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Safety and feasibility audit of a home-based drug-transitioning approach for patients with pulmonary arterial hypertension: an observational study

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Abstract

Background: Newer endothelin receptor antagonists (ERAs) used to treat patients with pulmonary arterial hypertension (PAH) are associated with fewer drug–drug interactions than bosentan and require less monitoring. This, combined with a pharmacokinetic basis for improved efficacy, means there may be a clinical rationale for changing therapies. However, this can be challenging and few data on its safety in patients with PAH are available.

Aims: At the Royal Free Hospital in London, UK, home-based medication transitioning has been standard practice since 2009 to avoid unnecessary hospital visits for patients, unless there is a clinical imperative. In this audit of standard practice we evaluated the consequences of adopting such a strategy when transitioning PAH patients between ERA therapies.

Methods and results: Using a Clinical Nurse Specialist-led, home-based transitioning strategy, 92 patients with PAH were transitioned from bosentan to macitentan or ambrisentan. Observational data were analysed retrospectively. The majority of patients were female with PAH associated with connective tissue disease and their ERA was changed in the hope of improving efficacy. The process was well tolerated with no adverse events associated with the process. Seventeen patients died during the study (macitentan, $n = 5$; ambrisentan, $n = 12$). None of the deaths was considered related to ERA treatment. The majority of patients remained clinically stable, based on WHO functional class and exercise capacity.

Conclusion: An established home-based transitioning strategy can be adopted safely for patients with PAH changing ERA therapies. Most patients remained stable and the therapy change was well tolerated.

Keywords

Pulmonary arterial hypertension, endothelin receptor antagonist, transitioning

Introduction

Pulmonary arterial hypertension (PAH) is one of five forms of pulmonary hypertension (PH), specifically involving the pre-capillary pulmonary vasculature.[1,2] In PAH, increases in pulmonary artery pressures place strain on the right ventricle, ultimately leading to right ventricular failure and death.[3] PAH can be idiopathic or can occur in association with a number of systemic diseases.[3] Prior to the advent of modern, PAH-targeted therapy, estimated median survival for patients with idiopathic PAH was 2.8 years.[4]

In addition to general and supportive therapeutic measures, PAH is treated using specific drug therapies targeting three key pathophysiological pathways. Prostacyclin analogues and prostacyclin receptor agonists target the prostacyclin pathway, phosphodiesterase type 5 inhibitors and

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guanylate cyclase stimulators target the nitric oxide pathway, and endothelin receptor antagonists (ERAs) target the endothelin pathway.[3,5] ERAs act to inhibit the endothelin receptors and thereby block the vasoconstrictive effects of endothelin, which is pathologically increased in PAH.[6]

Bosentan was the first available ERA and has been shown to result in improvements in 6-minute walk distance (6MWD) and World Health Organization functional class (WHO FC) as well as haemodynamics and time to clinical worsening in PAH of different aetiologies.[7–11] In more recent years two further ERAs, macitentan and ambrisentan, have been licensed for the treatment of PAH. Macitentan has a favourable pharmacokinetic profile and is not associated with the hepatic risk that necessitates monthly monitoring of patients receiving bosentan.[12,13] In a novel event-driven trial, compared with placebo, macitentan significantly reduced the risk of morbidity and mortality among PAH patients.[14] Unlike bosentan and macitentan, which target both endothelin receptor subtypes, ambrisentan targets the endothelin A receptor responsible for vasoconstriction, selectively.[10] Ambrisentan exhibits fewer drug–drug interactions, and has an improved hepatotoxicity profile compared with bosentan.[15,16] It has also been shown to delay clinical worsening in PAH when used as initial combination therapy with a phosphodiesterase type 5 inhibitor (AMBITION).[17] By contrast, in the COMPASS trial, the addition of bosentan in patients receiving sildenafil has not been shown to delay clinical worsening significantly.[18] With the expanded treatment options available to physicians managing patients with PAH there is often a sound pharmacological and clinical rationale for changing patients from bosentan to one of the newer ERAs, to reduce side effects (usually transaminitis) or in the hope to achieve greater efficacy. However, although there is a pharmacokinetic basis for improved efficacy, no head-to-head trials have been conducted to compare efficacy of the different ERAs directly.

To achieve safe and efficient therapeutic transitions we aimed to determine whether an established home-based strategy at the Royal Free Hospital in London, UK could be utilised to transition PAH patients between different ERAs and sought to monitor the success of this approach.

