Healthcare resource utilization and progression in patients with pulmonary arterial hypertension initiated on monotherapy with macitentan versus other endothelin-receptor antagonists

AUTHORS: Carly J. Paoli[1], Louise Huafeng Yu[2], Ambika Satija[3], Sherry Shi[2], Béatrice Libchaber[2], Marjolaine Gauthier-Loiselle[2], Sumeet Panjabi[1]

AFFILIATIONS: [1] Johnson & Johnson Innovative Medicine, LLC. Titusville, NJ, USA; [2]Analysis Group, Inc. Montreal, QC, Canada; [3]Analysis Group, Inc. Boston, MA, USA

Background

- Pulmonary arterial hypertension (PAH) is a rare, debilitating condition characterized by abnormally high blood pressure in pulmonary arteries and increased vascular resistance which can lead to right heart failure and ultimately death.[1]
- Endothelin-receptor antagonists (ERAs), namely macitentan (first approved October 18, 2013), ambrisentan (first approved June 15, 2007), and bosentan (first approved November 20, 2001), are standard-of-care PAH treatments. While current ESC/ERS Guidelines recommend initial combination therapy for low and intermediate risk patients, treatment with ERA monotherapy is among the recommended strategies for patients with PAH who have cardiopulmonary comorbidities, which is very common in the United States (US).[2-4]
- Some studies have demonstrated better outcomes with macitentan relative to other ERAs.[5-8] However, evidence to recommend one ERA over another is lacking.

Objective

To assess healthcare resource utilization (HRU) and PAH progression among treatment-naïve patients with PAH initiated on monotherapy with macitentan or other ERAs (i.e., ambrisentan or bosentan) in the US.

Methods

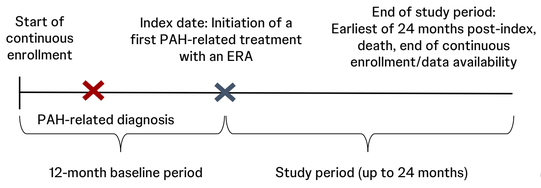
Data source

- The Komodo Health Research claims database was used to identify adults diagnosed with PAH with data spanning January 1, 2016 to March 31, 2023.

Study design and population

- A retrospective cohort study design was used (**Figure 1**).
- Eligible adult patients with PAH whose first observed PAH-related treatment was ERA monotherapy (index date: initiation date) were classified into mutually exclusive cohorts based on the index treatment regimen: (1) macitentan or (2) other ERA (i.e., bosentan or ambrisentan).
- The baseline period was defined as the 12-month period before the index date. The study period spanned from the index date until the earliest of 24 months post-index, death, end of continuous enrollment, and end of data availability.
- The study population excluded patients diagnosed with chronic thromboembolic pulmonary hypertension (CTEPH), erectile dysfunction, or pregnancy/labor during the baseline or study periods.

Figure 1: Study design (Index date: Anytime between January 1, 2016 and March 31, 2023)



Abbreviations: ERA: endothelin-receptor antagonists; PAH: pulmonary arterial hypertension.

Measures, outcomes, and statistical analyses

- Patient characteristics were measured at the index date or during the baseline period, and PAH-related HRU (hospitalizations, readmissions within 30 days, emergency department visits, and outpatient visits) and PAH progression endpoints were measured during the study period.
- Entropy balancing was used to balance cohorts based on key patient characteristics during baseline: age, gender, race, region, insurance type, year of index, time from first observed PAH-related diagnosis to the index date, Quan-Charlson comorbidity index,[3] and simplified PAH risk score.[9] A standardized difference of <0.2 was considered well-balanced.
- PAH-related HRU was identified based on days with medical claims with a recorded PAH-related diagnosis (ICD-10-CM: I27.0, I27.20, I27.21, I27.89) and assessed per patient per month (PPPM). PAH-related HRU rates were compared across balanced cohorts using quasi-Poisson regression and reported as incidence rate ratios (IRRs).
- PAH progression was defined as the first of PAH-related hospitalization, addition of injectable prostacyclin pathway agents other than intravenous selexipag, atrial septostomy, lung transplant, and death. Time from index date to PAH progression was evaluated using weighted Kaplan-Meier (KM) analysis.

Results

- A total of 357 and 322 patients were included in the macitentan and other ERA cohorts (ambrisentan [92%]; or bosentan [8%]), respectively.
- Before weighting, compared to the other ERA cohort, the macitentan cohort was more likely to be from the south and less from the northeast, less likely to be Medicaid-insured, and more likely to have cardiopulmonary comorbidities (**Table 1**).
- After weighting, baseline characteristics were balanced across cohorts (all standardized differences <0.2).

