THE ASEAN JOURNAL OF MILITARY AND PREVENTIVE MEDICINE

ISSN (e): 3031-870X
Vol. 2 No.1 (2025)
https://journal.ajmpm.net/

DOI: https://doi.org/10.47353/ajmpm.v2i1.20

Stem Cell Transplantation Therapy in Systemic Sclerosis: A Systematic Review

Arif Rachman[1]*, Prihati Pujowaskito[2], Arfiyanti[3], Arya Duta Dharma[4], Dinda Puspa[4], Jafar Elyas[4], Ilham Syahputro[4], Nuzuludz Dzikra[4], Nabil Ramaseno[4], Ni Made Ayu Widiyasih[4], Muhammad Zhafran Maulana[4], Shalya Regita[4], Ruth Je Deborah Octavia[4]

[1]Department of Cell Biology and Biomolecular, Faculty of Medicine, Indonesian Defense University, Bogor, Indonesia;
[2]Department of Cardiology and Vascular Medicine, Faculty of Medicine, Indonesian Defense University, Bogor, Indonesia;
[3]Department of Nutrition, Faculty of Medicine, Indonesian Defense University, Bogor, Indonesia;
[4]Medical Study Program, Faculty of Medicine, Indonesian Defense University, Bogor, Indonesia.

***Correspondence email:** arif.rachman@idu.ac.id*

Abstract

Background: Systemic sclerosis (SSc) is a chronic autoimmune disease characterized by systemic inflammation, vascular dysfunction, progressive fibrosis, multiorgan involvement, and impaired quality of life. Autologous hematopoietic stem cell transplantation (HSCT) has been investigated as an option for patients with severe SSc who respond inadequately to conventional immunosuppressive therapy.

Methods: A systematic search was conducted in the Cochrane Library and PubMed using terms related to stem cell transplantation, hematopoietic stem cell transplantation, systemic sclerosis, stem cell therapy, immunomodulatory therapy, and cyclophosphamide. Eligible studies were randomized controlled trials involving adults with diffuse or limited SSc, autologous HSCT as the intervention, and cyclophosphamide or other immunomodulatory therapy as the comparator. Study selection, data extraction, and risk-of-bias assessment were performed systematically, and the selection process was documented using a PRISMA flow diagram.

Discussion: Three randomized controlled trials involving 250 participants were included. Selective non-myeloablative HSCT improved event-free survival, while selective myeloablative HSCT showed benefits in survival analysis and skin-related outcomes. Quality-of-life improvements were reported with selective HSCT approaches. However, HSCT was associated with a higher risk of serious adverse events than cyclophosphamide.

Conclusion: Autologous HSCT may provide clinical benefit in selected patients with severe SSc, but careful risk-benefit assessment, strict patient selection, and long-term monitoring are essential.

Keywords: systemic sclerosis; hematopoietic stem cell transplantation; autologous transplantation; cyclophosphamide; systematic review; skin fibrosis.

Background

Systemic sclerosis (SSc), also known as scleroderma, is a rare chronic autoimmune disease characterized by immune dysregulation, vasculopathy, and progressive fibrosis. The

disease may affect the skin, subcutaneous tissue, lungs, gastrointestinal tract, kidneys, and cardiovascular system. Clinically, SSc is commonly categorized into limited cutaneous and diffuse cutaneous subtypes. Diffuse disease with early internal organ involvement is associated with substantial morbidity, functional impairment, and reduced quality of life.[1,2]

Current treatment strategies aim to reduce vascular injury, control immune-mediated inflammation, and limit fibrotic progression. Conventional approaches include vasoactive agents and immunosuppressive therapy, particularly for complications such as Raynaud phenomenon, pulmonary arterial hypertension, renal crisis, skin thickening, and interstitial lung disease. However, patients with aggressive or refractory SSc may continue to experience progressive disease despite standard therapy.[2]

Autologous hematopoietic stem cell transplantation (HSCT) has emerged as a potential disease-modifying intervention for selected patients with severe SSc. The rationale of HSCT is based on intensive immunosuppression followed by immune reconstitution, which may reduce autoreactive immune activity and alter the profibrotic inflammatory milieu. This systematic review aims to evaluate the efficacy and safety of autologous HSCT compared with cyclophosphamide-based therapy in adults with SSc, with emphasis on survival, skin outcomes, pulmonary function, quality of life, and treatment-related harms.[1,3,4]

Methods

Study design and reporting framework

This study was designed as a systematic review of randomized controlled trials evaluating autologous HSCT for SSc. The study selection process was documented using a PRISMA flow diagram.

