ESC European Society of Cardiology

European Journal of Heart Failure (2025) **27**, 476–478
doi:10.1002/ejhf.3543

INVITED EDITORIAL

Tailored therapies for patients affected by systemic sclerosis with primary heart involvement: The role of rituximab

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This article refers to 'Add-on rituximab for primary heart involvement associated with systemic sclerosis: A step forward in the tailored treatment of myocarditis?' by M. De Santis *et al.*, published in this issue on pages 473–475.

Systemic sclerosis (SSc) is a rare autoimmune connective tissue disease with multi-organ involvement.[1] Classic manifestations include Raynaud phenomenon, skin involvement (limited or diffuse cutaneous SSc), gastrointestinal involvement, and SSc-interstitial lung disease (ILD), while less common manifestations can involve pulmonary arterial hypertension and cardiac manifestations (pericardial or cardiac involvement).[1] Experts have proposed SSc with primary heart involvement (pHI) as a broad term to describe different cardiac manifestations.[2] The prevalence of clinical SSc-pHI is still unknown and might be underestimated. In previous studies, the proportion of patients with SSc-pHI varies from 10% to 40% of patients with SSc, according to different applied definitions and different tools used to detect cardiac involvement.[2,3] Common clinical cardiac features may include impaired contractility and relaxation, arrhythmias, myocarditis and pericardial disease. Despite uncertainty in definition and epidemiology, cardiac involvement is among the most frequent causes of death in SSc, representing a major issue for rheumatologists and cardiologists taking care of patients with this disorder.

Organ-specific therapies have improved the outcomes of these patients, with data also generated by randomized clinical trials.[1] Mycophenolate mofetil (MMF), methotrexate (MTX), cyclophosphamide, and rituximab (RTX), which can be used for the treatment of diffuse cutaneous SSc, are agents that have been tested to treat inflammatory cardiomyopathy both in the setting of SSc or other systemic autoimmune disorders.[4] In addition, treatment algorithms according to experts to treat patients with cardiac involvement suggest the use of MMF or high-dose corticosteroids plus medications for heart failure as first-line therapies in patients with myocarditis associated with SSc, and intravenous cyclophosphamide or RTX as second-line therapy. MMF or MTX are proposed as second-line therapy for patients with pericardial involvement poorly responsive to low-dose steroids or non-steroidal anti-inflammatory drugs or colchicine or hydroxychloroquine.[5] Still limited data can guide the treatment of patients with SSc-pHI, thus data on the use specific agents in patients with SSc-pHI and their outcome are relevant to improve clinical practice. In this view, the correspondence by De Santis *et al.*[6] offers us the experience of their centre on the use of RTX on top of MMF therapies in patients with SSc-pHI. Even if RTX, a B-cell depleting agent, has been proposed for the treatment of patients with SSc, anecdotal data exist on the use of RTX in patients with SSc-associated myocarditis or inflammatory cardiomyopathy. This letter also represents the opportunity to remind heart failure specialists and general cardiologists of the challenges and the potential new drugs to treat patients with SSc-pHI.

The first relevant data is that among 350 patients with SSc treated between 2016 and 2023, 37 (11%) were diagnosed with SSc-pHI,[6] in line with previous observations of myocarditis detection with cardiac magnetic resonance imaging (CMRI) in 10–11% of patients with SSc.[3] It should be noted that the inclusion used by De Santis *et al.* to describe cardiac involvement was broad despite being based on CMRI parameters and can have included patients without cardiac inflammation at the time of the assessment.[7] Among the 37 patients in their single-centre cohort, five patients were treated with intravenous RTX (1 g 2 weeks apart, every 6 months) on top of MMF therapy at a stable maximum tolerated dose (2-3 g/day). CMRI performed after 12 months showed in three out of four patients partial improvements in some CMRI parameters, while one patient was initially excluded due to anaphylaxis during RTX infusion. These three patients had a mild increase in

The opinions expressed in this article are not necessarily those of the Editors of the *European Journal of Heart Failure* or of the European Society of Cardiology. doi: 10.1002/ejhf.3467.

