Combining datasets as well as therapies shows improved outcome in connective tissue disease associated pulmonary hypertension

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The article of Khanna et al [1] is an important summary of more than two decades of progress in management of connective tissue disease (CTD) associated pulmonary hypertension (PH) that provides an important platform for further advances. It also clearly shows the positive impact of current practice with combination therapy introduced early and an emphasis on proactive screening to make an early diagnosis of PH.

PH remains a major cause of death in some forms of CTD and is challenging to manage in the context of multisystem complications and potentially overlapping pathogenetic mechanisms. This is particularly true for systemic sclerosis (SSc) for which PH has been shown to be associated with high mortality in small observational cohorts [2] as well as larger more comprehensive datasets. Fortunately, there has been substantial progress in managing some forms of PH, notably pre-capillary pulmonary arterial hypertension (PAH). This clinical progress has been built upon a foundation of robust pivotal clinical trials and underscored by observational cohorts and registries that explore long term outcomes on standard licensed therapies. Of these registries some include all forms of PH [3,4] whereas others focus on PAH of specific disease associations [5].

The classification of PH was fundamentally changed in 1998 at the Second WHO meeting in Evian when 5 subgroups were proposed to reflect different pathogenic mechanisms for PH. This template has been refined and updated at subsequent meetings that became designated World Symposia in Pulmonary Hypertension for the third and subsequent meetings occurring at 5 yearly intervals. The most recent was the 6th World Symposium in Nice in 2018 [6].(Table 1) The latest classification retains the basic groups that differentiate primary vasculopathy from secondary causes of PH with the associated diagnosis including CTD for group 1 PAH. Definition of these different forms of PH, and especially group I PAH is central to therapeutic advances because by linking forms of PH with likely shared pathogenesis it allowed trials to recruit mixed cohorts including PAH-CTD and so led to these groups being included within the licensed indication as regulatory approval was obtained based upon robust phase 3 clinical trials.

Terminology matters in CTD-PAH because the real progress has been made for patients with Group 1 pre-capillary pulmonary arterial hypertension. This needs to be distinguished based upon the 2018 World Symposium classification from other frequent causes of PH in CTD that include Group 2 PH due to cardiac disease and associated with elevated post-capillary pressure and Group 3 PH due to hypoxia from lung fibrosis or muscle weakness. As in idiopathic and familial forms of PAH, improvements in Group 1 PAH are underpinned by the use of pulmonary vasodilator drugs of three classes which most recently became all available in oral formulation. The first orally active drug was bosentan, an endothelin receptor antagonist (ERA), approved by FDA in November 2001. Pivotal trials showed benefit for exercise distance measured using a six minute walk test. CTD-PAH showed a blunted but congruent response to the overall study population and this allowed this subgroup to be included within the regulatory approval [7]. The same trial template was used for licensing studies of PDE5 inhibitors that work as agonists of the nitric oxide pathway [8] and more recently for the oral soluble guanylate cyclase stimulator riociguat that works on the same pathway [9].

Prostacyclin agonists have been available for many years for parenteral use and later given by inhalation, but it was the oral prostacyclin receptor agonist selexipag that really offered the full potential to target all three pathways easily in PAH and especially in CTD-PAH [10]. This was important because more recently efficacy of new therapies including selexipag and macitentan have been approved based on much larger and more robust clinic trials that assess mortality and morbidity in a composite outcome of “time to clinical worsening” between treatment arms [9,10]. Moreover, because the therapeutic landscape changed, approved therapies became widely available, which enabled trials to permit appropriate background treatment and test the benefit of adding a new agent on top of one or even two approved drugs. Importantly, these event driven studies show much more comparable relative benefit of treatment in the CTD-PAH subgroup and also the SSc-PAH group. This is important because cohort and other studies, including pooled individual patient data analysis from some earlier PAH trials, show that outcomes including survival are especially poor in SSc-PAH [11,12].