Methods

This was an audit of standard practice at the Royal Free Hospital, a national centre for diagnosis and management of PAH in the UK. The audit included all patients with right heart catheterisation (RHC)-confirmed PAH who were transitioned from bosentan to macitentan or ambrisentan between January 2013 and August 2016, using a home-based transitioning protocol. Patients were transitioned from bosentan because of side effects, abnormal liver function tests or inadequate response (defined as >2 criteria consistent with an intermediate-risk profile according to the European Society of Cardiology guidance criteria[3]). Data were collected prospectively as part of the National Audit Programme and analysed retrospectively. The investigation conforms with the principles outlined in the Declaration of Helsinki.

Transitioning protocol

Decisions to change from one ERA to another were taken principally during clinic visits (either at the Royal Free Hospital or one of our seven outreach clinics) and the protocol for changing medications was discussed with the patient prior to their leaving the hospital. The decision of whether to change to ambrisentan or macitentan was at the discretion of the clinician. Where changes were deemed necessary between clinic visits, patients were telephoned by the Clinical Nurse Specialist (CNS), prior to issuing the prescription. During this call the CNS covered the rationale for the change in medication and explained the revised dosing schedule and the potential for adverse events (AEs) or drug–drug interactions as well as ensuring that the patient understood how they could contact the PH team. It was deemed safe and feasible to transition patients at home if they were able to give informed consent for their review to be conducted via telephone and there were no clinical concerns to preclude this approach. Patients were not eligible for telephone clinics if they had underlying neurological or psychiatric conditions which could impact on their ability to understand and retain information, communication barriers or were non-compliant with respect to medication, frequency of blood tests or scheduled telephone appointments. Patients were sent their new medication and associated information via the standard recorded delivery postal service to ensure traceability. The pack included information on all aspects of the drug, blood monitoring system, and methods of contacting the clinical team between formal reviews to discuss concerns or queries. Patients were able to contact the clinical team via telephone or service email. Out of hours arrangements were in place via the cardiology team. On receipt of the medication, the patient was contacted by the nursing team who educated the patient on their new medication, following a standard pro forma over the phone. The patient was instructed to take their last dose of bosentan on the evening of their transition date and to commence the new ERA the following morning. All patients were reviewed 3−4 weeks after the change in therapy via a telephone consultation or a face-to-face outpatient clinic appointment, determined by patient convenience (e.g. proximity to the hospital), the clinical status of the patient and other relevant factors, at a date and time agreed with the patient. At this review, potential side effects were identified. Patients were also instructed to call the CNS-led advice line, or email the dedicated service account, to report AEs or to discuss any concerns, in which case scheduled review could be brought forward. Reported AEs were escalated immediately by the CNS to the medical team.

Table 1. Baseline demographics and characteristics.

	Macitentan (n = 49)		Ambrisentan (n = 43)	
Characteristic	n	BL*	n	BL*
Age, years	49	58 ± 14	43	64 ± 15
Sex, % female	49	73	43	81
PAH aetiology, n (%)	49		43	
PAH-CTD		30 (61)		24 (56)
iPAH		10 (20)		8 (19)
PAH-CHD		2 (4)		3 (7)
Other		7 (15)		8 (27)
6MWD, m	43	314 ± 151	39	276 ± 148
WHO FC	47		43	
I		1 (2)		0
II		10 (21)		2 (5)
III		33 (70)		39 (90)
IV		3 (6)		2 (5)
Laboratory parameters				
NT-proBNP (pmol/L)	41	212 ± 383	35	134 ± 207
AST (IU/L)	35	25.2 ± 13.7	22	33.7 ± 28.5
ALT (IU/L)	47	24.3 ± 28.3	40	28.9 ± 36.7
Haemoglobin (g/L)	37	127 ± 25	37	125 ± 29

Unless otherwise specified data are presented as mean ± SD. *Last assessment prior to therapy change. 6MWD: 6-minute walk distance; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CHD: congenital heart disease; CTD: connective tissue disease; iPAH: idiopathic pulmonary arterial hypertension; NT-proBNP: N-terminal pro-brain natriuretic peptide; PAH: pulmonary arterial hypertension; WHO FC: World Health Organization functional class.

Outcomes

Post-transition AEs, 6MWD, WHO FC and blood data were collected at the patient's next clinic appointment, approximately 3−6 months post-transition. For 6MWD, a ± 40 m absolute change was considered to be clinically meaningful. Blood samples were taken for measurements of haemoglobin, liver enzymes (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) and N-terminal pro-brain natriuretic peptide (NT-proBNP). A repeat RHC was performed in the majority of patients at a clinically appropriate time. Patients with missing data were excluded from the relevant analysis.

