Characteristics, treatment patterns and outcomes of pulmonary arterial hypertension patients by ethnicity: real-world data from the combined OPUS/OrPHeUS studies

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Introduction

- According to 2020 US Census data, 18.7% of the US population identify as Hispanic/Latino[1]. However, there is an under-representation of Hispanic/Latino ethnic minorities in most pulmonary arterial hypertension (PAH) clinical studies; out of 18 major PAH randomized controlled trials, ethnicity data were reported in only 3, with Hispanic/Latino patients on average comprising 12%[2]. Overall, data on the safety and efficacy of PAH-specific therapies in these populations are scarce[3].
- Differences between ethnic minority groups in the prevalence of PAH subtypes, disease severity and outcomes have been described, which may mean that underrepresented minority groups have different patient journeys[4-6].
  - Differences in treatment patterns have been suggested between racial and ethnic groups; in a recent US study, Hispanic patients (of whom 99% were White) were less likely to be treated with PAH-specific therapy than non-Hispanic White or Black/African American patients, even after adjustment for PAH etiology[5].
- The OPsumit® USers registry (OPUS) and OPsumit® Historical USers cohort (OrPHeUS) captured real-world data on patients newly initiated on the endothelin receptor antagonist macitentan in the United States and comprises a larger proportion of racial and ethnic minorities than is typically seen in clinical trials[7].

Objective

- This analysis describes patient characteristics, treatment patterns, safety, and outcomes in patients with PAH by ethnicity (Hispanic/Latino or not Hispanic/Latino) in the combined OPUS/OrPHeUS dataset.

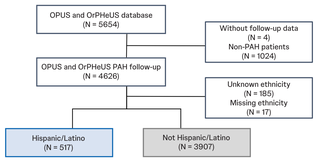
Methods

- OPUS was a prospective, observational drug registry (Apr 2014–Jun 2020; NCT02126943) and OrPHeUS was a retrospective medical chart review (Oct 2013–Mar 2017; NCT03197688)[7] of patients newly initiating macitentan.
- Patients enrolled in OPUS were not allowed to participate in OrPHeUS.
- In OPUS and OrPHeUS, information was collected per routine clinical practice and no assessments were mandated. Ethnicity was collected in the electronic case report form as 'Hispanic/Latino' or 'Not Hispanic/Latino'.
- All analyses were descriptive; no comparative analyses were performed.

Results

Baseline Characteristics

Figure 1: Patient disposition



155 sites contributed to the combined OPUS and OrPHeUS database. Patients with unknown or missing ethnicity were excluded from these analyses. PAH: pulmonary arterial hypertension.

- Of the 4626 patients with PAH in OPUS/OrPHeUS, 11.2% were Hispanic/Latino

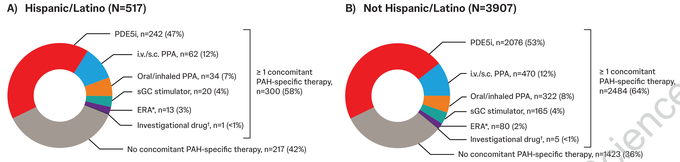
Table 1: Patient demographics and characteristics at macitentan initiation

	Hispanic/Latino N=517	Not Hispanic/Latino N=3907
Age at diagnosis – years; median (Q1, Q3)	53 (39, 63)	60 (48, 70)
Female sex – n (%)	403 (77.9)	2939 (75.2)
Race – n (%)		
White	378 (73.1)	2991 (76.6)
Black or African American	10 (1.9)	703 (18.0)
Other*	119 (23.0)	204 (5.2)
Missing	10 (1.9)	9 (0.2)
Time from diagnosis – n (%)	**503 (97.3)**	**3813 (97.6)**
Months; median (Q1, Q3)	6.9 (1.1, 38.7)	7.9 (1.4, 40.3)
≤6 months before macitentan initiation (incident) – n (%)	246 (48.9)	1750 (45.9)
PAH etiology – n (%)		
Idiopathic PAH	252 (48.7)	2168 (55.5)
Heritable PAH	4 (0.8)	59 (1.5)
Drug- and toxin-induced PAH	26 (5.0)	192 (4.9)
Associated PAH:		
Connective tissue disease	129 (25.0)	1062 (27.2)
HIV infection	3 (0.6)	34 (0.9)
Portal hypertension	32 (6.2)	156 (4.0)
Congenital heart disease	66 (12.8)	206 (5.3)
Other†	5 (1.0)	15 (0.4)
Relevant medical history‡ – n (%)		
Hypertension	239 (46.2)	1959 (50.1)
Obesity (BMI ≥30 kg/m²)	177 (34.2)	1142 (29.2)
Diabetes mellitus	110 (21.3)	899 (23.0)
Hepatic comorbidities	98 (19.0)	559 (14.3)
Edema	56 (10.8)	830 (21.2)
Anemia	60 (11.6)	633 (16.2)
Renal insufficiency	26 (5.0)	454 (11.6)
Other prescribed therapies – n (%)		
Diuretic therapy	260 (50.3)	2290 (58.6)
Oxygen therapy	140 (27.1)	1454 (37.2)
Anticoagulant therapy	122 (23.6)	1074 (27.5)
Calcium channel blocker therapy	63 (12.2)	601 (15.4)