A third area of progress was the use of initial combination treatment that strongly suggested that combining an ERA with a PDE5 inhibitor was better than either treatment alone. This was the pretext of the AMBITION trial that showed just that and confirmed equivalent benefit in CTD and SSc-PAH [13]. These trials have underpinned practice over the past decade and in SSc especially moved PAH from being untreatable and inevitably leading to early death with a median survival of only 12 months from diagnosis [2] to a highly treatable complication. Single centre studies have suggested benefit [14] but the article in this issue really shows how much outcomes have improved by pooling data from high quality event driven trials and large well collected clinical cohorts.

The article of Khanna et al [1] is a timely and important paper because previous well-performed meta-analyses of the early pivotal trials had suggested the opposite that PAH-CTD outcomes were not better and that high-cost drugs may not be justified and that other approaches to treatment were needed. It is notable because the present analysis again confirms that outcomes are worse in CTD-PAH than in idiopathic or familial forms of PAH, the impact of treatments should no longer be regarded as insignificant. This is a practice changing observation, especially now that many of the drugs are available in generic formulations and so the cost of modern PAH treatment has fallen at the same time as its true value is convincingly demonstrated.

Whilst the apparent improvement in overall survival in PAH-CTD is encouraging, it is important to recognise that there are multiple confounding factors that could also lead to apparent gains. These include the increased emphasis on PH and PAH due to available therapies that increases vigilance, awareness and may lead to greater diagnosis of milder cases or cases at an early stage. This may also lead to lead time bias. In addition, the establishment of screening methods and algorithms such as DETECT (the first evidence-based algorithm for the screening of PAH in SSc) and others could result in earlier detection and diagnosis and milder cases being detected. Finally, better organisation of care and co-ordinated management may improve outcome and survival even when there is no major benefit from treatments. However, it seems unlikely that these factors would have a major

impact because regular screening has been a management cornerstone for PAH-CTD for many years and so increased detection likely occurred before more treatment became available.

In conclusion, it is now clear there is strong evidence for the value of combination therapies in CTD-PAH. This includes PAH targeted drugs often used in combination and the concurrent use of immunosuppression and PH specific drugs in cases of PAH-CTD due to SLE or MCTD [15]. Not all treatment can be translated from idiopathic to CTD-PAH and the large registries also underscore this. A good example is oral anticoagulation that may improve overall survival in idiopathic PAH but be associated with higher mortality in patients with CTD-PH [3]. But unfortunately, PAH-CTD is still not cured, most cases will die from right heart failure and so there is still much unmet need and work to be done. It is exciting that new drugs targeting different pathways or mechanisms are looking promising (bardoxelone (NCT02036970), sotatercept (NCT03496207)) and in the future these and other approaches may also be added to the armamentarium.

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Table 1. Classification of Pulmonary Hypertension (Nice 2018 World Symposium)

Group 1: PAH	Idiopathic PAH	**Group 3: PH due to lung disease**	Obstructive lung disease
	Heritable PAH		Restrictive lung disease*
	Drug- and toxin-induced		Other lung disease with mixed restrictive/obstructive pattern
	PAH associated with: CTDs***** HIV Portal hypertension Congenital heart disease Schistosomiasis		Hypoxia without lung disease
			Developmental lung disorders
	PAH with venous/capillary involvement (PVOD)*		
Group 2: PH due to left heart disease	PH due to heart failure with preserved LVEF*	**Group 4: PH due to pulmonary artery obstructions**	Chronic thromboembolic PH*
	PH due to heart failure with reduced LVEF*		Other pulmonary artery obstructions
	Vascular heart disease		
	Congenital/acquired cardiovascular conditions leading to post-capillary PH		
		Group 5: PH with unclear and/or multifactorial mechanisms	Haematological disorders
			Systemic and metabolic disorders
			Others
			Complex congenital heart disease

*Mixed patterns of PH with more than one mechanism are frequent in CTD. See reference 6 for more detailed description of current classification

CTDs: Connective tissue diseases, LVEF: left ventricular ejection fraction, PAH: pulmonary arterial hypertension, PH: pulmonary hypertension, PVOD: pulmonary veno-occlusive disease