Data sources and search strategy

The literature search was conducted using the Cochrane Library and PubMed databases. Search terms included “Stem Cell Transplantation,” “Hematopoietic Stem Cell Transplantation,” “HSCT,” “Systemic Scleroderma,” “Systemic Sclerosis,” “Stem Cell Therapy,” “Immunomodulatory Therapy,” and “Cyclophosphamide.” The PubMed search strategy was reported as: ((((Stem Cell Transplantation) OR (Hematopoietic Stem Cell Transplantation) OR (Stem Cell Therapy) OR (Immunomodulatory Therapy)) AND (Systemic Scleroderma)).

Eligibility criteria

The eligibility criteria were defined using the PICO framework. The population was adults aged 18 years or older diagnosed with diffuse or limited SSc. The intervention was any form of autologous HSCT. Comparators included cyclophosphamide or other immunomodulatory therapies, either as monotherapy or in combination. Outcomes included effectiveness and safety, particularly survival, event-free survival, modified Rodnan Skin Score (mRSS), forced vital capacity (FVC), quality-of-life measures, and adverse events. Exclusion criteria were non-full-text articles, observational studies, non-human studies, and studies published in languages other than English.

Study selection and data management

Search results were organized using Microsoft Excel. Duplicate records were removed, followed by title and abstract screening according to the predefined eligibility criteria. Potentially eligible full-text reports were then assessed independently. Disagreements during study selection were resolved through discussion among the authors. The final selection process was summarized in a PRISMA flow diagram.

Data extraction

Data extraction was performed independently, and discrepancies were resolved by consensus. Extracted information included study characteristics, participant profiles, intervention protocols, comparator regimens, follow-up duration, and clinical outcomes. Extracted data were entered into Review Manager 5 software and checked for accuracy.

Risk-of-bias and certainty assessment

Risk of bias was assessed according to recommended guidelines for randomized controlled trials. The certainty of evidence was evaluated using GRADE criteria where applicable. Quality-of-life outcomes included the Health Assessment Questionnaire Disability Index (HAQ-DI), the Short Form Health Survey (SF-36), and the EQ-5D Visual Analogue Scale (VAS).

Discussion

Study selection and included evidence

A total of 4,205 citations were identified through database searches, with six additional records identified from other sources. After removal of duplicates, 3,024 unique records remained. Following title and abstract screening, 2,837 records were excluded, leaving 187 full-text citations for assessment. Fourteen records representing data from three randomized controlled trials met the inclusion criteria.

The included trials were the Autologous Non-Myeloablative Hematopoietic Stem-Cell Transplantation for Systemic Sclerosis (ASSIST) trial by Burt et al., the Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial by van Laar et al., and the Scleroderma: Cyclophosphamide or Transplantation (SCOT) trial by Sullivan et al. The trials evaluated different HSCT strategies, including non-selective non-myeloablative HSCT, selective non-myeloablative HSCT, and selective myeloablative HSCT, using cyclophosphamide-based therapy as the comparator. The total number of participants across the three trials was 250, with 125 receiving HSCT.[3,1,4]