Percentages may not add up to 100% due to rounding. *Includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander or Other. †Includes pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis or persistent pulmonary hypertension of the newborn. ‡At or before macitentan initiation. BMI: body mass index; HIV: human immunodeficiency virus; PAH: pulmonary arterial hypertension; Q1, Q3: interquartile range.

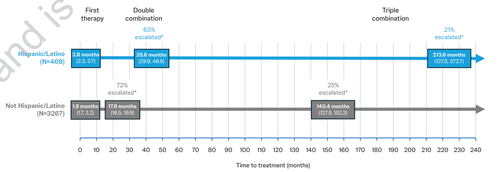
Treatment Patterns

Figure 3: PAH-specific therapies at macitentan initiation



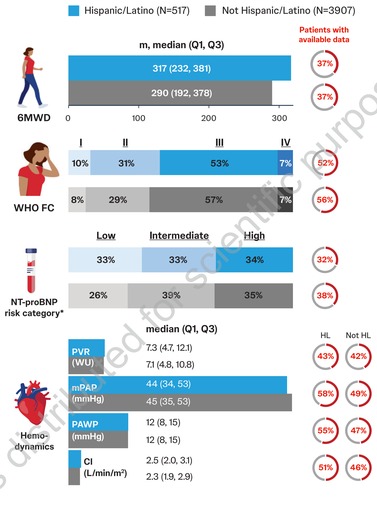
Patients could receive more than one type of concomitant therapy. *Other ERA can be the result of the entry of the same end date/start date for previous/current therapies, or due to imputation of one or both of the dates. †Only in OrPHeUS. ERA: endothelin receptor antagonist; i.v./s.c.: intravenous/subcutaneous; PAH: pulmonary arterial hypertension; PDE5i: phosphodiesterase 5 inhibitor; PPA: prostacyclin pathway agent; sGC: soluble guanylate cyclase.

Figure 4: Median time from diagnosis to PAH-specific therapy – Kaplan-Meier estimates (95% CL)



Patients with an incomplete date of diagnosis, or a diagnosis date after the date of initiation of first PAH therapy were excluded from these analyses. *Calculated as number of patients with event over entire observation period/total number of patients. CL: confidence limit. PAH: pulmonary arterial hypertension.

Figure 2: Baseline disease characteristics



*Low: BNP <50 ng/L, NT-proBNP <300 ng/L; Intermediate: BNP 50-300 ng/L, NT-proBNP 300-1400 ng/L; High: BNP >300 ng/L, NT-proBNP >1400 ng/L[1,2]. 6MWD: 6-minute walk distance; BNP: brain natriuretic peptide; CI: cardiac index; HL: Hispanic/Latino; mPAP: mean pulmonary arterial pressure; NT-proBNP: N-terminal proBNP; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; Q1, Q3: interquartile range; WHO FC: World Health Organization functional class; WU: Wood Units.