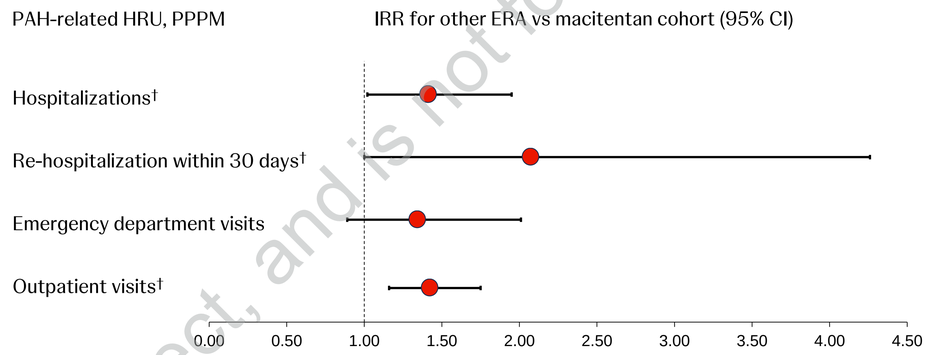
Table 1: Patient demographics and clinical characteristics

Patient characteristics	Macitentan monotherapy N = 357	Other ERA monotherapy: Before weighting N = 322	Std. diff.	Other ERA monotherapy: After weighting N=322	Std. diff.
On the index date					
Age, years, mean ± SD [median]	58.9 ± 13.4 [60.0]	56.5 ± 15.2 [58.0]	0.17	58.9 ± 13.4 [60.0]	0.00
Female, n (%)	257 (72.0)	248 (77.0)	0.12	232 (72.0)	0.00
Region, n (%)					
South	172 (48.2)	124 (38.5)	0.20†	162 (50.4)	0.04
West	75 (21.0)	85 (26.4)	0.13	68 (21.0)	0.00
Midwest	43 (12.0)	43 (13.4)	0.04	39 (12.0)	0.00
Northeast	46 (12.9)	67 (20.8)	0.21†	41 (12.9)	0.00
Unknown	21 (5.9)	3 (0.9)	0.28†	12 (3.7)	0.10
Race, n (%)					
White	132 (37.0)	143 (44.4)	0.15	119 (37.0)	0.00
Black or African American	73 (20.4)	70 (21.7)	0.03	66 (20.4)	0.00
Hispanic or Latino	62 (17.4)	40 (12.4)	0.14	56 (17.4)	0.00
Asian or Pacific Islander	16 (4.5)	4 (1.2)	0.20†	14 (4.5)	0.00
Other	7 (2.0)	11 (3.4)	0.09	6 (2.0)	0.00
Unknown	67 (18.8)	54 (16.8)	0.05	60 (18.8)	0.00
Insurance type, n (%)					
Commercial	146 (40.9)	104 (32.3)	0.18	116 (36.0)	0.10
Medicaid	72 (20.2)	107 (33.2)	0.30†	65 (20.2)	0.00
Medicare	115 (32.2)	78 (24.2)	0.18	104 (32.2)	0.00
Unknown	24 (6.7)	33 (10.2)	-	37 (11.6)	0.17
Year of index date, n (%)					
2017	50 (14.0)	72 (22.4)	0.22†	45 (14.0)	0.00
2018	62 (17.4)	58 (18.0)	0.02	56 (17.4)	0.00
2019	75 (21.0)	60 (18.6)	0.06	68 (21.0)	0.00
2020	38 (10.6)	45 (14.0)	0.10	35 (10.8)	0.00
2021	59 (16.5)	46 (14.3)	0.06	53 (16.5)	0.00
2022	68 (19.0)	37 (11.5)	0.21†	61 (19.0)	0.00
Time from first observed PAH-related diagnosis to the index date (days), mean ± SD [median]	366.7 ± 478.6 [198.0]	367.5 ± 444.2 [221.0]	0.00	366.7 ± 478.6 [189.0]	0.00
During the baseline period					
Quan-Charlson comorbidity index,[10] mean ± SD [median]	3.6 ± 2.4 [3.0]	3.3 ± 2.4 [3.0]	0.15	3.6 ± 2.4 [3.0]	0.00
Comorbidities,* n (%)					
Cardiopulmonary comorbidities	324 (90.8)	269 (83.5)	0.22†	281 (87.1)	0.12
Systemic hypertension	286 (80.1)	231 (71.7)	0.20†	253 (78.4)	0.04
Diabetes mellitus	144 (40.3)	101 (31.4)	0.19	120 (37.1)	0.07
Coronary artery disease	148 (41.5)	116 (36.0)	0.11	145 (45.0)	0.07
Obesity	154 (43.1)	123 (38.2)	0.10	136 (42.1)	0.02
Interstitial lung disease	75 (21.0)	66 (20.5)	0.01	63 (19.6)	0.04
Simplified PAH risk score,[9] mean ± SD [median]	16.3 ± 6.9 [19.0]	16.0 ± 7.1 [18.0]	0.04	16.3 ± 6.9 [19.0]	0.00

† Standardized difference >0.2 Abbreviations: SD: standard deviation; Std. diff.: standardized difference.
Note: *Patients could have more than one comorbidity (i.e., comorbidities were not mutually exclusive).