Statistical methods

For each parameter monitored, a basic descriptive analysis was conducted and/or mean ± SD values were calculated. Values were compared between groups and before and after treatment change. A 2-year Kaplan–Meier estimate of survival was performed. Patients were censored at the date of their last known review.

Results

Patient demographics and baseline characteristics

Between January 2013 and August 2016, 92 patients were transitioned from bosentan to macitentan (n = 49) or ambrisentan (n = 43). Nine patients received epoprostenol prior to (macitentan, n = 2; ambrisentan, n = 1) or post (macitentan, n = 4; ambrisentan, n = 2) therapy change.

Patient baseline demographics and characteristics are given in Table 1. The majority of patients were female (macitentan, 73%; ambrisentan, 81%) and patients who changed to ambrisentan were generally older. In both groups the most common aetiology was PAH associated with connective tissue disease.

The most common reason for changing treatments was inadequate response (92% in those changing to macitentan, and 77% in those changing to ambrisentan). One patient was transitioned to macitentan due to side effects, while four were transitioned from bosentan to ambrisentan for this reason (rash, n = 2; headache, n = 1; worsening oxygen saturation, n = 1). The remainder were transitioned because of abnormal liver function tests.

Feasibility and safety

All patients were transitioned safely from bosentan to macitentan or ambrisentan using the home-based strategy. One patient who changed from bosentan to ambrisentan experienced diarrhoea and was consequently changed again to macitentan, and one patient who was initially transitioned to ambrisentan was changed back to bosentan due to intolerance. Five patients died within 6 months of transitioning (macitentan, n = 3; ambrisentan, n = 2). None of the deaths was considered related to ERA treatment.

Table 2. Adverse events in patients transitioned to macitentan or ambrisentan.

Adverse event	Macitentan	Ambrisentan
Ankle oedema	7	12
Headache	4[a]	4[b]
Muscle cramps	1	–
Joint ache	1	–
Cold symptoms/nasal stuffiness	2	–
Stomach ache	1	–
Nausea/vomiting	2[c]	–
Dizziness	1	1
Epistaxis	–	3
Appetite/weight loss	–	2
Pruritus	–	1
Worsening circulation	–	1[d]
Facial flushing	–	1
Dry cough	–	1

[a]Resolved in two patients by first review.
[b]Resolved in one patient when dose decreased.
[c]Resolved by first review.
[d]Patient had connective tissue disease.

Mild ankle oedema was reported in seven patients who changed to macitentan and in 12 patients transitioned to ambrisentan. Twelve other AEs were reported by seven patients receiving macitentan and 13 AEs were reported by 10 patients receiving ambrisentan (Table 2). All AEs were possibly related to the treatment and were in keeping with AEs reported in clinical trials, none were considered directly related to the transitioning protocol itself.

Effectiveness

Clinical evaluation. The nature of the study precludes any comparison of effectiveness between treatments. The majority of patients with both pre- and post-transition data remained clinically stable. WHO FC deteriorated in four patients who changed to macitentan and two who changed to ambrisentan (Figure 1(a)). Clinically meaningful changes in 6MWD were similar in patients receiving macitentan and ambrisentan (Figure 1(b)). Six patients originally changed to ambrisentan were changed again to macitentan because of an inadequate response. One patient was changed back to bosentan for the same reason. All other patients remained on their initial transition medication.

Haemodynamic parameters. A total of 39 patients (macitentan, $n = 25$; ambrisentan, $n = 14$) had full pre- and post-transition RHC data available. Mean ± SD values pre- vs. post-transition in macitentan patients were 51.2 ± 9.0 vs. 47.0 ± 12.2 mmHg for mean pulmonary arterial pressure (mPAP), 3.3 ± 1.0 vs. 3.6 ± 1.1 L/min/m^2 for cardiac index and 10.7 ± 4.2 vs. 9.0 ± 3.9 mmHg for right atrial pressure (RAP). For ambrisentan patients, mean ± SD values

