Open Journal of
Clinical & Medical
Case Reports

Volume 2 (2016)
Issue 2

ISSN 2379-1039

Macitentan in a Complex Patient Cohort – A Case Series

Arshad A. Khan, MBBS; Nicholas J. Collins, FRACP*

Nicholas J Collins, FRACP
Cardiovascular Department, John Hunter Hospital, Newcastle, NSW Australia.
Tel: +02-4921-3000; Email: nicholas.collins@hnehealth.nsw.gov.au

Abstract

Macitentan is a new dual endothelin-receptor antagonist (ERA) with evidence supporting reduced morbidity and mortality in pulmonary arterial hypertension (PAH) in clinical trials. We describe our initial experience with macitentan in a complex patient cohort. Eleven patients with complex clinical characteristics commenced therapy. Of note, the patients' baseline characteristics were significantly different from those in clinical trials. During limited follow up 6 discontinued therapy due to worsening peripheral oedema or dyspnoea with 1 death. There was no adverse effect on liver function during the study period. In an initial single centre experience with a group of complex, older PAH patients, macitentan was relatively poorly tolerated, noting limited patient numbers and short follow up. This potentially reflects the increased potency of macitentan; further prospective assessment in older patients is required.

Keywords

Pulmonary arterial hypertension; Right heart failure; Phosphodiesterase inhibitor; Endothelin receptor antagonist

Abbreviations

PAH: Pulmonary Arterial Hypertension; ERA: Endothelin receptor antagonist; 6MWT – 6 (six) minute walk test

Introduction

Pulmonary arterial hypertension (PAH) is a complex syndrome characterized by sustained elevation of pulmonary vascular resistance resulting in progressive right heart failure and death [1]. Endothelin-1 is now recognised as pathogenic in pulmonary arterial hypertension and plays an important role in pulmonary vasoconstriction and smooth muscle proliferation. Two types of endothelin receptors (type A and B) have been identified, with endothelin receptors located in the pulmonary and systemic vasculature, including renal endothelium [2]. Endothelin-receptor antagonists (ERAs) including recently available macitentan, are frequently used in PAH management. Compared to existingagents, macitentan demonstrates superior tissue penetration and a longer duration of action allowing for once daily dosing [3]. The SERAPHIN trial demonstrated reduced morbidity and mortality among treatment naïve and previously treated patients when commenced on macitentan [4,5]. The use of macitentan beyond the clinical trial experience in complex patients remains limited at this early stage.

Case Report

We report a case series assessing the use of macitentan to assess the tolerability of this agentin a patient cohort felt to have complex disease as reflected by age, functional class, intolerance to medical therapy and underlying haemodynamics.

We reviewed the first 11 patients commenced on macitentan 10mg daily in our centre, reflecting our initial experience with this agent. All patients had undergone diagnostic right heart catheterization at baseline with regular echocardiography and6-minute walk testing (6MWT) performed. Liver function was assessed at baseline and at 3-month intervals. The majority of these patients (n=8, 73%) had previously been trialled on pulmonary hypertension specific therapies with inadequate clinical response or intolerance noted; baseline characteristics are described in table one. Of note, the patients' baseline characteristics were significantly different from those in the SERAPHIN trial [3], with our cohort older (65±14vs. 45.5±14.99 years, $p < 0.0001$) and with likely more advanced disease as assessed by 6MWT (252±118 vs. 363±93.2m, p:0.001) and baseline haemodynamics (systolic pulmonary artery pressure: 69±22vs. 53.5±17.6mmHg, p: 0.005). Three (27%) patients were treatment naive in our cohort with 6 (55%) previously trialled on alternate ERA therapyin contrast to the SERAPHIN trial in which no patients had previously failed ERA therapy. During a mean follow up of 3.5±2.6 months, 1(9%) patient died and6 (55%) discontinued macitentan (Figure One) due to adverse events with worsening peripheral oedema the most common cause for discontinuation (n=4, 67%); no adverse effects on liver function was noted. There was, however, a non-significant improvement in 6MWT (252m vs 293m, p: 0.4), improvement in functional class and reduction in systolic pulmonary artery pressure (73mmHg vs 68mmHg, p: 0.6) as measured by echocardiography during the study period (Table Two).

