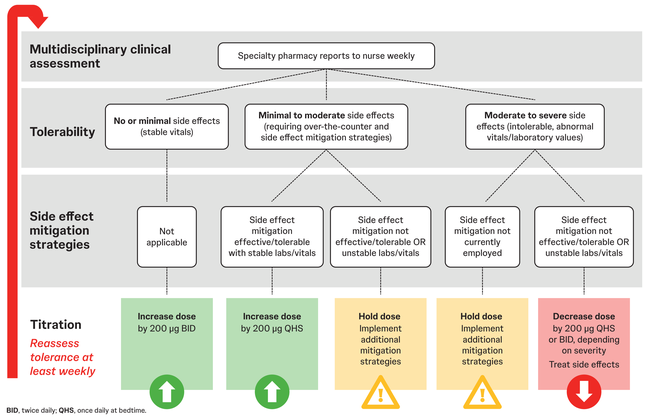
Objective

- To describe real-world oral selexipag dosing patterns and persistence at an expert center in California, USA, that uses a site-specific, multidisciplinary, nurse-directed protocol (RN-protocol)

Methods

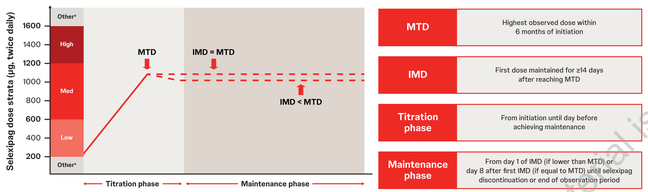
- This was a retrospective chart review of patients with PAH initiated on oral selexipag between January 1, 2018, and March 31, 2023, at a single center that employs an RN-protocol entailing frequent follow-up to individually manage side effects and tailor selexipag titration (**Figure 1**)
- Dosing patterns and persistence were reported during follow-up, which spanned from selexipag initiation (i.e., the index date) to the earliest of 14 months after index, the last assessment, lung transplant, or death
- Study definitions for titration and dosing were adapted from SelexiPag: tHe usErs dRug rEgistry (SPHERE)[5] (**Figure 2**)
- Statistical analysis was conducted as follows:
  - Patient characteristics and dosing patterns were summarized using descriptive statistics
  - Kaplan–Meier analysis was used to describe time to maintenance and persistence
  - Factors associated with selexipag discontinuation were identified via Cox regression analysis

Figure 1. Multidisciplinary, nurse-directed protocol (RN-protocol) for selexipag titration



BID, twice daily; **QHS**, once daily at bedtime.

Figure 2. Study definitions adapted from SPHERE[5]



MTD	Highest observed dose within 6 months of initiation
IMD	First dose maintained for ≥14 days after reaching MTD
Titration phase	From initiation until day before achieving maintenance
Maintenance phase	From day 1 of IMD (if lower than MTD) or day 8 after first IMD (if equal to MTD) until selexipag discontinuation or end of observation period

*The 'other' dose category includes doses <200 or >1600 µg.
BID, twice daily; **IMD**, individualized maintenance dose; **Med**, medium; **MTD**, maximum tolerated dose; **SPHERE**, SelexiPag: tHe usErs dRug rEgistry.

Results

Baseline characteristics

- This was an interim analysis of 120 patients (final target is 200 patients) (**Figure 3**)

Figure 3. Baseline demographic and clinical characteristics

Study population	Race/ethnicity[a]	PAH[a]	Comorbidities[a]
120 patients	54% White	Drug/toxin induced[b] 47%	Hypertension 34%
66% female	17% Hispanic/Latino	Idiopathic 17%	Obstructive sleep apnea 33%
	11% Asian	CTD 8%	Obesity 22%
Median age 51 years	8% Black/African American	51% WHO FC III/IV PAH	47% had a history of methamphetamine use
		Median 1.3 years from diagnosis[c]	

8% transitioned from other PPA → oral selexipag

71% received triple therapy (selexipag + ERA + PDE5i)

[a]Categories shown for race/ethnicity, PAH etiology, and comorbidities represent the most common and are not mutually exclusive. [b]Drug- or toxin-induced etiology included drugs such as methamphetamine and fenfluramine/phentermine. [c]Diagnosis date was unknown for 24% of patients. **CTD**, connective tissue disease; **ERA**, endothelin receptor antagonist; **PAH**, pulmonary arterial hypertension; **PDE5i**, phosphodiesterase type 5 inhibitor; **PPA**, prostacyclin pathway agent; **WHO FC**, World Health Organization functional class.

Oral selexipag dosing patterns

- Over a median period of 14 months, 104/120 (87%) patients achieved maintenance (median IMD, 800 µg twice daily), with relatively even distribution across low-, medium-, and high-dose strata (**Table 1**)
- Patients had a mean of 3.1 dose escalations and 0.3 step-downs during titration
  - Dose adjustments continued into the maintenance period, with a mean of 1.9 dose escalations and 1.1 step-downs for patients after reaching their IMD
- During titration, there was substantial variability among patients in the time between dose escalations (median, 14.7 days [interquartile range, 10.0–23.0])

Table 1. Oral selexipag dosing patterns during the titration and maintenance phases

