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Opsumit:
The Importance of Public Funding

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Opsumit – The Importance of Public Funding

Pulmonary arterial hypertension (PAH) is a rare, debilitating, progressive and life-threatening disease that leads to considerable morbidity and premature mortality. When PAH is left untreated or is sub-optimally treated, patients deteriorate rapidly, leading to right heart failure and premature mortality in all etiologies (1-3). Prior to the availability of PAH-specific therapies, the survival of patients with PAH was poor; median survival following diagnosis was documented as only 2.8 years, with survival rates of 68%, 48% and 34% at 1, 3 and 5 years, following diagnosis, respectively (1, 4).

Over the last two decades, ten novel therapies for PAH have been developed, approved by Health Canada, and some have become available to treat PAH patients. Unfortunately, despite treatment, most patients remain very ill and the prognosis of PAH remains poor, indeed worse than several common types of cancer (5). For example, most treated PAH patients still have impaired functional capacity and impaired health-related quality of life (HRQoL). Moreover, most patients face progressive increases in pulmonary vascular resistance leading to right-heart failure, complications such as hospitalization, and eventually, premature death (6).

It is clear that when patients suffer such complications of PAH, including objective clinical worsening and hospitalization, these PAH-morbidity events are strongly predictive of a higher risk of subsequent death. A recent novel "landmark"-type analysis specifically assessed the impact of PAH-morbidity events on the risk of subsequent mortality based on data from the two largest randomized controlled trials in PAH: the SERAPHIN study of macitentan and the GRIPHON study of selexipag (7-9). The SERAPHIN and GRIPHON trials individually reported that treatment with either macitentan or selexipag, respectively, was associated with clinical benefits, including specifically reduced long-term disease progression. The landmark study confirmed a strong association between such episodes of clinical worsening (e.g. markers of disease progression) in individual PAH patients and their risk of mortality.

The recognition of this important connection in the course of an individual PAH patient's disease has emphasized the need for treatment strategies that help avoid disease progression and hospitalization in order to reduce future premature mortality. Additionally, recent published proceedings from the 6th World Symposium on Pulmonary Hypertension (WSPH) include recommendations and guidelines for measurable treatment goals that aid prediction of mortality risk in PAH (10, 11).

To achieve treatment goals associated with low mortality risk, the individualized management of PAH requires complex treatment strategies that include supportive and general measures as well as combinations of different drug therapies (11, 12). Optimized combination therapy geared to individual

patients requires choices between a range of available therapies based on patient disease severity and progression, as well as consideration of known side effect profiles, risks of potential drug–drug interactions, and expected efficacy. Physicians therefore require access to all available therapeutic options to maximise the likelihood of achieving treatment goals, to optimally reduce the risk of disease progression and mortality related to PAH.

Currently in Canada there are ten approved therapies for PAH management, which target important pathways implicated in the pathogenesis of PAH: endothelin (ET), nitric oxide, and prostacyclin. In particular, it is considered critical to target the ET pathway, and there are three approved oral endothelin receptor antagonist (ERA) medications that do so: macitentan (Opsumit®), bosentan (Tracleer®), and ambrisentan (Volibris) (Table 1). These agents have comparable mechanisms of action, but their respective pharmacological and therapeutic characteristics show a number of important differences. They also differ in terms of their therapeutic indications within the PAH disease spectrum. Macitentan was first approved in 2013 by Health Canada but is not reimbursed by any of the provincial formularies outside of Quebec. This restricted availability limits treatment options and could potentially worsen individual PAH patient outcomes.

Below, we highlight previous and recent data that demonstrate the pharmacological and therapeutic benefits of macitentan compared to bosentan and ambrisentan in support of the need to add macitentan to the provincial formularies.

Structural differences

The structural differences between macitentan and the ERAs currently available in Canada (bosentan and ambrisentan) are important as they result in different pharmacological properties in terms of bioavailability and receptor interactions (Figure 1). In turn, these properties determine the relative therapeutic potential of the drugs. For instance, the structure of macitentan confers physicochemical properties including increased lipophilicity and low levels of ionization that allow superior tissue penetration (13). Macitentan blocks both ETA and ETB receptors with high potency (13, 14), which is desirable since selectively blocking only one of these two ET receptor subtypes does not fully inhibit the important pathophysiologic effects of ET-1 on vascular pathology in PAH, including fibrosis (15, 16) or vasoconstriction (17-19). Macitentan also has a unique profile of receptor-binding kinetics, combining high affinity (13, 14) and sustained blockade due to slow dissociation kinetics, even in the presence of high ET-1 concentrations (20). As a result, macitentan has over a 15-fold longer receptor occupancy half-life compared to bosentan or ambrisentan. Under conditions of fluctuating ET-1 concentrations in vivo, the slowly dissipating antagonism of macitentan is expected to block the ET-1 pathway more effectively than the other ERAs (20).

Differences in clinical profile

As PAH is a serious, progressive disease that ultimately results in premature death due to right-sided heart failure, the clinical management of PAH patients should be guided by consideration of potential long-term morbidity and mortality (6). Macitentan treatment demonstrated reduced morbidity and mortality in patients with PAH in long-term placebo-controlled clinical trial (7). Although there have been no direct comparative randomised controlled trials between ERAs, long-term outcomes with macitentan during the SERAPHIN trial (7, 21) have been more favourable than those seen with bosentan in the COMPASS-2 trial (22). Treatment with macitentan almost halved the occurrence of morbidity and mortality compared with placebo (7), whereas bosentan treatment did not result in any significant reductions in these outcomes (Table 2) (22).

