Impact of immunosuppression on development and outcome of systemic sclerosis-associated pulmonary arterial hypertension

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Abstract

Objective

Pulmonary arterial hypertension (PAH) is a frequent and severe complication of systemic sclerosis (SSc). Despite the improvements achieved in recent decades, PAH remains a cause of significant clinical burden, and treatment mainly relies on a combination of vasodilatory and anti-proliferative agents, following the same therapeutic approach used for idiopathic PAH.

Methods

We retrospectively analysed the records of 607 patients reviewed in our centre. PAH was defined as pre-capillary pulmonary hypertension (mPAP ≥ 25mmHg, PVR >3WU, PCWP <15mmHg) in absence of significant hypoxic component (patients with clinically significant airway disease, or with interstitial lung disease and FVC <70%, were excluded from PAH group). Early immunosuppression (IS) was defined as treatment within the first 5 years after SSc onset with conventional or biologic disease-modifying anti-rheumatic drugs (DMARDs), or a prednisone-equivalent dose ≥10mg/day.

Results

Out of 607 patients, 77 received a diagnosis of PAH. Early immunosuppression was not associated with reduced odds of developing PAH (OR 0.74, p=0.495). However, when analysing individual immunosuppressive agents, early treatment with mycophenolate mofetil was associated with a significant protective effect (OR 0.12; p=0.048). Immunosuppressive treatment was associated with a significant reduction in mortality risk (HR 0.41; p=0.045), attributable to the effect of hydroxychloroquine, which was the only agent showing an impact on survival (HR 0.04; p= 0.004).

Conclusion

In this retrospective monocentric study early treatment with mycophenolate was associated with reduced odds of developing SSc-PAH, while treatment with hydroxychloroquine showed a significant improvement in survival in patients with established SSc-PAH.

Key words

systemic sclerosis, pulmonary arterial hypertension, immunosuppression, mycophenolate, hydroxychloroquine

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Introduction

Pulmonary arterial hypertension (PAH) is a frequent complication of systemic sclerosis (SSc), with 8 to 13% of patients expected to develop it during the disease course (1, 2). Moreover, SSc-PAH bears the highest mortality rate amongst CTD-PAH, with 3-year survival of 47% (3).

SSc-PAH involves a complex pathophysiological process which is orchestrated by the combined action of vasoactive and pro-angiogenic factors, inflammatory cytokines, products of autoimmunity, platelet activation and endothelial to mesenchymal transition. This translates into an initial vascular injury which leads to an aberrant fibroproliferative or aberrant repair process, ultimately leading to obliterative pulmonary vasculopathy and progressive loss of function (4). Support for the role of immune cells in the development of SSc-PAH emerged in the last years. Gene expression profiling documented monocyte or macrophage dysfunction, as well as elevated pro-inflammatory cytokines, which discriminated SSc-PAH patients from SSc patients with no PAH and healthy controls (5). Further, autoantibodies targeting angiotensin II receptor and endothelin receptor have been associated with presence of SSc and SSc-PAH (6, 7). These antibodies demonstrated an agonistic function *in vitro*, and high titres predicted development and mortality of SSc-PAH in a prospective analysis (7). Additionally, autoantibodies have an important role in predicting risk and prognosis of SSc-PAH (8). In contrast to other disease-related manifestations, such as ILD, cutaneous and musculoskeletal involvement, immunosuppression is not recommended as a treatment of SSc-PAH. In the last years, some studies have explored the role of immunosuppression in this setting, with inconclusive evidence. Most notably, a recent underpowered double-blind randomised placebo control clinical trial investigated the safety and efficacy of B-cell depletion through rituximab in SSc-PAH. The study did not meet the primary endpoint, represented by improvement in 6 minutes walking distance (6MWD) at week 24 (even though a trend favouring treatment arm was identified), but showed some possible benefit in improving 6MWD when data until week 48 were considered (9).