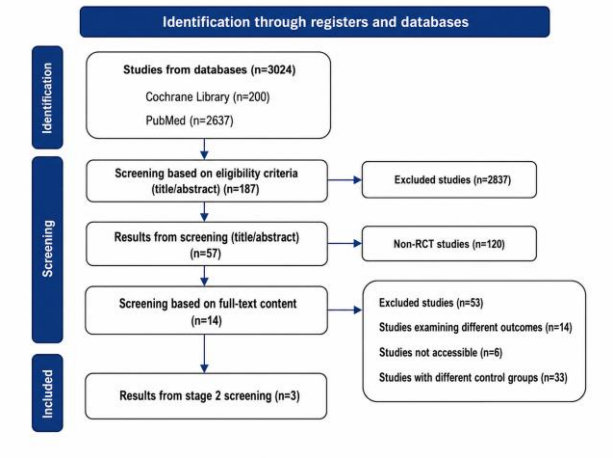

Figure 1. *Study flow diagram.*

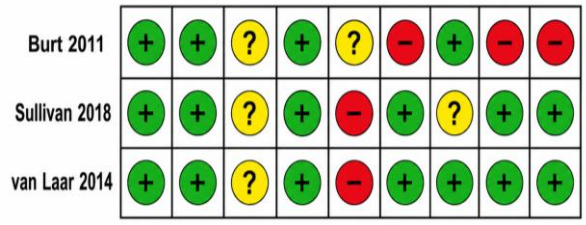

Figure 2. *Risk-of-bias summary.*

Table 1. *Characteristics of included randomized controlled trials.*

Characteristic	ASSIST (Burt 2011)	ASTIS (van Laar 2014)	SCOT (Sullivan 2018)
Study design	RCT, single-center	RCT, multicenter (29 sites in 10 European countries)	RCT, multicenter (26 sites in North America)
Research subjects	19 participants (10 HSCT, 9 cyclophosphamide); median age 45 years; 89% female; 79% white; median disease duration 13–18 months	156 participants (79 HSCT, 77 cyclophosphamide); median age 44 years; 59% female; 81% white; median disease duration 1.4 years	75 participants (36 HSCT, 39 cyclophosphamide); median age 46 years; 64% female; 80% white; median disease duration 27.1 months
Inclusion criteria	Diffuse SSc with mRSS ≥15 and organ involvement ≤5 years	Diffuse SSc with mRSS ≥15, internal organ involvement ≤4 years	Diffuse SSc with major organ involvement, DLCO ≥45%, and FVC ≥45%
Intervention	Non-selective non-myeloablative HSCT. Mobilization:	Selective non-myeloablative HSCT. Mobilization:	Selective myeloablative HSCT. Mobilization: G-CSF

Characteristic	ASSIST (Burt 2011)	ASTIS (van Laar 2014)	SCOT (Sullivan 2018)
	cyclophosphamide 2 g/m² + filgrastim. Conditioning: cyclophosphamide 200 mg/kg + rabbit ATG.	cyclophosphamide 4 g/m² + filgrastim. Conditioning: cyclophosphamide 200 mg/kg + rabbit ATG.	leukapheresis. Conditioning: cyclophosphamide 120 mg/kg, equine ATG, total body/partial radiation.
Comparator	Intravenous cyclophosphamide 1 g/m² monthly for 6 months	Intravenous cyclophosphamide 750 mg/m² monthly for 12 months	Intravenous cyclophosphamide 500 mg/m² once, followed by 750 mg/m² monthly for 11 months
Outcomes reported	mRSS, FVC, and quality of life	Event-free survival and change in mRSS	Event-free survival, change in FVC, mRSS, and quality of life
Duration of follow-up	12 months	Median 5.8 years	Median 72 months

Efficacy outcomes

Across the three included RCTs, overall mortality did not differ significantly between HSCT and cyclophosphamide. However, survival analyses suggested that selective non-myeloablative HSCT and selective myeloablative HSCT may provide advantages over cyclophosphamide in selected patients. In the ASTIS trial, selective non-myeloablative HSCT significantly improved event-free survival at 48 months compared with cyclophosphamide, with moderate certainty of evidence. In the SCOT trial, selective myeloablative HSCT showed improved survival in the intention-to-treat analysis.[1,3,4,7]

Clinically meaningful improvements in quality of life were reported with selective non-myeloablative HSCT and selective myeloablative HSCT compared with cyclophosphamide, although the certainty of evidence was low. Quality-of-life measures included HAQ-DI, SF-36, and EQ-5D VAS. Improvements in skin outcomes, particularly mRSS, were also reported, most notably with selective myeloablative HSCT.[1,3,4]

Table 2. *Survival and event-free survival comparison.*

Subgroup/outcome	Number of studies	Number of participants	Statistical method	Effect size
Overall mortality	3	-	Risk Ratio (M-H, Random, 95% CI)	Subtotal
Selective non-myeloablative autologous HSCT	1	156	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.44, 1.85]

Subgroup/outcome	Number of studies	Number of participants	Statistical method	Effect size
Selective myeloablative autologous HSCT	1	75	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.24, 1.43]
Non-selective non-myeloablative autologous HSCT	1	19	Risk Ratio (M-H, Random, 95% CI)	Unpredictable
Event-free survival	2	-	Hazard Ratio (IV, Random, 95% CI)	Subtotal
Selective non-myeloablative autologous HSCT	1	-	Hazard Ratio (IV, Random, 95% CI)	0.34 [0.16, 0.74]
Selective myeloablative autologous HSCT	1	-	Hazard Ratio (IV, Random, 95% CI)	0.54 [0.23, 1.27]