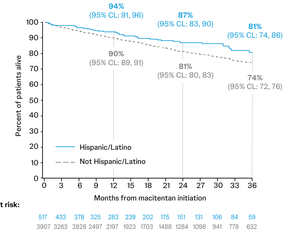
Safety and Outcomes

Table 2: Adverse events and discontinuations (OPUS only)

	Hispanic/Latino N=274	Not Hispanic/Latino N=1980
Exposure to macitentan (OPUS/OrPHeUS) – months; median (Q1, Q3)	**13.1 (5.5, 26.8)**	**14.6 (5.1, 29.5)**
Patients with ≥1 AE – n (%)	**204 (74.5)**	**1613 (81.5)**
Most common (>10%) AEs by Preferred Term – n (%)		
Dyspnea	42 (15.3)	481 (24.3)
Headache	40 (14.6)	235 (11.9)
Peripheral edema	24 (8.8)	217 (11.0)
Nausea	23 (8.4)	209 (10.6)
Patients with ≥1 SAE – n (%)	**119 (43.4)**	**1051 (53.1)**
Most common (>5%) SAEs by Preferred Term – n (%)		
Dyspnea	26 (9.5)	291 (14.7)
Pneumonia	12 (4.4)	152 (7.7)
Hypoxia	6 (2.2)	109 (5.5)
Respiratory failure	10 (3.6)	104 (5.3)
Acute respiratory failure	2 (0.7)	106 (5.4)
Anemia	5 (1.8)	101 (5.1)
Patients with ≥1 AESI		
Edema events – n (%)	71 (25.9)	573 (28.9)
Anemia/hemoglobin decrease events – n (%)	11 (4.0)	222 (11.2)
Hepatic events (OPUS/OrPHeUS) – n/N (%)	37/517 (7.2)	235/3907 (6.0)
Patients discontinuing macitentan (OPUS/OrPHeUS) – n/N (%)		
Due to an AE	77/517 (14.9)	721/3907 (18.5)
Due to another reason	124/517 (24.0)	685/3907 (17.5)
Missing reason	27/517 (5.2)	283/3907 (7.2)

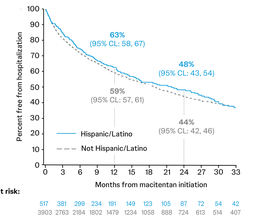
AE: adverse event; AESI: AE of special interest; SAE: serious AE; Q1, Q3: interquartile range.

Figure 5: Kaplan-Meier estimates of survival from macitentan initiation



CL: confidence limit.

Figure 6: Kaplan-Meier estimates of time from macitentan initiation to first all-cause hospitalization



Four patients in the Not Hispanic/Latino group had a hospitalization with a missing start date and were excluded from the analysis. Curves are cut at the point where <10% of patients remain at risk[10]. CL: confidence limit.

Key points

Hispanic/Latino patients were **younger at diagnosis** and more likely to have **congenital heart disease-associated PAH** than non-Hispanic/Latino patients

Median time to combination therapy:

- **1.5 years** for **non-Hispanic/Latino** patients
- **3 years** for **Hispanic/Latino** patients

The majority of patients in both groups **were not escalated to triple therapy**

Conclusions

In this population of patients with PAH newly initiating macitentan, Hispanic/Latino patients tended to be younger at diagnosis, were more likely to have congenital heart disease-associated PAH and less likely to have idiopathic/heritable PAH than non-Hispanic/Latino patients.

Hispanic/Latino patients had a slightly longer time from diagnosis to initial PAH-specific therapy and took longer to escalate to double combination and triple combination therapy.

The safety profile of macitentan was generally comparable between the two groups with the tendency of slightly lower incidence of adverse events reported in Hispanic/Latino patients.

Kaplan-Meier estimates of time from macitentan initiation to first all-cause hospitalization were similar between the groups, while estimates of survival in Hispanic/Latino patients were slightly higher than in non-Hispanic/Latino patients (acknowledging overlapping confidence intervals).

Clinical Implications

Data on the use of PAH-specific drugs in Hispanic/Latino patients can inform treatment decisions and may help to close ethnicity health equity gaps.

Disclosures

LMG has served as a Scientific Committee member for Johnson & Johnson; received research grants from Aerovate, Altavant, Gossamer Bio, Johnson & Johnson, Merck, and United Therapeutics; received consultant fees from Aerovate, Bayer, Gossamer Bio, Johnson & Johnson, L.L.C, Merck and United Therapeutics. LMG is a speaker bureau for Bayer, Johnson & Johnson, Merck, and United Therapeutics.

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