The aim of this study was to assess whether early immunosuppression could impact development of SSc-PAH and whether immunosuppression could alter its clinical outcome.

Materials and methods

We retrospectively analysed the electronic records of an unselected cohort of patients of the Scleroderma Unit of the Royal Free Campus, London, screening visits from January 1st 1995 and December 31st 2023. To be included in the study, patients were required to meet the 2013 ACR/EULAR classification criteria for SSc and have at least 2 follow-up appointments. Date of SSc onset was defined as the date of first non-Raynaud's symptom. Diagnosis of PAH was considered when haemodynamic parameters measured at right heart catheterisation (RHC) were meeting the 2015 ESC/ERS definition of PAH (*i.e.* mean pulmonary artery pressure ≥25mmHg, pulmonary vascular resistances >3WU, pulmonary capillary wedge pressure <15mmHg) (10). Patients with interstitial lung disease (ILD) and precapillary pulmonary hypertension (PH) were excluded from the PAH group if radiological extension at high resolution computed tomography was more than 20% or a forced vital capacity was lower than 70%. Compound PH phenotypes were included in the PAH category if PAH was considered the main component. Organ-based complications were defined as previously described by Nihtyanova *et al.* (11). Severe gastrointestinal involvement was defined as presence of gastric antral vascular ectasia (GAVE) requiring blood transfusion, intestinal pseudo-obstruction, or requirement of enteral or parenteral nutrition. Early immunosuppression (IS) was defined as treatment within the first 5 years after SSc onset with conventional or biologic disease-modifying anti-rheumatic drugs (DMARDs), or a prednisone-equivalent dose ≥10mg/day. PAH-specific treatment comprised treatment with endothelin receptor antagonists,

phosphodiesterase 5 inhibitors, soluble guanylyl cyclase stimulators, prostacyclin analogues or prostacyclin receptor agonists. In the first part of the study, patients were divided in 3 categories, based on the timing of immunosuppressive treatment: early IS, late IS (immunosuppressive treatment 5 years after SSc onset), no IS. Outcomes of interest were development of PAH and time from SSc to PAH diagnosis. The second part of the study was a survival analysis including only the patients who developed PAH. Here, patients were divided into 2 groups: 'never IS' and 'ever IS'.

Descriptive statistics, logistic and linear regression, and survival analysis were performed with STATA-18 software package. Continuous variables were expressed as median and interquartile range (IQR); categorical variables were expressed as frequencies. Comparison between continuous variables was done through Mann-Whitney test or Kruskal-Wallis test, as appropriate. Comparison between categorical variables was done through Fisher exact test or Pearson's χ^2, as appropriate. The effect of immunosuppression on the hazard of developing PAH was evaluated using multivariable logistic or linear regression analysis, as appropriate. Survival was analysed using Kaplan-Meier survival estimates and multiple Cox regression model. This study was done in compliance with the Declaration of Helsinki (12). *p*-values lower than 0.05 were considered statistically significant.

Results

A total of 629 patients were screened, and 607 were included in the study cohort, whose characteristics are outlined in Table I. Patients in the 'early IS' group had a higher percentage of males, diffuse cutaneous subset, ILD, scleroderma renal crisis (SRC), and severe cardiac involvement. Additionally, they were more frequently anti-topoisomerase I (ATA) or anti-RNA polymerase III (ARA) positive, while anticentromere antibodies (ACA) were more commonly found in the 'late IS' group and were even more frequent inthe 'never IS' group. Comparing immunosuppressive treatment, patients in the 'early IS' group received treatment with mycophenolate mofetil (MMF), azathioprine (AZA) and cyclophosphamide (CYC) more frequently, while patients in the 'late IS' group were more frequently treated with hydroxychloroquine (HCQ).

Table I. Demographic, clinical, therapeutic and serological characteristics of the cohort, stratified by timing of immunosuppression.

