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Connective tissue disease-related pulmonary arterial hypertension

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A B S T R A C T

Over the past two decades, there have been several advances in the assessment and management of connective tissue disease-related pulmonary arterial hypertension (CTD-PAH) that improved outcomes of the treatment of this lethal disease, and this will be the focus of this study. Systemic sclerosis is the leading cause of CTD-PAH, followed by systemic lupus erythematosus, mixed connective tissue disease, idiopathic inflammatory myositis, rheumatoid arthritis, and Sjogren's syndrome. Clinical registries have been invaluable in informing about the burden of disease, risk and prognostic factors, and temporal trends with respect to treatment and outcome in CTD-PAH. The major advances have centered on improved disease classification and diagnostic criteria, screening and early diagnosis, the emergence of evidence-based therapies including combination goal-orientated treatment strategies, and the establishment of centers with expertise in PAH.

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Introduction

Autoimmune connective tissues diseases (CTD) refer to a heterogeneous group of conditions characterized by immune dysfunction, leading to end organ damage due to inflammation, endothelial dysfunction, and fibrosis. Clinical observational registries have been invaluable in describing real-life patients, treatment patterns, and prognostic outcomes of an otherwise rare and diverse group of conditions that can be complicated by pulmonary arterial hypertension (PAH), which is associated with significant morbidity and mortality. Although CTD-PAH will be described more broadly, the focus of this study is on systemic sclerosis-related PAH (SSc-PAH) as the leading cause of CTD-PAH worldwide, thereby providing a unique window to various aspects of pulmonary hypertension assessment and management.

Updated classification of pulmonary hypertension

Pulmonary hypertension (PH) refers to a hemodynamic and pathophysiological state defined by an increase in mean pulmonary artery pressure (PAP) $\geq$ 25 mmHg at rest as assessed by right heart catheterization (RHC), and is further subclassified according to the pulmonary artery wedge pressure (PAWP) into precapillary (PAWP $\leq$ 15 mmHg) or postcapillary PH (PAWP > 15 mmHg) [1]. In general, precapillary PH develops in the setting of pulmonary vascular diseases, where obstructive remodeling of the pulmonary arteries results in elevated pulmonary vascular resistance (PVR). By contrast, post-capillary PH develops due to passive transmission of elevated PAWP without necessarily an increase in PVR.

As PH can be the consequence of different clinical conditions, the current PH classification has been further divided into key groups determined according to shared pathophysiology and approach to therapy (Table 1) [2]. Clinical groups included in precapillary PH are PAH (group 1), PH due to lung diseases (group 3), chronic thromboembolic PH (group 4), and PH with unclear and/or multifactorial mechanisms (group 5), while postcapillary PH chiefly comprises PH due to left heart disease (group 2).

Epidemiology of CTD-PAH

Registry data have shown that CTD-PAH is the second leading cause of PAH (~25% of all cases), next to idiopathic PAH (~46%) [3]. SSc-PAH accounts for almost 75% of cases of CTD-PAH; the remaining, in order of decreasing frequency, are due to systemic lupus erythematosus (SLE, 8–19%), mixed connective tissue disease (MCTD, 8–9%), rheumatoid arthritis (RA, 3–5%), dermatomyositis/polymyositis (DM/PM, 4%), undifferentiated connective tissue disease (2%), and Sjogren's syndrome (1%) [4,5].

Approximately 1 in 10 SSc patients will develop PAH in his/her lifetime. However, much less is known about the true incidence of SSc-PAH, with one longitudinal observational study reporting an incidence rate of 0.61 cases per 100 patients years, in 384 SSc patients with no “high risk” features for PH assessed noninvasively over a mean period of 41.03 $\pm$ 5.66 months [6]. This relatively low incidence increases considerably among patients with significant “high risk” factors for PH (systolic PAP at transthoracic echocardiography (TTC) > 40 mmHg and/or diffusing capacity for carbon monoxide (DLCO) < 55% predicted and/or forced vital capacity (FVC)/DLCO ratio > 1.6), with a recent study reporting the frequency of PH in this population to be 10% at 2 years, 13% at 3 years, and 25% at 5 years [7]. Data on the prevalence of PAH in CTDs other than SSc are much less reliable because of the lack of RHC-based studies, but prevalence rates using RHC have been reported in SLE (0.005–9.3%) [8].

Survival in CTD-PAH: poorer than iPAH

In the vast majority of patients, SSc-PAH is a progressive disease associated with significant mortality. In a recent large systematic study, inclusive of 17 studies and 2011 SSc patients with PAH, 1-, 2-, and 3-year pooled survival rates were reported at 82% (95% CI 79–85%), 67% (95% CI 63–72%), and 56% (95% CI 51–61%), respectively [9].

The poor prognosis of SSc-PAH patients compared to patients with iPAH has been recognized in a number of studies. In the REVEAL registry, 641 patients with CTD-PAH (including 399 patients with

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