Dosing pattern	Titration phase (n=120)	Maintenance phase (n=104)
Selexipag dose strata, n (%)[a]	MTD	IMD
Low (200 to <600 µg twice daily)	28 (23%)	26 (25%)
Medium (600 to <1200 µg twice daily)	46 (38%)	37 (36%)
High (1200–1600 µg twice daily)	41 (34%)	37 (36%)
Other (<200 or >1600 µg twice daily)	5 (4%)	4 (4%)
No. of dose escalations		
Mean [median] (IQR)	3.1 [3.0] (1.0–5.0)	1.9 [1.0] (1.0–3.0)
Patients with ≥2 dose escalations, n (%)	103 (86%)	93 (89%)
Time between dose escalations, days		
Mean [median] (IQR)	18.5 [14.7] (10.0–23.0)	59.1 [43.4] (19.0–81.3)
No. of step-downs		
Mean [median] (IQR)	0.3 [0.0] (0.0–0.0)	1.1 [1.0] (0.0–2.0)
Patients with ≥2 step-downs, n (%)	6 (5%)	28 (27%)
Time between step-downs, days		
Mean [median] (IQR)	55.5 [52.0] (26.0–73.0)	116.3 [92.0] (58.6–157.8)
Patients who discontinued selexipag, n (%)[b]	14 (12%)	16 (15%)

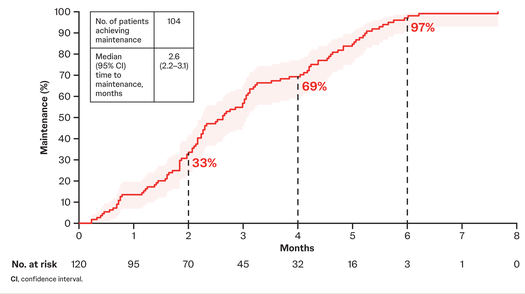
[a]MTD is reported for the titration phase and IMD for the maintenance phase. [b]Two patients died during the titration phase and therefore did not reach maintenance.
IMD, individualized maintenance dose; **IQR**, interquartile range; **MTD**, maximum tolerated dose.

- Median time to maintenance based on Kaplan–Meier analysis was 2.6 months (95% confidence interval, 2.2–3.1) (**Figure 4**)

Oral selexipag persistence

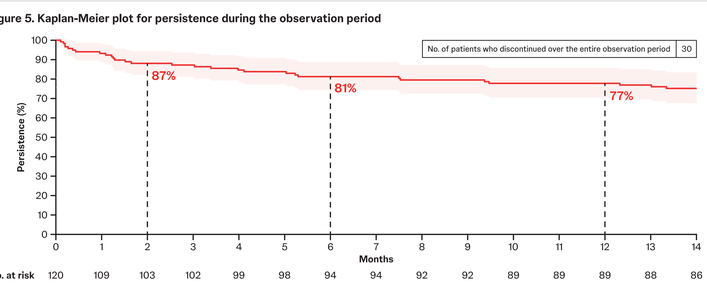
- Persistence was 87% at month 2 and 77% at month 12 in the overall sample (**Figure 5**)
- The highest rate of discontinuation occurred within 2 months of treatment initiation, and most discontinuations were due to an inability to tolerate treatment
- In the titration and maintenance phases, 80% and 81% of patients experienced adverse events (AEs) respectively, with 22% and 30% experiencing severe AEs in each of these respective phases
- The most common AEs were headache (62%), nausea (38%), muscle pain (36%), and diarrhea (32%)

Figure 4. Kaplan–Meier plot for time to maintenance



CI, confidence interval.

Figure 5. Kaplan-Meier plot for persistence during the observation period



- Compared with patients who continued treatment, a higher proportion of those who discontinued had World Health Organization functional class III/IV PAH and chronic obstructive pulmonary disease at initiation; they were also more likely to have AEs that were categorized as severe while using selexipag (**Table 2**)

Table 2. Factors associated with oral selexipag discontinuation

Parameter	Patients who discontinued selexipag (n=30)	Patients who did not discontinue selexipag (n=90)	Hazard ratio (95% CI)[a]	*P* value[a]
WHO FC III/IV PAH at initiation, n (%)	22 (73%)	39 (43%)	3.7 (1.6–8.4)	<0.01
COPD at initiation, n (%)	6 (20%)	7 (8%)	3.4 (1.3–8.8)	<0.05
No. of different AEs				
Mean [Median] (IQR)	2.1 [2.0] (1.0–3.0)	2.8 [3.0] (1.3–4.0)	0.6 (0.4–0.8)	<0.001
Severe AEs, n (%)	17 (57%)	30 (33%)	3.7 (1.6–8.5)	<0.01

[a]Cox proportional hazards backward selection model fit to identify demographic and clinical characteristics associated with oral selexipag discontinuation during the entire observation period. Variables identified as statistically significant ($P<0.05$) are reported. **AE**, adverse event; **CI**, confidence interval; **COPD**, chronic obstructive pulmonary disease; **IQR**, interquartile range; **PAH**, pulmonary arterial hypertension; **WHO FC**, World Health Organization functional class.

Limitations

- Due to the retrospective study design, analysis relied on routinely collected clinical data and a number of patients had missing data of interest (e.g., risk parameters)
- The study findings may not be generalizable to patients with PAH outside of this expert center in California

Conclusions

- A site-specific, multidisciplinary, nurse-directed protocol enabled the majority (~80%) of patients who initiated oral selexipag to reach their IMD and remain on treatment
- Real-world experience of successful dose titration was often >2 weeks between doses, which is longer than protocolized in the GRIPHON trial[2]
  - AEs and dose adjustments were common even after achieving maintenance
- Consistent with the findings from GRIPHON, median IMD was 800 µg twice daily, indicating that titration to higher doses of selexipag is not always necessary to achieve a tolerable therapeutic dose
- Findings suggest that a slower titration schedule, with side effect mitigation and dose adjustments beyond titration, may promote persistence
- Most discontinuations occurred within 2 months of treatment initiation, highlighting the importance of greater clinical engagement in the early stages of selexipag treatment

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