Demographic and clinical characteristics				
	Early IS (n=206)	Late IS (n=114)	No IS (n=287)	*p*-value
Age at SSc onset	49 (40-59)	46 (36-55)	50 (50-57)	0.025
Female sex	151 (73.3%)	100 (87.7%)	266 (92.7%)	**<0.001**
DcSSc	118 (57.3%)	25 (17.4%)	18 (6.3%)	**<0.001**
PAH	11 (5.3%)	21 (14.6%)	45 (15.7%)	**<0.001**
Time to PAH (yrs)	10.5 (5 – 16)	11 (5 – 16)	11 (5 – 17)	0.581
ILD	129 (62.7%)	56 (49.1%)	47 (16.4%)	**<0.001**
SRC	14 (6.8%)	5 (4.4%)	6 (2.1%)	**0.032**
Severe cardiac involvement	12 (5.8%)	3 (2.6%)	3 (1%)	**0.008**
Severe GI involvement	1 (0.5%)	5 (2.6%)	2 (0.7%)	**0.017**
Treatment characteristics				
Mycophenolate mofetil	101 (49%)	47 (41.2%)		**0.002**
Azathioprine	45 (21.9%)	13 (11.4%)		**0.001**
Cyclophosphamide	60 (29.1%)	16 (14%)		**<0.001**
Methotrexate	33 (16%)	27 (23.7%)		0.654
Hydroxychloroquine	35 (17%)	41 (36%)		**0.003**
Pred ≥10mg/day	54 (26.2%)	21 (18.4%)		0.324
Others	2 (0.9%)	4 (3.5%)		0.718
Serological characteristics				
	Early IS (n=193)	Late IS (n=103)	Never IS (n=243)	
ACA	15 (7.7%)	42 (40.8%)	167 (68.8%)	**<0.001**
ATA	77 (39.9%)	27 (26.2%)	22 (9.1%)	**<0.001**
ARA	46 (23.9%)	9 (8.7%)	14 (5.5%)	**<0.001**
ANA+ENA-	28 (14.5%)	7 (6.8%)	10 (4.1%)	**<0.001**
Other	31 (16%)	23 (22%)	35 (14%)	0.643

IS: immunosuppression; DcSSc: diffuse cutaneous SSc; PAH: pulmonary arterial hypertension; ILD: interstitial lung disease; SRC: scleroderma renal crisis; ACA: anticentromere antibodies; ATA: anti-topoisomerase I antibodies; ARA: anti-RNA polymerase III antibodies; ANA+ENA-: ANA-positive but ENA-negative; Other: anti-U1RNP, -ThTo, -Ku, -Ro, -La, -heterogeneous nuclear RNP, -Sm, -U3RNP, -PmScl, and ANA-negative.

Table II. Odds ratios with 95% confidence intervals for development of SSc-PAH.

	PAH development		
	OR	95% CI	*p*-value
MMF	0.12	0.01 – 0.98	**0.048**
Age at SSc onset	1.01	0.99-1.04	**0.145**
Female sex	0.71	0.27 – 1.86	0.485
DcSSc	0.53	0.14 – 1.99	0.351
ILD	2.99	1.35 – 6.61	**0.007**
SRC	7.9	1.33 – 46.89	**0.023**
Severe cardiac involvement	0.25	0.02 – 2.7	0.258
Severe GI involvement	3.29	0.29 – 36.82	0.334
ACA	2.87	1.12 – 7.31	**0.027**
ATA	0.17	0.04 – 0.68	**0.012**
ARA	0.35	0.05 – 2.29	0.272
ANA+ENA-	0.69	0.17 – 2.85	0.607

OR: odds ratio; CI: confidence interval; DcSSc: diffuse cutaneous systemic sclerosis; ILD: interstitial lung disease; SRC: scleroderma renal crisis; ACA: anticentromere antibody; ARA: anti-RNA polymerase III antibody.

PAH development

During a median follow up time of 21 years (IQR 14–27.75), a total of 77 pa-

Table III. Demographic, clinical and serological characteristics of PAH cohort.