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T2-mapping and extracellular volume (ECV) parameters, which are considered markers able to detect myocardial oedema, at baseline with a subsequent improvement. At the same time, no impact was observed on left ventricular ejection fraction (LVEF). One of these three patients who had a mild increase in high-sensitivity troponin levels, normalized troponin levels at follow-up. Patient 4, who had no change/mild increase in T2-mapping and ECV parameters, had significantly increased T1-mapping parameter and a borderline T2-mapping parameter. Likely this patient had a fibrotic, more than an inflammatory phenotype. Similar changes in laboratory markers and CMRI parameters were observed in the second cohort of five patients with SSc-pHI, matched by sex and autoantibody, who were treatment-naïve at the time of pHI diagnosis and then initiated with MMF.[6] It remains unclear whether minimal changes in T2-mapping and ECV parameters in the absence of consistent improvement in LVEF can be clinically meaningful in both groups. Even if ventricular arrhythmias are reported at baseline in two out of four patients who received RTX, no data are reported on arrhythmic patterns in the follow-up.

Several intrinsic limitations can be ascribed to the minimal number of cases in these series, even if it remains the largest cohort of well-characterized patients with SSc-pHI treated with RTX. Suspicion for pHI arose because of a broad spectrum of clinical manifestations, including new onset dyspnoea, palpitation, angina, syncope, ventricular arrhythmia on 24 h Holter electrocardiographic monitoring, or elevated serum myocardial enzymes. Thus the precise cardiac manifestation remains elusive. In fact, only one patient in the group treated with RTX had reduced LVEF and increased B-type natriuretic peptide (BNP) plasma levels whereas the other four patients had preserved LVEF and normal BNP levels. In addition, no patients had late gadolinium enhancement (LGE) on CMRI, that is uncommon in patients with myocarditis associated with SSc. LGE has been observed in 83% of patients with SSC and myocarditis in another series of 18 patients where CMRI scan was repeated following administration of different immunosuppressive agents, mostly including cyclophosphamide (11 out of 18; 61%, and RTX administered only in 1 patient).[8] Likely patients with different phenotypes of cardiac involvement were included, mostly with mild forms of myocarditis. Likely, the benefits of RTX could be expected in patients with active myocarditis and more severe clinical manifestations and CMRI pathologic findings. It could be possible that in this report, the signal from the potential benefit of RTX was underestimated by the mild SSc-pHI at baseline.

Using propensity-score weighting controls, Caforio *et al.*[4] showed safety and efficacy of prolonged tailored immunosuppressive therapy, in biopsy-proven immune-mediated myocarditis, irrespective of histology (i.e. either lymphocytic or non-lymphocytic), and clinical presentation (i.e. with or without heart failure). Extra-cardiac immune-mediated disease, mainly SSc, was reported in 58 (16%) of the overall population and 32 (35%) of those receiving tailored immunosuppression. However, biopsy was not performed in patients initiated with RXT in the study by De Santis *et al.* Although the occurrence of myocarditis is recognized among the complications of SSc, the lack of proven inflammation might lead to the treatment of patients with no clear indications for immunosuppressive therapy. In a previous series of seven patients with SSc and newly developed clinical symptoms of heart disease (heart failure, chest pain, or palpitations), six had evidence of LGE

