Comment on: Impact of early immuno-suppressive therapy on pulmonary arterial hypertension in systemic sclerosis: a single-centre real-world study

Sirs,

We read with great interest the recent article by Rodolfi *et al*. evaluating the impact of early immunosuppressive therapy on the occurrence and outcomes of pulmonary arterial hypertension (PAH) in systemic sclerosis (SSc) patients (1). The authors are to be congratulated for conducting this large single-centre retrospective cohort involving 607 patients, which provides valuable insights into one of the most severe complications of SSc. In this cohort, PAH was identified in 77 patients (12.7%). Importantly, early initiation of immunosuppressive therapy did not significantly reduce the risk of PAH (OR 0.74; p=0.495). However, the use of mycophenolate mofetil within the first years of disease onset conferred a significant protective effect (OR 0.12; p=0.048), while hydroxychloroquine (HCQ) use was independently associated with improved survival (HR 0.04; p=0.004). These findings are noteworthy for several reasons. First, the absence of a universal protective effect from 'early immunosuppression' contrasts with the marked benefit of mycophenolate, pointing to a drug-specific rather than class-wide effect. Prior studies have highlighted the efficacy of mycophenolate in stabilising interstitial lung disease in SSc (2), and the present results suggest that vascular remodelling may also be attenuated by this therapy. This hypothesis warrants prospective and mechanistic evaluation. Second, the striking survival advantage with HCQ is both intriguing and unexpected. HCQ is widely prescribed in connective tissue diseases for its immunomodulatory and antithrombotic properties (3), yet robust outcome data in SSc remain scarce. The possibility that HCQ may exert vasculoprotective or endothelial-stabilising effects in SSc-PAH deserves validation in larger cohorts and ideally randomised controlled trials. Third, the study underscores the heterogeneity of treatment response in SSc. Stratifying patients by clinical phenotype, autoantibody profile, and early organ involvement could clarify which subgroups derive the greatest benefit from specific immunomodulatory strategies. Finally, while the findings are compelling, it is important to acknowledge the study's limitations, including its retrospective single-centre design, the limited number of PAH cases, and the lack of power to evaluate the effect of biologic agents. These constraints highlight the need for multicentre, prospective studies to confirm the observed associations. In conclusion, this important study demonstrates that while early immunosuppression overall may not prevent PAH in SSc, mycophenolate appears to provide significant protection and HCQ may offer a survival benefit. These results open new perspectives for optimising treatment strategies in SSc-PAH, reinforcing the need for further mechanistic and controlled investigations.

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