	Ever IS (n=30)	Never IS (n=42)	*p*-value
Age at SSc onset (yrs)	50 (45.25 – 56)	54 (48 – 59.75)	0.162
Female sex	26 (87%)	37 (88%)	0.565
Age at PAH diagnosis	62 (58-68)	66.5 (62-72)	0.074
mPAP at PAH diagnosis (mmHg)	29 (26 – 33.25)	32 (26-40)	0.2328
DcSSc	**6 (20%)**	**0**	**0.004**
ILD	**18 (60%)**	**6 (14.6%)**	**<0.001**
SRC	2 (6.5%)	2 (4.7%)	0.556
Severe cardiac involvement	0	1 (2.4%)	0.583
Severe GI involvement	1 (3.3%)	0	0.417
	PAH specific therapy		
ERA	20 (66.7%)	20 (48.7%)	0.104
PDE5i	20 (66.7%)	21 (51.2%)	0.145
PC analogue	3 (10%)	10 (24.4%)	0.106
Double therapy	12 (40%)	14 (34.1%)	0.369
Triple therapy	3 (10%)	1 (2.4%)	0.192
No therapy	4 (13.3%)	7 (16.7%)	0.483
	Antibody status		
	Ever IS (n=28)	Never IS (n=35)	
ACA	**16 (55.2%)**	**31 (86.1%)**	**0.006**
ATA	3 (10%)	0	0.084
ARA	2 (6.7%)	0	0.195
PM/Scl	0	1 (2.8%)	0.556
Other	3 (10.3%)	1 (2.8%)	0.227
ANA+ENA-	2 (6.7%)	2 (5.6%)	0.607
ANA-	3 (10%)	1 (2.8%)	0.229

IS: immunosuppression; DcSSc: diffuse cutaneous SSc; ILD: interstitial lung disease; SRC: scleroderma renal crisis; ERA: endothelin receptor antagonist; PDE5i: phosphodiesterase 5 inhibitor; PC: prostacyclin; ACA: anticentromere antibodies; ATA: anti-topoisomerase I antibodies; ARA: anti-RNA polymerase III antibody.

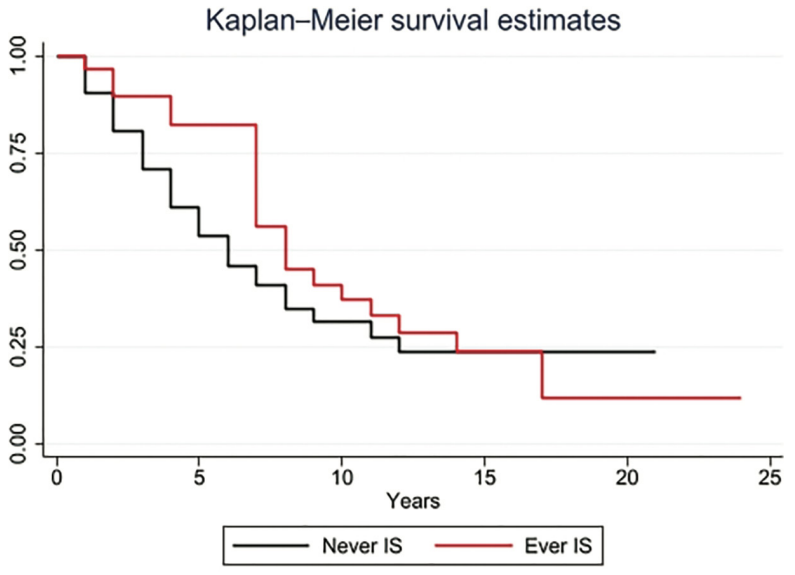

Fig. 1. Kaplan-Meier survival estimates curve comparing patients receiving immunosuppressive treatment and patients never receiving immunosuppressive treatment.

