7. Bero L, Chartres N, Diong J, Fabbri A, Ghersi D, Lam J, *et al.*. The risk of bias in observational studies of exposures (ROBINS-E) tool: concerns arising from application to observational studies of exposures. *Syst Rev* 2018;7:242.
8. Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965;58:295–300.
9. Fedak KM, Bernal A, Capshaw ZA, Gross S. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. *Emerg Themes Epidemiol* 2015;12:14.
10. Hume D. A treatise on human nature. London: Clarendon Press; 1739.
11. Gershon AS, Jafarzadeh SR, Wilson KC, Walkey AJ. Clinical knowledge fro observational studies everything you wanted to know but were afraid to ask. *Am J Respir Crit Care Med* 2018;198:859–867.
12. Ioannidis JPA. Contradicted and initially stronger effects in highly cited clinical research. *JAMA* 2005;294:218–228.
13. MacMahon S, Collins R. Reliable assessment of the effects of treatment on mortality and major morbidity, II: observational studies. *Lancet* 2001;357: 455–462.
14. Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, *et al.*; International Stroke Trial Collaborative Group; European Carotid Surgery Trial Collaborative Group. Evaluating non-randomised intervention studies. *Health Technol Assess* 2003;7:iii–x, 1–173.
15. Bosco JLF, Silliman RA, Thwin SS, Geiger AM, Buist DSM, Prout MN, *et al.* A most stubborn bias: no adjustment method fully resolves confounding by indication in observational studies. *J Clin Epidemiol* 2010;63:64–74.
16. Vandenbroucke JP. When are observational studies as credible as randomised trials? *Lancet* 2004;363:1728–1731.
17. Vandenbroucke JP. Why do the results of randomised and observational studies differ? *BMJ* 2011;343:d7020.
18. Sox HC, Greenfield S. Comparative effectiveness research: a report from the Institute of Medicine. *Ann Intern Med* 2009;151:203–205.

Reply to Albert

From the Authors:

We thank Dr. Albert for the comments about our ATS Research Statement (1). We agree that well-performed randomized clinical trials (RCTs) can produce high-quality evidence for making inferences about the causal effects of an intervention on outcomes. However, for most cases, evidence from high-quality RCTs for outcomes that are critical to decision-making does not exist or is insufficient for informing a course of action with confidence. For example, of 19 guideline recommendations in the recently published 2020 asthma guideline update from the National Asthma Education and Prevention Program, only 3 were based on high-quality evidence (2). The ATS Research Statement explains the framework proposed by the Grading of Recommendations Assessment, Development and Evaluation working group in cases in which there is insufficient evidence from RCTs. We stand by this framework for decision-making but acknowledge the need to update the framework as new evidence emerges. ■

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References

1. Gershon AS, Lindenauer PK, Wilson KC, Rose L, Walkey AJ, Sadatsafavi M, *et al.* Informing healthcare decisions with observational research assessing causal effect. An official American Thoracic Society Research Statement. *Am J Respir Crit Care Med* 2021;203:14–23.
2. Cloutier MM, Baptist AP, Blake KV, Brooks EG, Bryant-Stephens T, DiMango E, *et al.*; Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI) administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC). 2020 focused updates to the Asthma Management Guidelines: a report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. *J Allergy Clin Immunol* 2020;146:1217–1270.

Multiple Manifestations of Systemic Sclerosis Affect Walk Distance

To the Editor:

We welcome the novel report on the efficacy of B-cell depletion in the treatment of pulmonary arterial hypertension (PAH) associated with

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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. ■

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References

1. Zamanian RT, Badesch D, Chung L, Domsic RT, Medsger T, Pinckney A, *et al.*; NIH ASC01 Study Group. Safety and efficacy of B-cell depletion with rituximab for the treatment of systemic sclerosis associated pulmonary arterial hypertension: a multi-center, double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2021;204:193–285.
2. Gaine S, Simonneau G. The need to move from 6-minute walk distance to outcome trials in pulmonary arterial hypertension. *Eur Respir Rev* 2013; 22:487–494.
3. Sanges S, Launay D, Rhee RL, Sitbon O, Hachulla É, Mouthon L, *et al.* A prospective study of the 6 min walk test as a surrogate marker for haemodynamics in two independent cohorts of treatment-naïve systemic sclerosis-associated pulmonary arterial hypertension. *Ann Rheum Dis* 2016; 75:1457–1465.
4. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166:111–117.
5. Goswami RP, Ray A, Chatterjee M, Mukherjee A, Sircar G, Ghosh P. Rituximab in the treatment of systemic sclerosis-related interstitial lung disease: a systematic review and meta-analysis. *Rheumatology (Oxford)* 2021;60:557–567.
6. Avouac J, Guerini H, Wipff J, Assous N, Chevrot A, Kahan A, *et al.* Radiological hand involvement in systemic sclerosis. *Ann Rheum Dis* 2006;65:1088–1092.

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.

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