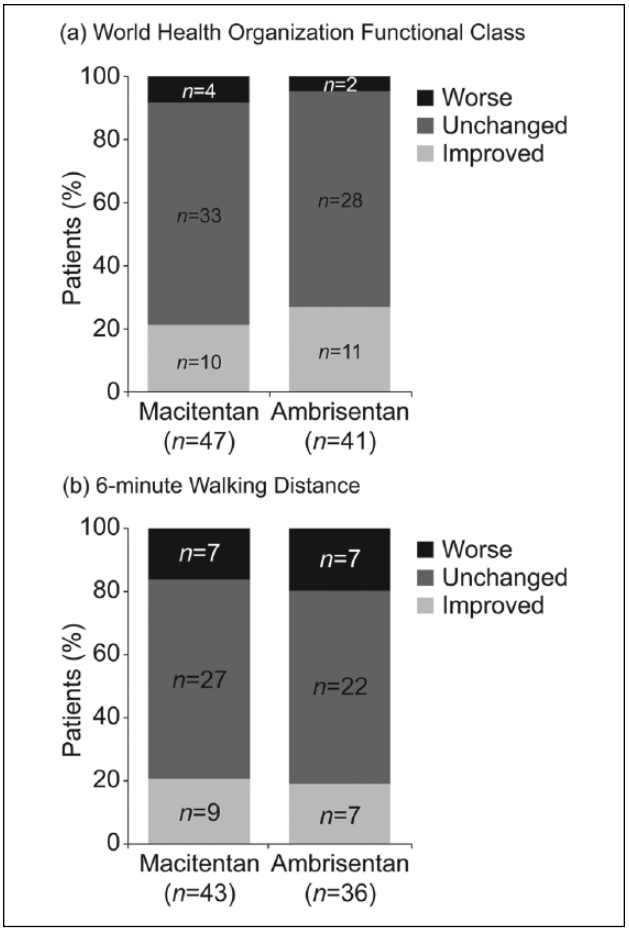

Figure 1. Clinical parameters. Number of patients with worse, unchanged and improved clinical parameters post-transition. (a) Post-transition change in World Health Organization functional class in patients changed to macitentan ($n = 47$) or ambrisentan ($n = 41$). (b) Post-transition change in 6-minute walking distance based on a 40 m cut-off value for a clinically meaningful change in patients changed to macitentan ($n = 43$) or ambrisentan ($n = 36$).

pre- vs. post-transition were 43.1 ± 10.7 vs. 40.5 ± 8.4 mmHg for mPAP, 2.8 ± 0.9 vs. 3.3 ± 1.2 L/min/m^2 for cardiac index and 8.4 ± 3.6 vs. 8.2 ± 2.6 mmHg for RAP.

Laboratory parameters. In patients with both pre- and post-transition data available, mean haemoglobin levels were comparable between groups both prior to and after the transition from bosentan (Figure 2(a)). ALT and AST levels were also comparable prior to and following the transition from bosentan to macitentan. However, ALT and AST levels appeared lower following the transition from bosentan to ambrisentan (Figure 2(b) and (c), respectively). This difference was largely a reflection of a reduction in liver enzymes in patients with high values prior to the therapy change (ALT, $n = 2$; AST, $n = 1$). Mean ± SD NT-proBNP peptide levels pre- vs. post-transition were 211 ± 383 vs.

