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Vasodilatory Therapeutics in the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) Cohort

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Abstract

The Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) registry was designed to advance the understanding of the pathogenesis of pulmonary arterial hypertension (PAH) in systemic sclerosis (SSc). This registry provides the opportunity to examine both microvascular and macrovascular complications in SSc. In this manuscript we review SSc-PAH therapies and report on their use in the PHAROS registry.

Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterized by the triad of vasculopathy, fibrosis and immunological abnormalities. Endothelial cell activation and dysfunction are central to the disease pathogenesis and may result in an imbalance of normal vasodilatory and vasoconstrictive mediators synthesized and released by vascular endothelial cells as well as neurological derived vasodilators and vasoconstrictors [1,2]. SSc-vasculopathy manifests as a spectrum of microvascular and macrovascular complications with the most severe and readily visible clinical symptoms being finger-tip digital ulcerations (DU) and pulmonary arterial hypertension (PAH) [3]. PAH is the leading cause of mortality in SSc, thus the role of vasodilatory therapies in SSc could have a major impact on morbidity and mortality [4,5]. The Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) cohort is a collaborative, multicenter study based in North America that was established to prospectively follow two groups of patients with SSc: those with incident PAH and those considered at high risk for developing PAH. In this manuscript we review therapeutics for PAH and discuss the strength of the PHAROS for evaluating the epidemiology of SSc-vasculopathy.

General Measures for PAH

Consensus guidelines for the treatment of PAH recommend the use of 1) supplemental oxygen in patients who are hypoxic at rest or with exercise (oxygen saturation < 90%), 2) diuretics for the management of right heart failure and volume overload and 3) digoxin for management of refractory right heart failure complicated by atrial arrhythmias [6]. The role of anticoagulation for SSc-vasculopathy is debated and use with caution is advised [7-9]. The effect of oxygen on DU is not well established, but the Food and Drug Administration (FDA) has recently reclassified the topical oxygen chamber for extremities (TOCE), a device intended to surround a patient's limb and apply humidified oxygen topically at a pressure slightly greater than atmospheric pressure to aid healing of chronic skin ulcers, from class III to class II [10].

Calcium Channel Blockers

Calcium channel blockers (CCB) have many potential beneficial effects on vessel integrity, including enhancement of endothelial nitric oxide (NO) production, lipid antioxidant activity and inhibition of smooth muscle migration and proliferation [11]. While high dose CCB have been shown to be effective in a subset of patients with idiopathic pulmonary hypertension (IPAH) [12], the prevalence of SSc-PAH patients who demonstrate acute vasodilation during hemodynamic testing is only about 1% [13]. Thus, while the IPH patients who demonstrate acute response to vasodilation with a CCB trial are more likely to benefit long-term from this therapeutic [13], CCB is not recommended for SSc-PAH patients. Although there are several studies showing improvement of Raynaud's phenomenon (RP) in patients with SSc using CCB, there is little published data on the effect of CCB on DU [5,14,15]. While it is suggested that a CCB may be an appropriate background therapy for DU management [5], it is not recommended in SSc-PAH algorithms [6,16]. While the role of CCB in SSc-vasculopathy management remains to be determined, the PHAROS registry provides this opportunity.

Phosphodiesterase-5 Inhibitors

Sildenafil, vardenafil, and tadalafil are the three commercially

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available phosphodiesterase-5 inhibitors (PDE-5Is). Sildenafil and tadalafil are FDA approved for use in PAH in the United States. A post-hoc analysis of connective tissue disease related PAH found improvements in functional class, hemodynamics and six minute walk distance (6MWD) in patients treated with sildenafil 20 mg orally three times daily for 12 weeks, however, no further improvement was noted at higher doses [17]. In a study of tadalafil 40 mg taken orally daily in connective tissue disease PAH, while improvement was seen over half of the participants were on therapy with bosentan at enrollment [18]. Small studies have also indicated that sildenafil and tadalafil are effective in reducing the severity of RP and promoting the healing of DU [19-21]. Tadalafil was used as an as add-on therapy to other vasodilators and was found to improve symptoms of RP, heal and prevent new DUs and improves quality of life in patients with resistant secondary RP [21]. Studies on the utility of PDE-5Is, as monotherapy and in combination with other vasodilators, for both SSc-PAH and SSc-DU are ongoing. This monotherapy and combination data is captured in the PHAROS registry.