Discussion

We report a case series of patients with PAH differing from those seen in randomised trials, which tended to enrol younger patients, with less advanced disease and without a background of prior therapy [4]. While macitentan use in patients with progressive disease is clearly attractive given its favourable pharmacological properties, we note there remains limitation with use in complex patients. Given the similarities between macitentan and existing ERA agents, it could be anticipated that patients intolerant to or failing ERA therapy would experience difficulty transitioning onto macitentan and develop similar side effects, as noted in our cohort. The aetiology of peripheral oedema and increased dyspnoea in patients receiving endothelin receptor antagonists remains unknown, however, has been attributed to peripheral vasodilatation and renal tubular dysfunction with associated fluid retention [6]. Previously it was felt that the incidence of peripheral oedema was higher in selective endothelin receptor antagonists, such as ambrisentan, in contrast to dual receptor antagonism, reflecting the possible role of unopposed enthothelin-1 action on endothelin B receptorsin the peripheral vasculature resulting in vasodilatation [7]. Our data suggests, however, that oedema remains problematic in potent dual endothelin receptor antagonist use. Renal effects of endothelin-1 include limiting sodium and fluid reabsorption, with ERA agents therefore predisposing to fluid retention. Animal studies have confirmed the obviation of fluid retention with ERA use when endothelin receptors are absent from the nephron. This implies fluid retention is mediated by renal endothelin receptors when ERA agents are used [2]. While this represent a small, early, single centre experience, limited by patient number and follow up, this cohort offers important insights into the anticipated challenges in applying clinical trial data to a complex *real-world*

population.

Conclusions

Older patients, patients with progressive disease and those intolerant of existing therapy are a complex group not well represented in randomised studies, and the use of potent ERA agents, such as macitentan should be used with caution.

