Treatment of drug- and toxin-induced pulmonary arterial hypertension (PAH): Real-world experience with macitentan

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INTRODUCTION

- Drugs- and toxins-associated/induced pulmonary arterial hypertension (D&T-APAH) is a form of PAH associated with exposure to specific drugs and toxins, including certain anorexigens, amphetamines and the tyrosine kinase inhibitor dasatinib.
- Macitentan 10 mg (Opsumit®) is an oral endothelin receptor antagonist approved for the long-term treatment of PAH to delay disease progression and reduce hospitalisation.
- For patients refractory to drug therapy, or who show disease progression despite multiple drug therapies, lung transplantation remains an important option.
- The OPsumit® USers Registry (OPUS) and OPsumit® Historical USers cohort (OrPHeUS) study were initiated to characterise the safety profile of macitentan and to describe clinical characteristics and outcomes of patients newly treated with macitentan in a real-world, post-marketing setting; both studies include patients with D&T-APAH.

PURPOSE

- To describe demographics, disease characteristics, treatment patterns, safety, hospitalisation and survival of D&T-APAH patients in the combined OPUS/OrPHeUS data set.

METHODS

Study design

- OPUS is a prospective, multicentre, US observational drug registry (Apr 2014 – present; NCT02126943).
- OrPHeUS was a retrospective, multicentre, US medical chart review (Oct 2013 – Dec 2016; NCT03197688).
- Both studies included patients newly treated with macitentan, regardless of diagnosis and prior/ongoing PAH therapy.
- Patients enrolled in OPUS were not allowed to participate in OrPHeUS.

Analyses

- Data cut-off for OPUS was Jan 2020; data observation period for OrPHeUS was Oct 2013 – Mar 2017.
- Baseline demographics and disease characteristics, treatment patterns, liver function tests, hospitalisations and survival are described for D&T-APAH patients with follow-up data and are descriptively compared with idiopathic/heritable PAH (I/HPAH) patients from the same data set.
- PAH aetiology was determined by the site investigators. The class of drug associated with D&T-APAH diagnosis was not collected.
- In OPUS, adverse events (AEs), including hepatic adverse events (HAEs), were collected via the electronic case report form. The Independent Liver Safety Data Review Board (ILSDRB) reviewed and assessed all case reports of hepatic adverse events of special interest (HAESI).
- In OrPHeUS, HAEs and HAESIs were identified from data in the medical charts and pharmacovigilance reporting and reviewed by the ILSDRB.

RESULTS

- PAH WHO Group 1 patients with follow-up data in OPUS/OrPHeUS (N = 4279) included 215 (5.0%) D&T-APAH and 2400 (56.1%) I/HPAH patients.

Figure 1: Geographical distribution of D&T-APAH patients in OPUS/OrPHeUS

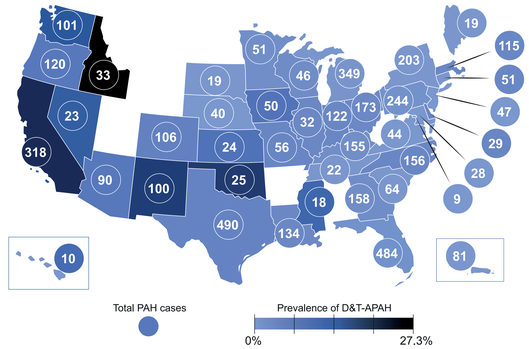


Table 1. Demographics and baseline characteristics at macitentan initiation

	I/HPAH N = 2400	D&T-APAH N = 215
Age – median (Q1, Q3) years	65 (53, 73)	51 (45, 59)
Female sex – n (%)	1752 (73.0)	156 (72.6)
Time from diagnosis – n	2344	206
Median (Q1, Q3) months	7.3 (1.4, 38.3)	10.5 (1.0, 46.2)
≤6 months before enrolment – n (%)	1094 (46.7)	84 (40.8)
>6 months before enrolment – n (%)	1250 (53.3)	122 (59.2)
Race – n	2387	214
Black or African American – n (%)	376 (15.8)	20 (9.3)
American Indian or Alaska Native – n (%)	22 (0.9)	0
Native Hawaiian or Other Pacific Islander – n (%)	12 (0.5)	2 (0.9)
White – n (%)	1857 (77.8)	180 (84.1)
Other – n (%)	120 (5.0)	12 (5.6)
WHO FC – n	1303	115
I – n (%)	110 (8.4)	12 (10.4)
II – n (%)	389 (29.9)	30 (26.1)
III – n (%)	725 (55.6)	65 (56.5)
IV – n (%)	79 (6.1)	8 (7.0)
6MWD – n	842	72
Median (Q1, Q3) m	289 (195, 375)	363 (285, 420)

6MWD: 6-minute walk distance; WHO FC: World Health Organization Functional Class.

Table 2. Haemodynamic characteristics at macitentan initiation

	I/HPAH (N = 2400)		D&T-APAH (N = 215)	
	Median (Q1, Q3)	n	Median (Q1, Q3)	n
mPAP, mmHg	44 (35, 53)	1139	50 (43, 60)	103
mRAP, mmHg	10 (6, 14)	1036	11 (7, 17)	98
PAWP, mmHg	12 (9, 15)	1082	11 (8, 15)	102
PVR, Woods units	7.2 (4.8, 10.9)	919	10.0 (6.9, 14.0)	92
CI, L/min/m²	2.3 (1.9, 2.9)	953	2.1 (1.7, 2.6)	92

CI: cardiac index; mPAP: mean pulmonary arterial pressure; mRAP: mean right atrial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance.

