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Letters-to-the-Editor

Letter to the Editor Regarding "Autologous Hematopoietic Stem Cell Transplantation for Systemic Sclerosis: A Systematic Review and Meta-Analysis"

Mandana Nikpour [1,2], Alicia Calderone [2], Lauren Host[3], Paul Cannell [4], Janet Roddy [3,*]

[1] Department of Medicine, The University of Melbourne at St. Vincent's Hospital Melbourne, Fitzroy, Victoria, Australia
[2] Department of Rheumatology, St. Vincent's Hospital Melbourne, Fitzroy, Victoria, Australia
[3] Department of Rheumatology, Fiona Stanley Hospital, Murdoch, Western Australia, Australia
[4] Department of Haematology, Fiona Stanley Hospital, Murdoch, Western Australia, Australia

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We read with interest the recent systematic review and meta-analysis of Shouval et al. [1] *Biology of Blood and Marrow Transplantation* with the same subject matter as our own article, "Autologous stem cell transplantation in systemic sclerosis: a systematic review," in *Clinical and Experimental Rheumatology* in 2017 [2]. Using a broader search strategy than our own, Shouval et al. [1] were only able to identify 1 additional retrospective analysis and 1 randomized controlled trial comparing autologous hematopoietic stem cell transplantation (AHSCT) with standard immunosuppressive therapy in patients with systemic sclerosis (SSc). The results of the retrospective study [3] and the SCOT trial [4] were unpublished at the time of writing our systematic review [2]. Even if they had been available, we did not consider that a meta-analysis was possible because the primary outcomes varied among included trials and were reported at different time points after treatment. Importantly, the outcomes of modified Rodnan Skin Score and forced vital capacity are dynamic variables, and these results should not be pooled for meta-analysis if they are not measured at the same time point.

Common outcomes evaluated in the reviewed studies included all-cause and treatment-related mortality, disease progression, organ dysfunction, and quality of life. It is unclear why the topic of progression/event-free survival (P/EFS) was not discussed in the systematic review of Shouval et al. [1] P/EFS defined as survival without mortality, major organ failure, or progression of SSc in the SCOT, ASTIS, and ASSIST randomized controlled trials of AHSCT in SSc [4-6] is arguably a more clinically relevant efficacy measure in this patient population than overall survival.

In the per-protocol population of the SCOT trial (participants who received a transplant or completed ≥9 doses of cyclophosphamide), the P/EFS survival at 1 year was 100% in both treatment (33/33) and control group (34/34) [4]. In the ASTIS trial it was 83% (71/79) in the treatment and 89% (66/79) in the control group [5], and in the ASSIST trial it was 100% (10/10) in the treatment group compared with 89% (8/9) in the cyclophosphamide group [6].

In the per-protocol population of the SCOT trial P/EFS at 4.5 years was 79% in the transplantation group and 50% in the cyclophosphamide group ($P = .02$) [4]. In the ASTIS trial the 4-year P/EFS was reported as 81% in the transplantation group and 74% in the cyclophosphamide group, with a time-varying hazard ratio of .34 (95% confidence interval, .16-.74; $P = .006$) [5]. In 3 retrospective studies we reviewed [7-9] the 5-year P/EFS with AHSCT was reported, ranging from 55% to 70%, but the definition of EFS varied in these studies. [2]

In conclusion, although the systematic review by Shouval et al. is of interest, we caution in relation to the interpretation of meta-analyses of outcomes measured at different time points. We also highlight the importance of P/EFS as an important endpoint in randomized controlled trials of AHSCT in SSc.

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* Correspondence and reprint requests: Janet Roddy, The Department of Rheumatology, Fiona Stanley Hospital, 102-118 Murdoch Drive, Murdoch, Western Australia 6150, Australia.
E-mail address: jroddy@iinet.net.au (J. Roddy).
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