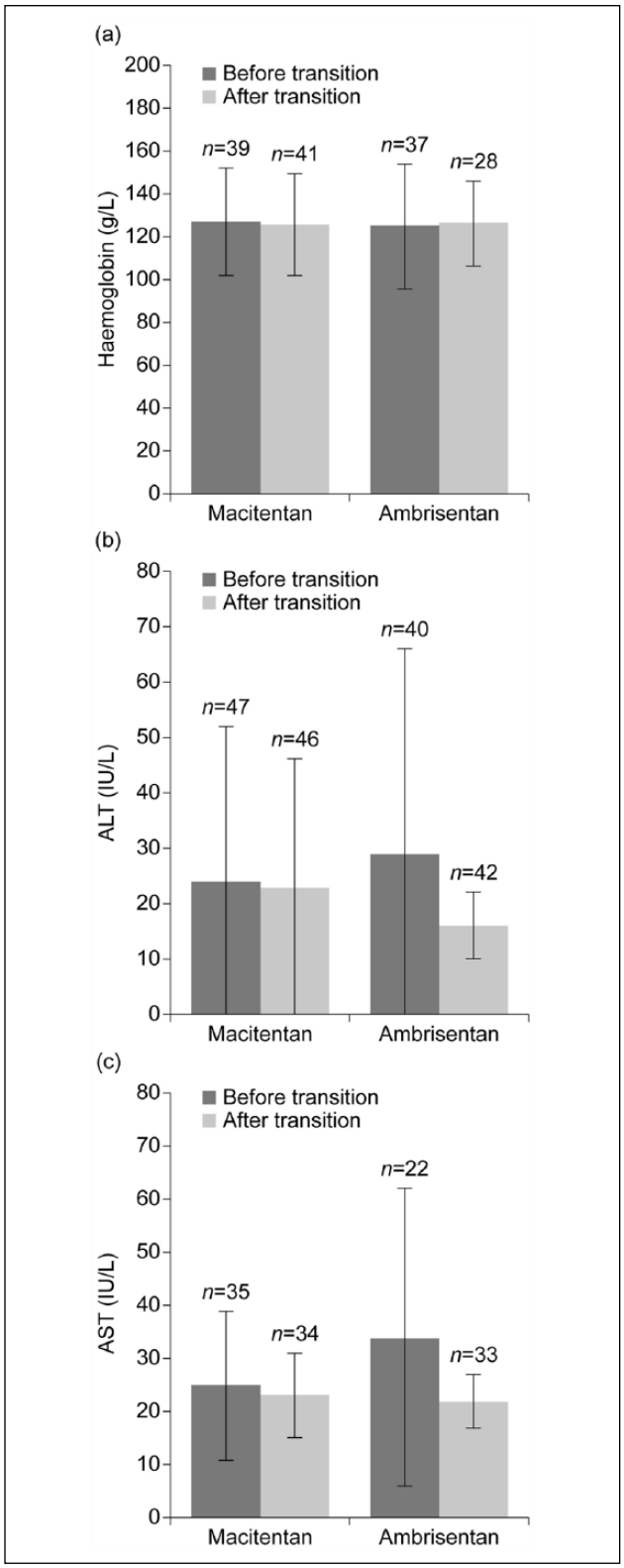

Figure 2. Laboratory parameters. Measured levels of (a) haemoglobin, (b) alanine aminotransferase (ALT) and (c) aspartate aminotransferase (AST) measured pre- and post-transition in patients changing from bosentan to macitentan or ambrisentan. Values are mean ± SD.

194 ± 538 pmol/L in macitentan patients and 134 ± 208 vs. 116 ± 163 pmol/L in ambrisentan patients.

Survival analysis. The median follow-up from date of transition to death/time of last review was 20.08 (IQR, 12.37–25.98) months. The Kaplan–Meier estimates of survival at 1 and 2 years post-transition for the overall population were 93.1% and 81.3%, respectively (Figure 3). Over the course of the entire study 17 patients died. Among these, four were receiving epoprostenol (macitentan, $n = 3$; ambrisentan, $n = 1$). Of the remaining 13, intravenous (IV) epoprostenol was declined by six patients and was deemed clinically inappropriate in a further three. In the remaining four patients, epoprostenol therapy was commenced but was discontinued due to safety concerns ($n = 3$) or compromised dexterity ($n = 1$).

Discussion

In this retrospective analysis of data collected prospectively as part of the National Audit Programme among patients with PAH of various aetiologies, we sought to assess the safety and feasibility of an established CNS-led, home-based treatment transition approach in PAH patients changing ERAs. Transitioning from bosentan to either macitentan or ambrisentan was achieved successfully in all patients and was well tolerated. No safety concerns related to the transition protocol itself or to the amended treatment were reported.

The majority of patients remained clinically stable, with unchanged or improved assessments of WHO FC and exercise capacity after the change in therapy. Relevant haemodynamic parameters were comparable pre- and post-transition, haemoglobin levels remained stable and liver enzymes remained within the normal range.

Treatment options for patients with PAH have expanded rapidly since the mid-1990s, with therapies from three drug classes available. Among these are the three ERAs, bosentan, macitentan and ambrisentan. Transitioning patients from one ERA to another due to tolerability or in the hope of greater efficacy is common and small studies have demonstrated this practice to be generally well tolerated.[16,19,20] However, although these drugs share a common mode of action, differences in how individual patients respond, both with respect to clinical effectiveness and tolerance, may be evident. In addition, due to the seriousness of PAH and the importance of sustained therapy, changing treatments may be considered undesirable to healthcare professionals or may place a strain on the resources needed to carry them out. This audit of our standard practice clearly demonstrates the feasibility of safely transitioning patients from bosentan to either macitentan or ambrisentan using a CNS-led home-based approach. Whilst we only report our experience of changing between ERA treatments, the methodology developed

