systemic sclerosis (SSc). In this study, the primary outcome measure was change in the 6-minute-walk distance (6MWD) (1). The 6MWD has some disadvantages as a primary outcome measure in a clinical trial of PAH (2), particularly in patients with SSc (3).

A number of factors affect the 6MWD in SSc aside from PAH, including interstitial lung disease (ILD), arthritis, muscle strength, conditioning, peripheral vascular disease, and nutritional status (4). However, the present study did not report the prevalence or the severity of these common SSc manifestations in the cohort, which raises the likelihood of confounding bias.

ILD affects 25–90% of patients with SSc and may precede or develop in parallel with PAH (5). In this study, although subjects with a TLC $<$70% predicted were excluded, patients with mild fibrosis on high-resolution computed tomography were eligible to participate. Rituximab (RTX) is an immunomodulatory drug that can inhibit ILD progression in SSc. This effect is not limited to patients with moderate or severe disease but has also been reported in subjects with mild ILD (5). Further characterization of pulmonary function of the study participants, including FVC% predicted and its response to treatment, would have been informative in Table 1 as well as Tables E2–7.0 in the work by Zamanian and colleagues.

Erosive arthritis has been reported in 18% and joint inflammation in up to 60% of patients with SSc (6). RTX is an established therapy for polyarthritis in systemic rheumatic diseases, including, but not limited to, rheumatoid arthritis. No data on joint inflammation were reported in this cohort, nor were changes in CRP (C-reactive protein) or erythrocyte sedimentation rate.

The prevalence of skeletal myopathy in SSc has been estimated to be at least 17% and more common in patients with respiratory impairment. RTX is a treatment option for inflammatory myopathies, and current data suggest that it is effective against immune-mediated myositis. It would have been informative to know the prevalence and severity of myopathy among the study participants before and after RTX treatment.

No changes in immunomodulatory background treatment were allowed during the study's first 24 weeks. It can be speculated that RTX treatment may have alleviated disease activity unrelated to PAH in the RTX arm. The same would not have been possible in the placebo group.

Besides the primary outcome measure, the authors included predefined secondary outcomes. No changes were seen in pulmonary vascular resistance or NTproBNP (N-terminal pro–B-type natriuretic peptide), factors that, in contrast to the 6MWD, are directly associated with the pulmonary circulation (1).

In summary, we conclude that RTX is an immunomodulatory agent that may improve several SSc disease manifestations. The 6MWD is a composite outcome measure to which pulmonary vascular function is only one out of multiple contributing factors (3, 4). Given the systemic nature of this disease (5, 6) and our current knowledge on RTX in rheumatology, we ask the authors to elaborate on changes in measures of ILD, arthritis, and myopathy over the course of the study. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Reply to Andréasson *et al.*

From the Authors:

We agree with the concern raised by Andréasson and colleagues in response to the rituximab trial, which tested B-cell depletion as a therapy for systemic sclerosis (SSc)-associated pulmonary arterial hypertension (PAH) (1). In short, we acknowledge that SSc is a multisystem disease and that putative improvements in the 6-minute-walk distance (6MWD) can be attributable to changes in conditions not directly related to PAH. We addressed this fundamental concern in the discussion section of the published manuscript (1) but agree that further analysis and discussion on this point is warranted.

Originally Published in Press as DOI: 10.1164/rccm.202104-1023LE on June 9, 2021

Andréasson and colleagues requested additional data on interstitial lung disease (ILD), arthritis, and myopathy over the course of the study. This cohort of SSc-PAH was primarily anticentromere antibody positive with a low prevalence of inflammatory manifestations (2, 3). At baseline, five participants (17%) in the rituximab group and one (3.6%) in the placebo group had mild ILD. Four (14%) participants in the rituximab group had a history of inflammatory arthritis, whereas no participants in the placebo group did. Only one participant in each group had a history of inflammatory myositis. Osteoarthritis or degenerative arthritis, which could affect ambulation, was a common comorbidity observed in 29 (51%) study participants and equally distributed between the treatment arms. This would be expected, as the mean age was 58.2 ± 9.1 years. However, rituximab would not be expected to impact this noninflammatory form of arthritis. Unfortunately, we did not collect postbaseline TLC and FVC, but baseline measures were not predictive of change in 6MWD at Week 24 or 48. We did not collect information on inflammatory markers or muscle enzymes, but standard musculoskeletal examinations were unchanged throughout the study, with the exception of one participant in the rituximab arm who experienced new joint swelling of the first metatarsal phalangeal joint at Week 24 that resolved by Week 48. In addition, we queried all participants whether they had a "musculoskeletal disorder that limits ambulation" before each 6MWD. Only one participant responded yes to this question at screening, with five responding yes at some point during the study. Given the serologic profile of our cohort, the lack of predictive value of the baseline TLC, and the lack of physical examination evidence of musculoskeletal inflammation over the course of the study, it is reasonable to suggest that the improvement in 6MWD in the rituximab group was related to effects on PAH.

SSc is a complex multisystem disease that has been linked to destructive B-cell immunity. We agree that evidence supporting the use of rituximab in the treatment of SSc-ILD and other manifestations of SSc is growing (4). Therefore, positive effects on pulmonary vascular disease with rituximab is certainly plausible. We agree that, in general, the 6MWD is affected by multiple systemic factors in patients with SSc. This trial made considerable efforts to enroll a homogenous population of SSc participants resulting in a cohort with minimal musculoskeletal features and pulmonary hypertension attributable to group I disease (i.e., SSc-PAH). The results of the trial should be interpreted in this context. Larger studies will be necessary to better delineate the effects of immunotherapy in this patient population. In conclusion, we thank our colleagues and hope that the knowledge conferred by this work can inform trial design for any future immunoadjuvant trials studying SSc-PAH. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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