- During the study period, the other ERA cohort had higher PPPM PAH-related outpatient visits (1.04 vs 0.73 PPPM, IRR: 1.42), hospitalizations (0.06 vs 0.05 PPPM, IRR: 1.41), and re-hospitalizations within 30 days (0.01 vs 0.01 PPPM, IRR: 2.07) compared to the macitentan cohort (all p<0.05; **Figure 2**). A similar trend was seen for emergency department visits, with higher rates in the other ERA relative to the macitentan cohorts, but this difference was not statistically significant (0.05 vs 0.04 PPPM, IRR: 1.34, p=0.16).

Figure 2: Comparison of PAH-related HRU across the macitentan and other ERA cohorts*

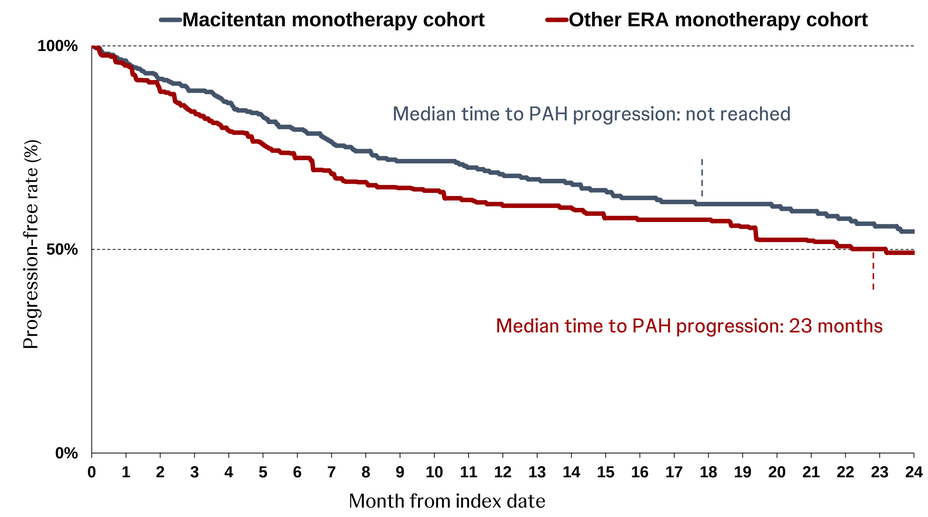


† P-value <0.05.

Abbreviations: CI: confidence interval; ERA: endothelin receptor antagonist; HRU: healthcare resource utilization; IRR: incidence rate ratio; PAH: pulmonary arterial hypertension; PPPM: per patient per month. Note: *An IRR> 1 indicated that the incidence rate of a given HRU event was greater in the other ERA monotherapy cohort relative to the macitentan monotherapy cohort.

- A higher proportion of patients in the other ERA cohort (137/322, 43%) relative to the macitentan cohort (128/357, 36%) experienced a PAH progression event during the study period. In the KM analysis, numerically higher proportions of patients in the macitentan cohort were free of any progression endpoints at 6 months (80% vs 73%), 12 months (68% vs 61%), and 24 months (54% vs 49%; **Figure 3**).

Figure 3: Time from index date to PAH progression across the macitentan and other ERA cohorts



Weighted cohorts	Progression-free rate	Time since index date: Rate at month 6	Rate at month 12	Rate at month 18	Rate at month 24
Macitentan monotherapy	KM rate, (%) and (95% CI)	79.5 (74.7, 83.4)	68.1 (62.5, 73.0)	61.2 (55.1, 66.6)	54.4 (47.8, 60.5)
	Patients at risk, N (%)	246 (68.9)	165 (46.2)	117 (32.8)	0 (0.0)
Other ERA monotherapy	KM rate, (%) and (95% CI)	72.5 (65.4, 78.3)	60.7 (53.0, 67.6)	57.3 (49.4, 64.5)	49.2 (40.8, 57.0)
	Patients at risk, N (%)	201 (62.4)	132 (40.9)	107 (33.2)	0 (0.0)

Abbreviations: CI: confidence interval; ERA: endothelin receptor antagonist; KM: Kaplan-Meier; PAH: pulmonary arterial hypertension.

Conclusions

Initiation with macitentan monotherapy in treatment-naïve PAH patients was associated with reduced rates of PAH-related HRU compared to other ERA monotherapies, suggesting improved disease management with macitentan.

Patients treated with macitentan had a numerically longer time to PAH progression compared to those on other ERA monotherapy, suggesting that macitentan may potentially offer better long-term disease control, although further research is needed to confirm this finding given the small sample size.

Limitations

Limitations of this study included the use of claims data, which may have led to misclassification of PAH patients due to coding inaccuracies, the contribution of unmeasured confounders (e.g., disease severity and hemodynamics) to observed treatment differences, potential heterogeneity in the comparison cohorts due to treatment modifications during the study period, and potential lack of generalizability to other populations (e.g., non-insured).

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Disclosures

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