Combination therapy has been shown to be highly effective at minimising the risk of PAH disease progression, thereby increasing patient survival (23). Macitentan has been shown to be effective in combination with other drug groups such as phosphodiesterase 5 (PDE-5) inhibitors, whereas bosentan has not demonstrated the same level of effectiveness (7, 22). Macitentan has been approved for both monotherapy and combination therapy in the treatment of PAH (24) while bosentan does not have this indication and there have been notes of caution regarding its use in combination with sildenafil (25). Indeed, international PAH clinical practice guidelines from the ESC/ERS (6) and the World PH Symposium both recognize that certain treatment combinations have demonstrated clinical benefit and are thus strongly recommended (eg. macitentan + PDE-5 inhibitor; ambrisentan + PDE-5 inhibitor), but others have not demonstrated benefit in studies (eg. bosentan + PDE-5 inhibitor) and thus are only weakly recommended. Macitentan also offers greater flexibility with regard to concomitant medications, such as anticoagulants; in contrast to bosentan, macitentan can often be co-administered with other common medications without the requirement for dose modifications (24, 26).

Macitentan has a favourable safety profile compared with other ERAs. Lower rates of edema were seen in the SERAPHIN trial compared with the AMBITION trial with ambrisentan, particularly during combination therapy (27). Data from a meta-analysis of 24 randomized controlled trials indicate that ambrisentan and bosentan significantly increased the risk of peripheral edema, whereas macitentan did not (28). Macitentan is also associated with a lower risk of hepatotoxicity compared with bosentan, but not ambrisentan (24, 28).

In conclusion, the most recent data and guidelines show a number of important differences between different ERA medications. Given its limitations, bosentan is not typically an appropriate first-line ERA for many newly diagnosed patients, especially in the increasing number of patients treated with combination therapy, as per guidelines and best practices, in order to optimally improve long-term clinical outcomes. Therefore, for many PAH patients, the only ERA that treating physicians can prescribe is ambrisentan.

Macitentan is an effective ERA with the greatest long-term benefit in clinical trials, an improved profile of safety and tolerability that can provide PAH patients and their doctors with increased flexibility in decisions on individualized treatment strategies. In particular, macitentan is effective as monotherapy as well as in combination with PDE-5 inhibitors. We, as treating clinicians and on behalf of PHA Canada, therefore strongly feel that this treatment should be reimbursed by the Canadian healthcare system for the treatment of PAH to allow optimization of treatment outcomes in PAH.

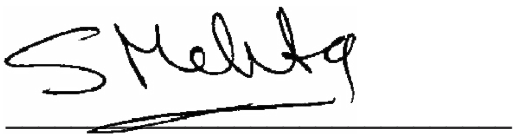

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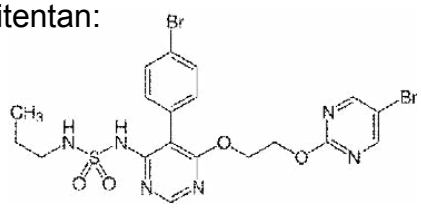
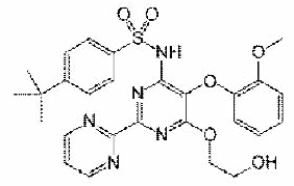
Figure 1: Chemical and spatial structures of macitentan, bosentan, ambrisentan and pyrimidine (29)

A

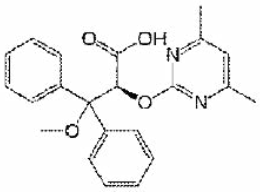
Macitentan:



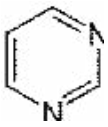
Bosentan:



Ambrisentan:

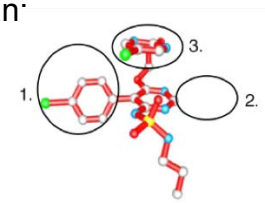


Pyrimidine:



B

Macitentan:



Bosentan:

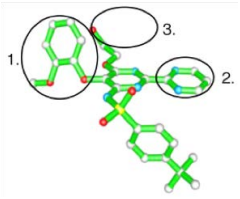


Table 1: Approved Health Canada indications for endothelin receptor antagonists

	Macitentan (24)	**Bosentan (26)**	**Ambrisentan (30)**
Long-term therapy	+	-	-
Combination therapy	+	-	+
PAH	WHO FC II to III	WHO FC III	WHO FC II to III
	Idiopathic	Idiopathic	Idiopathic
	Hereditary	Hereditary	-
	In association with **connective tissue disorders**	-	Associated with **connective tissue disorder**
	Associated with **corrected simple congenital heart defects**	In association with congenital **heart defects** and **Eisenmenger physiology**	-
	-	Association with **scleroderma** without significant interstitial lung disease	-
Systemic sclerosis	-	Reduction of number of new **digital ulcerations**	-
Data from randomized controlled studies			

Table 2: Evidence of clinically relevant efficacy – macitentan compared to bosentan

	Macitentan SERAPHIN $n_{Macitentan}$ = 242 $n_{Placebo}$ = 250	**Bosentan** COMPASS-2 $n_{Bosentan}$ = 159 $n_{Placebo}$ = 175
Time to disease progression or death Hazard ratio [CI] Significant effect	0.55 [0.32; 0.76]* +	0.83 [0.58; 1.19]† –
Hospitalization or death[1, 2] Hazard ratio [CI] Significant effect	0.50 [0.34; 0.75]* +	0.96 [0.67; 1.38]§ –
1. SERAPHIN: time to death or hospitalization for PAH 2. COMPASS-2: time to death or hospitalization for PAH or atrial septostomy or lung transplant until the end of the study *97.5% CI †97.31% CI §95% CI		