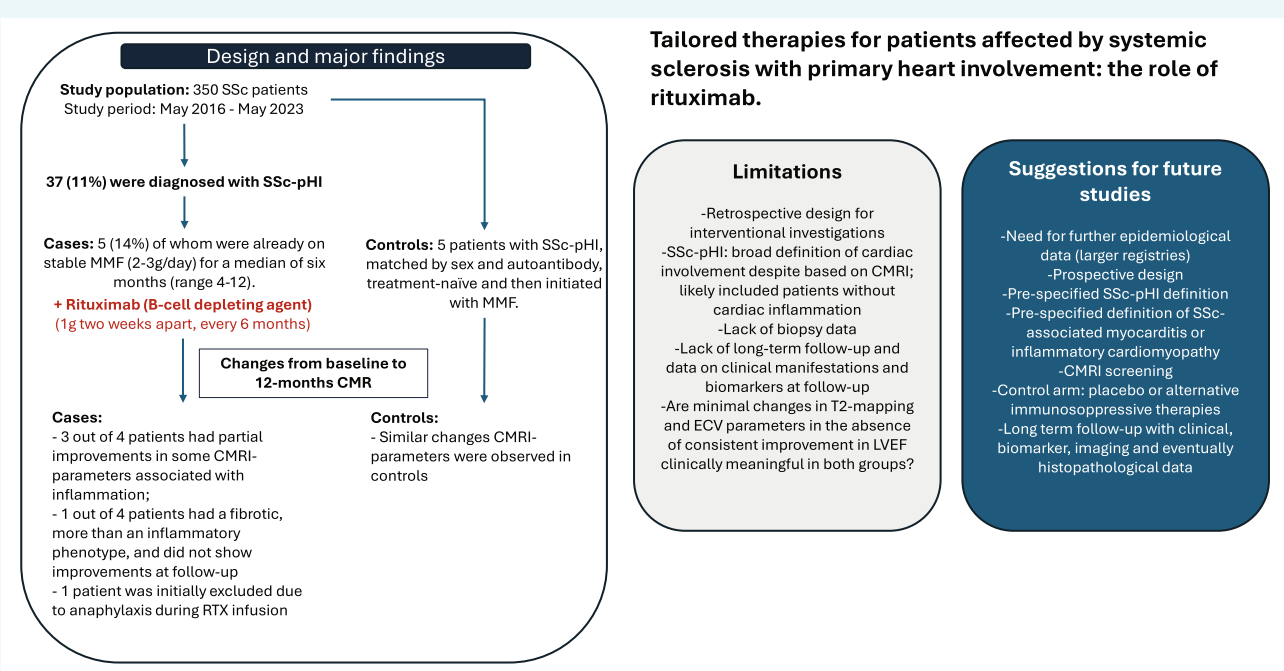

Figure 1 Summary of the design and major findings of the study by De Santis *et al.*, limitations and suggestions for future research. CMRI, cardiac magnetic resonance imaging; ECV, extracellular volume; LVEF, left ventricular ejection fraction; MMF, mycophenolate mofetil, pHI, primary heart involvement; RTX, rituximab; SSc, systemic sclerosis.

on CMRI, and six had signs of active myocarditis on endomyocardial biopsy without evidence of microvessel disease.[9] Steroids, cyclophosphamide, and azathioprine were used to treat these patients. At 5 years, two patients had a sudden cardiac death.[9]

Finally, long-term data are needed to define whether RTX should be continued or can be interrupted in patients who improved after 12 months.

This report should be seen as a hypothesis-generating study that could support the attempt to use RTX in patients with SSc and cardiac manifestation when already on stable dose of MMF or as an additional drug in acute myocarditis associated with SSc in native patients in addition to steroids or MMF depending on the severity of the clinical presentation. Large registries on the description of cardiac manifestations in patients with SSc and on the effects of different agents are needed to provide more data on the best guidance to treat this patient population with a mortality that remains significantly associated with heart involvement (*Figure 1*).

Conflict of interest: D.T. received speaker fees from Alnylam Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Pfizer and Roche Diagnostics. F.A. received a grant from the Italian Ministry of Health (GR-2019-12368506; principal investigator of the investigator-driven MYTHS [Myocarditis Therapy with Steroids] trial) and a grant from Italian Ministry of Health and NextGenerationEU (PNRR-MAD-2022-12376225) and was a consultant for Kiniksa, AstraZeneca and Cytokinetics, and is consultant for Lexeo. M.M. received personal fees of minimal amounts in the last 3 years from Amgen, Livanova and Vifor Pharma as a member of Executive or Data Monitoring Committees of sponsored clinical trials; from AstraZeneca, Abbott Vascular, Bayer, Boheringer Ingelheim and Edwards Therapeutics for participation in advisory boards and/or speeches at sponsored meetings.

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