Figure

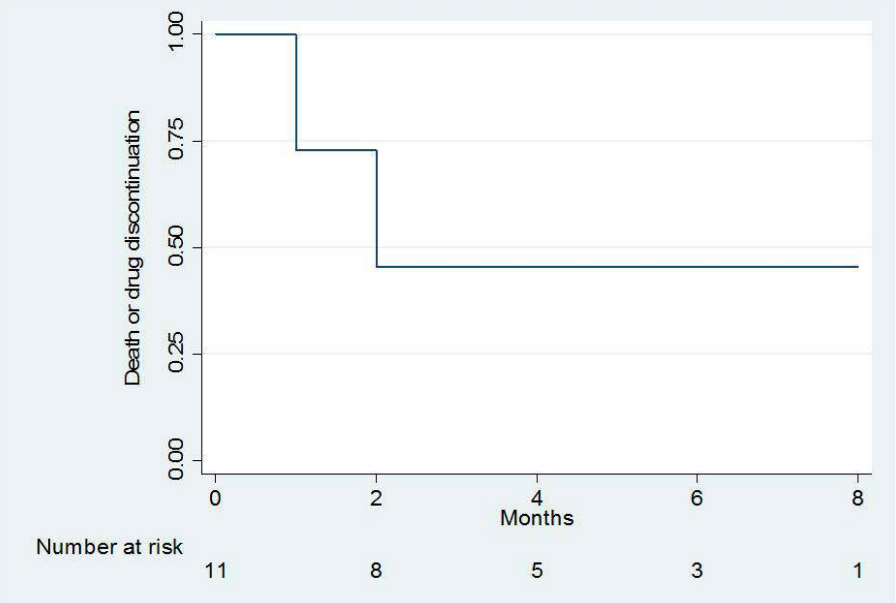

Figure1: Kaplan-Meier curve for death or drug discontinuation

Tables

No.	Age and gender	Duration of PAH (Months)	WHO Functional Class	Treatment Naïve	Baseline6-Minute walk distance	Baseline Mean PAP (mmHg)	CI ($L/m^{2)}$	Duration of macitentan (Months)	Reason for discontinuation
1	44/M	4	III	Yes	150	48	2.8	4	NA
2	64/F	12	III	Yes	160	37	2.2	2	Peripheral oedema
3	74/M	18	III	No	220	50	2.7	1	Worsening breathlessness
4	51/F	50	II	No	390	35	3.2	2	Worsening breathlessness
5	68/F	42	IV	No	180	47	2.4	1	Peripheral oedema
6	82/F	30	III	No	200	48	2.5	1	Peripheral oedema
7	77/M	30	III	No	170	40	2.6	7	NA
8	58/F	78	III	No	220	36	3.2	7	NA
9	67/F	48	II	No	450	50	2.1	8	NA
10	85/F	6	III	Yes	180	34	2.8	2	Peripheral oedema
11	44/F	30	II	No	450	41	3	4	NA

Table 1: Baseline characteristics

	Baseline	End of study period	P Value
Patients on Macitentan – No. %.	11(100)	5(45)	0.004
WHO Functional class – No. %.			
I and II	3(27)	5(45)	0.4
III and IV	8(73)	6(55)	0.4
Pulmonary artery systolic pressure on echocardiogram – mmHg (Mean±SD).	73±24	68±20	0.6
6-Min walk distance – m (Mean±SD).	252±118	293±123	0.4

Table 2: Outcomes

References

1. Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: The task force for the diagnosis and treatment of pulmonary hypertension of the european society of cardiology (esc) and the european respiratory society (ers), endorsed by the international society of heart and lung transplantation (ishlt). *European heart journal*. 2009;30:2493-2537.

2. Maguire JJ, Davenport AP. Endothelin receptors and their antagonists. *Seminars in nephrology*. 2015;35:125-136.

3.Iglarz M, Binkert C, Morrison K, Fischli W, Gatfield J, Treiber A, et al. Pharmacology of macitentan, an orally active tissue-targeting dual endothelin receptor antagonist. *The Journal of pharmacology and experimental therapeutics*. 2008;327:736-745.

4.Pulido T, Adzerikho I, Channick RN, Delcroix M, Galie N, Ghofrani HA, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *The New England journal of medicine*. 2013;369:809-818.

5. Channick RN, Delcroix M, Ghofrani HA, Hunsche E, Jansa P, Le Brun FO, et al. Effect of macitentan on hospitalizations: Results from the seraphin trial. *JACC. Heart failure*. 2015;3:1-8

6. Valerio CJ, Coghlan JG. Bosentan in the treatment of pulmonary arterial hypertension with the focus on the mildly symptomatic patient.*Vascular health and risk management*. 2009;5:607-619.

7.Trow TK, Taichman DB. Endothelin receptor blockade in the management of pulmonary arterial hypertension: Selective and dual antagonism. *Respiratory medicine*. 2009;103:951-962

Manuscript Information: Received: October 16, 2015; Accepted: January 19, 2016; Published: January 21, 2016

Authors Information: Arshad A. Khan, MBBS; Nicholas J. Collins, FRACP*
Cardiovascular Department, John Hunter Hospital, Newcastle, NSW Australia

Citation: Khan AA, Collins NJ. Macitentan in a complex patient cohort – a case series. Open J Clin Med Case Rep. 2016; 1068

Journal: Open Journal of Clinical and Medical Case Reports is an international, open access, peer reviewed Journal focusing exclusively on case reports covering all areas of clinical & medical sciences.

Visit the journal website at **www.jclinmedcasereports.com**

For reprints & other information, contact editorial office at **info@jclinmedcasereports.com**