CONCLUSIONS

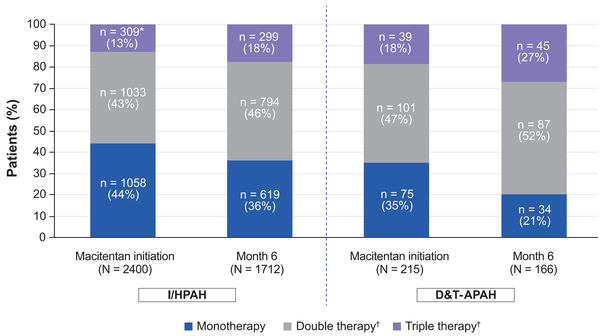
- **Compared with I/HPAH patients, D&T-APAH patients were generally younger, and a greater proportion were on double and triple therapy at macitentan initiation and at 6 months after macitentan initiation.**
- **In this descriptive analysis, survival was similar in both populations and there was a lower incidence of hospitalisations in the D&T-APAH patients.**
- **A limitation of this analysis is that PAH aetiology was investigator-assessed and not adjudicated in OPUS and OrPHeUS and data regarding the exact drug(s) associated with the D&T-APAH diagnosis were not collected.**

Table 3. Macitentan exposure at data cutoff

	I/HPAH N = 2400	D&T-APAH N = 215
Macitentan exposure – median (Q1, Q3) months	13.5 (5.0, 28.3)	14.1 (6.6, 28.2)
Exposure time – n (%)		
>12 months	1296 (54.0)	119 (55.3)
>18 months	989 (41.2)	92 (42.8)

Q1, Q3: interquartile range.

Figure 2. PAH therapy at macitentan initiation and at month 6



†Double therapy includes macitentan in combination with 1 other class of PAH therapy, triple therapy includes macitentan in combination with 2 other classes of PAH therapy. Classes of PAH therapy include phosphodiesterase type-5 inhibitors, prostanoids, soluble guanylate cyclase stimulator and / or investigational drug. *Includes 2 patients receiving 4 classes of PAH therapy.

Safety and tolerability

Table 4. Macitentan discontinuations

	I/HPAH N = 2400	D&T-APAH N = 215
Patients who discontinued macitentan – n (%)	955 (39.8)	66 (30.7)
Due to AE	418 (17.4)	24 (11.2)
Due to HAE	5 (0.2)	0
Not due to AE/HAE	413 (17.2)	33 (15.3)
Missing	119 (5.0)	9 (4.2)
KM estimates – % (95% CL)		
Free from discontinuation at 1 year	69.7 (67.8, 71.6)	76.3 (69.6, 81.8)

AE: adverse event; CL: confidence limit; HAE: hepatic adverse event; KM: Kaplan–Meier.

Table 5. Hepatic safety

	I/HPAH N = 2400	D&T-APAH N = 215
Hepatic adverse events (HAEs)		
Patients with ≥1 HAE – n (%)	187 (7.8)	20 (9.3)
Incidence rate – per-person year (95% CL)	0.06 (0.05, 0.06)	0.07 (0.04, 0.10)
KM estimates – % (95% CL)		
Free from HAE at 1 year	93.1 (91.9, 94.2)	93.4 (88.2, 96.3)
HAEs of special interest (HAESIs)		
Patients with ≥1 HAESI – n (%)	100 (4.2)	10 (4.7)
Incidence rate – per-person year (95% CL)	0.03 (0.02, 0.04)	0.03 (0.02, 0.06)
KM estimates – % (95% CL)		
Free from HAESI at 1 year	96.2 (95.3, 97.0)	97.1 (93.0, 98.8)
Liver function test abnormalities		
Patients with ALT/AST ≥3 × ULN – n (%)	69 (2.9)	6 (2.8)
Incidence rate – per-person year (95% CL)	0.02 (0.02, 0.03)	0.02 (0.01, 0.04)
KM estimates – % (95% CL)		
Free from ALT/AST ≥3 × ULN at 1 year	97.8 (97.0, 98.4)	97.1 (92.4, 98.9)
Patients with ALT/AST ≥3 × ULN and total bilirubin ≥2 × ULN – n (%)	9 (0.4)	0
Incidence rate – per-person year (95% CL)	0.003 (0.001, 0.005)	0
KM estimates – % (95% CL)		
Free from ALT/AST ≥3 × ULN and total bilirubin ≥2 × ULN at 1 year	99.8 (99.5, 99.9)	100 (100, 100)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CL: confidence limit; ULN: upper limit of normal.

Hospitalisations and survival

Table 6. Hospitalisations and deaths

	I/HPAH N = 2400	D&T-APAH N = 215
Hospitalisations		
Patients with ≥1 event – n (%)	900 (37.5)	64 (29.8)
Incidence rate – per person-year (95% CL)	0.34 (0.32, 0.37)	0.25 (0.19, 0.31)
KM estimates – % (95% CL)		
Free from hospitalisation at 1 year	66.5 (64.3, 68.6)	74.9 (67.7, 80.7)
Free from hospitalisation at 2 years	53.2 (50.6, 55.7)	62.4 (53.5, 70.1)
Deaths		
Number of patients – n (%)	302 (12.6)	25 (11.6)
Incidence rate – per person-year (95% CL)	0.09 (0.08, 0.10)	0.08 (0.05, 0.12)
KM survival estimates – % (95% CL)		
At 1 year	91.5 (90.1, 92.7)	91.2 (85.7, 94.6)
At 2 years	83.4 (81.3, 85.3)	86.7 (79.8, 91.3)

CL: confidence limit; KM: Kaplan–Meier.

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