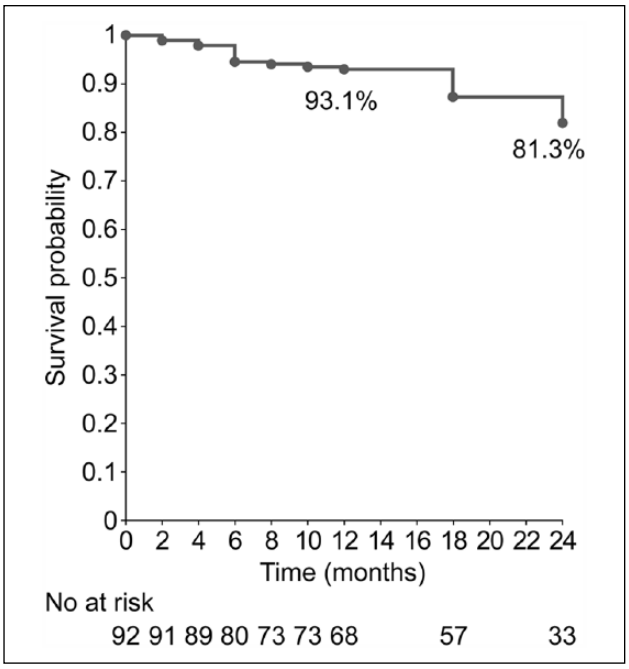

Figure 3. Survival analysis. Kaplan–Meier curve indicating the probability of survival among 92 patients transitioned from bosentan to either macitentan or ambrisentan. Patients were censored at the date of last known review.

here is widely applicable to nurses in PAH treatment centres and in the future could be adapted for other PAH therapies.

The strategy was developed and underpinned by academic and professional development of the Nurse Specialist team and was devised in response to changes to UK commissioning policy in 2009. As funding was agreed simultaneously at the time of decision to treat, bringing the patient to hospital for a second visit to initiate therapy within a short period would be expected to impact negatively on the patient experience both in terms of time and expense.

Formal CNS-led telephone clinics were set up as a mechanism to assess patients remotely. Telephone advice line services are recognised as providing a valuable contribution to patient care and have the potential to promote patient empowerment, safety and the use of self-management strategies.[21] We gained insight both from other specialties, such as renal and gastroenterology, within our hospital trust and external organisations to develop and implement this service. Structural and operational guidelines for this service were devised using key guidelines and policies from the Nursing and Midwifery Council,[22] Royal College of Nursing[21] and trust policy on information governance and data protection.

Eliciting appropriate information from patients during a telephone consultation can be challenging therefore it is vital to use a structured approach to ensure comprehensive and effective assessment. A number of consultation models exist to facilitate this and the Calgary–Cambridge approach was used by the nursing team to guide the consultation.[23]

Our standard practice audit has some limitations. Only observational data are presented, and follow-up was in routine clinical practice, thus minor AEs not routinely documented during clinical follow-up may have been underreported. The population undergoing a treatment change included a significant minority of patients who had been advised to consider IV therapy, but were unwilling or unable to manage complex therapeutic regimens. This may have resulted in some bias of the outcome data, and contributed to the rate of mortality reported. In addition, no effort was made to randomise patients between ambrisentan and macitentan, thus relative outcomes among patients transitioned to these treatments cannot be compared.

Conclusion

A home-based strategy allows changing ERA medications in patients with PAH to be achieved safely and effectively with efficient use of nursing resources.

Implications for practice

- Home-based transitioning of pulmonary arterial hypertension medication is feasible.
- The practice avoids unnecessary hospital visits.
- Patients remained clinically stable and the transition was well tolerated.
- The practice promotes efficient use of nursing resources.

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Declaration of conflicting interests

A Dawson has received travel grants and has participated in advisory boards for Actelion Pharmaceuticals Ltd. S Reddecliffe has received speaker fees and travel grants from Actelion Pharmaceuticals Ltd and has participated in advisory boards for Actelion Pharmaceuticals Ltd and Bayer. B Schreiber has received travel grants, speaker fees and educational grants and has participated in advisory boards for Actelion Pharmaceuticals Ltd and GlaxoSmithKline. B Schreiber has also received a travel grant from Bayer. JG Coghlan has received speaker fees, has acted as a consultant and participated in advisory boards for Actelion Pharmaceuticals Ltd, Bayer and Lilly, Endotronics, GlaxoSmithKline, Pfizer and United Therapeutics. JG Coghlan has received travel grants from Actelion Pharmaceuticals Ltd, Boston Scientific and GlaxoSmithKline and has also received unrestricted grants from Actelion Pharmaceuticals Ltd. C Coghlan has no conflicts of interest to disclose.

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