Endothelin Receptor Antagonists

Endothelin receptor antagonists (ERA) are a class of PAH-specific drugs that block the interaction of endothelin -1 (ET-1) with its receptors thereby interfering with the vasoconstrictive effects of ET-1. A nonselective ERA (bosentan) blocking both the endothelin-A and endothelin-B receptors and an endothelin-A receptor selective (ambrisentan) antagonist, are both FDA-approved for PAH and have shown efficacy in the treatment of PAH [22,23]. The European League Against Rheumatism (EULAR) recommends bosentan as initial therapy for SSc-PAH [24]. Case reports of patients showing improvement in their RP and DU while undergoing therapy with ERAs for PAH have led to randomized controlled trials investigating the efficacy of these agents for the treatment of RP and DU in patients with SSc [25,26]. Bosentan treatment reduced the occurrence of new DUs in patients with SSc but had no effect on DU healing [25]. An open-label study suggested that ambrisentan may promote the healing of DU, but larger placebo-controlled trials are necessary to confirm these results [27]. The longitudinal effect of ERA on SSC-PAH and SSc-DU is recorded in the PHAROS registry.

Prostacyclins

Prostacyclin analogs (epoprostenol, treprostinil and iloprost), are approved by the FDA for the treatment of PAH in the US [28-30]. Prostacyclins remain the standard of care for inpatients who are in New York Heart Association (NYHA) functional class IV [31]. It has been suggested that prostacyclin therapy might enhance endothelial progenitor cells (EPC) numbers and functions which may contribute to vasodilator treatment efficacy in PAH [32]. Prostacyclin analogues have been shown to accelerate the healing of DU, however, those agents found to be effective thus far require intravenous or subcutaneous delivery. A pilot trial of subcutaneous treprostinil for the treatment of digital ulcers in 5 SSc patients demonstrated that DU size significantly decreased and no new DU occurred on continuous therapy [33]. However, the authors concluded that although effective, the high rate of injection site reactions may limit the utility of this therapy for this indication. As newer medications, including oral prostacyclins are potentially approved for the treatment of PAH and DU, the role of the intravenous or subcutaneous prostacyclins may have to be reexamined with regards to combination therapy. Oral treprostinil is actively being studied for this indication. While oral formulations of prostacyclins have not shown efficacy in the treatment of RP and DU, this may reflect the dose used [34].

The Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS)

In the PHAROS SSc patient population (n=295) with complete data available regarding DU the mean disease duration is 8.0 years. At study enrollment 49% had PAH, 11% had pulmonary venous hypertension and 15% had pulmonary hypertension due to lung disease [35]. Therapies in this population included home oxygen therapy (n=83), PDE5-I (for RP and/or PAH; n=59), ERA (n=46) and prostacyclin analog use (n= 6). Evaluation of the longitudinal outcomes of SSc-vasculopathy in these patients on vasodilatory therapeutics is ongoing.

Conclusions

There remains a great clinical need for tolerable and affordable therapeutic options for SSc-vasculopathy. The role of oxygen therapy warrants further study in terms of a role in the management of vasculopathy in patients with SSc. Clinical registries like PHAROS provide the unique opportunity to evaluate both macrovascular and microvascular disease in SSc. Long term follow-up in this observational cohort registry will be instructive [36]. Previous PAH studies in SSc suggest that clarification of the role of combination vasodilatory therapy with PDE5-I, ERA, prostacyclin analogs and the role for CCB for SSc-vasculopathy is warranted.

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