tients developed PAH. After adjusting for confounding variables (sex, diffuse cutaneous subset, ILD, SRC, severe cardiac involvement, ACA, ATA, ARA), early immunosuppression was not associated with reduced odds of developing PAH (OR 0.74, 95% CI 0.31-1.76; *p*=0.495). However, when analysing single immunosuppressive agents, early treatment with MMF was associated with significantly reduced odds of developing PAH (OR 0.12, CI 0.01–0.98; *p*=0.048). Presence of ILD was associated with increased odds of developing PAH (OR 3.01, CI 1.37–6.63; *p*=0.006), as well as history of SRC (OR 6.53, CI 1.13–37.58; *p*=0.035). Among antibodies, ACA increased the odds of developing PAH (OR 2.92, CI 1.13–7.53; *p*=0.026), while ATA was associated with a lower incidence of PAH (OR 0.15, CI 0.04–0.62; *p*=0.009) (odds ratios depicted in Table II). Time to PAH was comparable between the 3 groups (*i.e.* 10.5 years for early immunosuppression, 11 years for late immunosuppression, and 11 years for no immunosuppression; *p*=0.581). On linear regression, early immunosuppression did not impact the time to development of PAH (r= -0.86, CI -13.03–11.31; *p*=0.887), and no other variable was significantly associated with time to PAH.

Outcome in PAH

Of the 77 patients that developed PAH, 72 had detailed clinical information to be included in survival analysis. Thirty patients received immunosuppressive treatment during the course of the disease ('ever IS' group) while 42 were never subjected to IS ('never IS' group). The immunosuppressive agents were mycophenolate mofetil (13 patients), azathioprine (7), methotrexate (7), cyclophosphamide (5), hydroxychloroquine (9), prednisolone (4) rituximab (1) and tocilizumab (1). Table III depicts the demographic, clinical and serological (the latter available only for 65 patients) characteristics of the cohort. Patients in the 'ever IS group' had more frequently a diffuse cutaneous phenotype and ILD while patients in the 'never IS' group were more frequently anticentromere positive. The values of mPAP at first RHC were comparable across the 2 groups (29mmHg for 'ever IS' group, 32mmHg for 'never IS' group; *p*=0.2328). In a median follow up time of 7 years (IQR 3–10) 53 patients (73.6%) died: 23 in the 'ever IS' and 30 in the 'never IS'. Median time of survival from PAH diagnosis

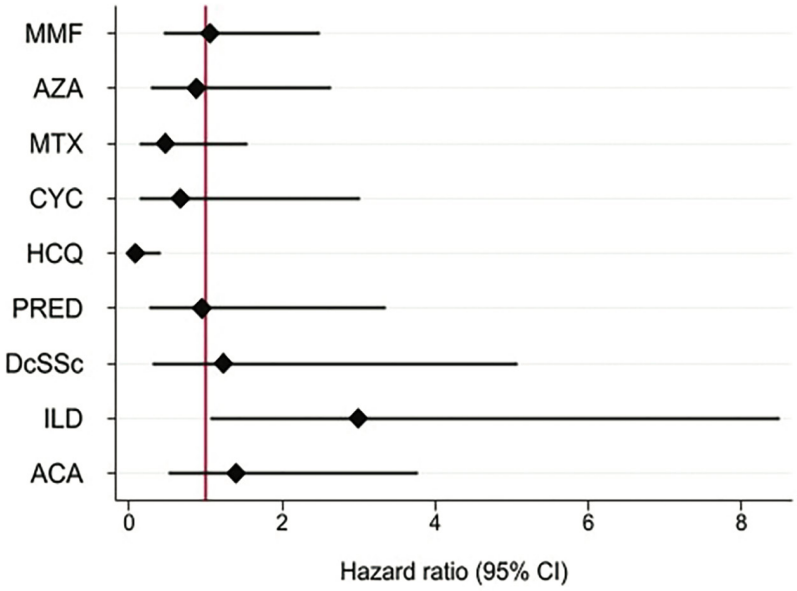

Fig. 2. Risk over time for mortality for individual immunosuppressive agents, adjusted for confounders. MMF: mycophenolate mofetil; AZA: azathioprine; MTX: methotrexate; CYC: cyclophosphamide; HCQ: hydroxychloroquine; pred: prednisolone ≥10 mg/day; DcSSc: diffuse cutaneous subset; ACA: anticentromere antibodies; ILD: interstitial lung disease.

Table IV. Risk over time for mortality for single immunosuppressive agents, adjusted for confounders.

	HR	95% CI	*p*-value
MMF	1.16	0.47 – 2.83	0.488
AZA	0.68	0.21 – 2.19	0.519
MTX	0.48	0.14 – 1.63	0.245
CYC	0.66	0.14 – 3.16	0.611
HCQ	**0.06**	**0.01 – 0.52**	**0.011**
Pred ≥10mg/day	0.93	0.25 – 3.46	0.918
DcSSc	1.03	0.22 – 4.91	0.962
ILD	2.93	0.99 – 8.61	0.050
ACA	1.43	0.51 – 4.09	0.501

MMF: mycophenolate mofetil; AZA: azathioprine; MTX: methotrexate; CYC: cyclophosphamide; HCQ: hydroxychloroquine; pred: prednisolone 10mg/day; DcSSc: diffuse cutaneous subset; ACA: anticentromere antibodies; ILD: interstitial lung disease.

was 7 years (IQR 5.5–9.5) for the 'ever IS' group and 4 years (IQR 2–6) for the 'never IS' group. In survival analysis, immunosuppression was associated with a statistically significant reduction in mortality risk (HR 0.41, CI 0.16–0.98; p=0.045). Figure 1 shows Kaplan-Meier survival estimates for 'ever IS' and 'never IS'. When analysing the individual immunosuppressants, hydroxychloroquine (HCQ) was the only agent associated with a significantly reduced mortality risk (HR 0.04, CI 0.06–0.37; p=0.004) (Fig. 2, Table IV). The indications for treatment with HCQ were inflammatory arthralgia (7 patients) and overlap with rheumatoid arthritis (2 patients). Of the 9 patients who received hydroxychloroquine, 2 died 17 years after PAH diagnosis.

Discussion

Preclinical and clinical data demonstrate a role for aberrant cellular and humoral response in the pathogenesis of SSc-PAH (5, 13, 14). However, the recommended treatment follows the same approach of idiopathic PAH and mainly relies on the combined action of vasodilators and anti-proliferative agents (15). There are currently no established strategies to target the immune-mediated component of SSc-PAH, which may account for the excess in mortality observed in SSc-PAH compared to its idiopathic counterpart (IPAH) (16).

In the first part of this study, we evaluated whether early IS could reduce the risk of developing SSc-PAH. Significantly fewer patients developed PAH in the early IS group; however, after adjusting for confounders, early immunosuppression was not associated with a reduced risk of developing PAH in the multivariable analysis. Additionally, early immunosuppression did not have an effect in delaying the onset of PAH, since time from SSc onset to PAH diagnosis was comparable across the 3 treatment subgroups. However, when considering the single treatment agents, early treatment with MMF was associated with a reduced risk of developing PAH. Mycophenolate is an established treatment for diffuse cutaneous involvement and ILD but has no clear-cut role in the management of the vasculopathic complications of SSc. Our study supports the concept that early treatment with MMF may reduce the likelihood to develop pre-capillary PH. These findings are in line with the described effect of MMF in alleviating thickening of pulmonary arterial walls and inhibiting abnormal vascular remodelling in a mouse model of PAH (17), and its reported efficacy in cases of CTD-associated PAH other than SSc (18). Interestingly, the putative protective effect of MMF was maintained after adjusting for presence of ILD, which represents one of the main indications for immunosuppressive treatment. A recent randomised prospective open label pilot trial compared MMF and placebo in adults with limited cutaneous SSc to explore whether treatment with MMF on top of standard of care may slow down disease progression (MINIMISE-Pilot trial; Identifier NCT04927390). The long-term follow up of these patients may provide additional evidence on whether treatment with MMF may protect against development of PAH. The second question of the study was whether immunosuppression could influence clinical outcomes in patients with an established diagnosis of PAH. Immunosuppression was associated with a reduced risk of mortality, an effect driven by the subgroup of patients receiving treatment with HCQ. HCQ is not an immunosuppressant rather an

immunomodulant agent, which is not infrequently prescribed to SSc patients who present inflammatory arthralgia and/or overlap with other rheumatic diseases (*e.g.* rheumatoid arthritis, Sjögren's syndrome). The role of HCQ in PAH has been already explored in a mouse model of induced PAH. In this setting, administration of chloroquine and HCQ has been shown to prevent the development of PAH, right ventricular hypertrophy, vascular remodelling, and deterioration of established PAH (19). Treatment was associated with increased apoptosis and reduced proliferation of pulmonary artery smooth muscle cells *in vivo*, an effect attributed to the blockade of autophagy and of the lysosomal degradation of bone morphogenetic protein type II receptor (BMPR-II) (19). The latter effect is especially relevant due to the established role of reduced BMPR2 in the pathogenesis of various forms of PAH (20). Additionally, Wu *et al*. reported a potent pulmonary vasodilatory effect of chloroquine in a rat model of PAH, owing to the antagonistic effect on pulmonary artery smooth muscle cell's calcium channels (21). Clinical evidence on the role of HCQ in SSc-PAH is presently limited. A large retrospective analysis by Boucher *et al*. reported a beneficial effect in preventing onset of SSc-PAH when initiated in the first 18 months of the disease (22). However, our study did not document an impact on development of SSc-PAH rather on its outcome.

All of the patients in this cohort met the 2013 ACR/EULAR criteria for SSc. This includes the 4 ANA-negative patients who satisfied the criteria on the basis of either diffuse cutaneous involvement (1 patient), or a combination of Raynaud's phenomenon, presence of ILD, and telangiectasias (the remaining 3 patients). Only one of them was among the recipients of HCQ and did not have an overlap CTD phenotype that might have contributed to PAH development or outcome.

We are cognisant of the limitations of this study. First, its retrospective nature limits the significance of our findings, which should be interpreted as hypothesis-generating rather than hypothesis-testing. Second, we did not employ the updated definition of PH (15), since most of the patients had RHC before the 2019 update was formulated and received standard of care monitoring and treatment according to the previous definition (10). Prospective studies employing the updated definition of PAH would be more informative in exploring the effect of immunosuppression in milder forms of PAH (23). However, the fact that PAH diagnosis was always supported by haemodynamic measures, strengthens the significance of our findings, since it allowed us to adjust for mean PAP at diagnosis. Third, due to the difficulty in retrieving the clinical records at various timepoints for some patients, it was not possible to consider the duration of immunosuppressive treatment as an additional variable. In addition, due to the limited number of events, it was not possible to separate single agent's effect in patients receiving more than one DMARD throughout the disease course. Fourth, being the analysed cohort historical, this study was not powered to test the effect of biologic agents since they were introduced as part of standard of care only in recent years. Finally, this is a single-centre study and the inclusion of patients from other centres would increase the significance of our findings. Future prospective, ideally multicentric, studies would be warranted to verify our hypothesis and strengthen the presented findings.

Conclusions

This retrospective monocentric study demonstrated that early treatment with mycophenolate mofetil is associated with reduced risk of development of PAH in SSc patients. Furthermore, treatment with HCQ has been linked to significant improvements in clinical outcomes in patients with SSc-PAH. Given the limitations of the retrospective approach, these findings support the emerging role of immunosuppression in SSc-PAH in addition to the standardised vasodilator and antiproliferative strategies in improving outcomes in SSc-PAH, which remains one of the most severe clinical complications. Further prospective research in this topic would thus be warranted.

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