Safety outcomes and certainty of evidence

Despite its potential efficacy, HSCT was associated with a higher risk of serious adverse events compared with cyclophosphamide. This finding is clinically important because HSCT requires mobilization, conditioning, profound immunosuppression, and careful post-transplant monitoring. Treatment-related mortality and severe complications remain central considerations when selecting candidates for HSCT.[1,3,4]

The certainty of evidence was limited by several methodological concerns. Blinding was not feasible because participants received transplantation, creating unclear performance bias and a high risk of detection bias. The non-selective non-myeloablative HSCT evidence was downgraded because of baseline differences between treatment groups. The ASSIST trial did not clearly report serious adverse events and was judged to have a high risk of selection bias. In addition, each HSCT category was represented by only one RCT, limiting generalizability.[3,5,6]

Clinical implications

The available evidence suggests that autologous HSCT may be considered for carefully selected patients with severe, progressive SSc, particularly those with diffuse cutaneous disease and evidence of internal organ involvement who have insufficient response to standard immunosuppression. However, the decision to use HSCT should involve multidisciplinary assessment, strict eligibility screening, counseling regarding potential benefits and harms, and treatment at experienced transplant centers.[1,3,4]

Cyclophosphamide remains an important comparator in the available RCTs, but newer or alternative immunosuppressive approaches, including mycophenolate mofetil, may offer a more favorable safety profile in some SSc manifestations. Therefore, HSCT should not be

viewed as a universal treatment for SSc, but rather as a high-intensity intervention for selected patients in whom potential long-term benefit outweighs procedural risk.[2]

Limitations

This review has several limitations. Only three RCTs were included, and each evaluated a different HSCT approach. Because of differences in transplantation protocols, conditioning regimens, participant characteristics, and follow-up durations, data pooling was not feasible. Two trials, ASSIST and SCOT, lacked sufficient statistical power to detect significant differences in some outcomes, including overall mortality and event-free survival. The limited number of studies also restricts the ability to define which patient subgroups benefit most from HSCT.

Future directions

Future studies should evaluate standardized HSCT protocols, longer follow-up periods, treatment-related harms, patient-reported outcomes, and comparisons with contemporary immunosuppressive therapies. Additional research is also needed to determine the safety and effectiveness of HSCT in patients with comorbidities and special risk conditions, including smokers and patients with cardiopulmonary involvement.[8,14,15]

Conclusion

Autologous HSCT has demonstrated potential benefits in selected patients with severe SSc, including improved event-free survival, reduced skin thickening, preservation or improvement of pulmonary function, and better quality-of-life outcomes. However, these benefits must be balanced against the increased risk of serious adverse events and treatment-related mortality. Current evidence supports the use of HSCT only after careful patient selection and individualized risk-benefit assessment. Further large-scale, well-designed, long-term trials are needed to establish standardized protocols and clarify the comparative effectiveness of HSCT against other available therapies.[1,3,4,7]

Acknowledgments

None

Author Contributions

All authors act as guarantors of the manuscript and fulfill the ICMJE authorship criteria. AR was the main investigator of this study. AR, PP, and AF conceived and designed the study. AR, AF, ADD, and DP developed the methodology of the study. ADD, DP, JE, IS, ND, NR, NMAW, MZM, SR, and RJDO participated in literature searching, study selection, data acquisition, data extraction, and data curation. AR, PP, and AF participated in data analysis

and interpretation of the study findings. ADD, DP, JE, IS, ND, NR, NMAW, MZM, SR, and RJDO drafted the manuscript. AR, PP, and AF critically revised the manuscript for important intellectual content and supervised the study. All authors reviewed, approved the final version of the manuscript to be published, and agree to be accountable for all aspects of the work.

Conflict of Interests

None

References

1. Van Laar JM, Farge D, Sont J, Naraghi K, Marjanovic Z, Larghero J, et al. Autologous hematopoietic stem cell transplantation versus intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis. JAMA. 2014;311(24):2490-2498.
2. Tashkin DP, Roth MD, Clements PJ, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel-group trial. Lancet Respir Med. 2016;4:708-719.
3. Burt RK, Shah SJ, Dill K, Grant T, Gheorghiade M, Schroeder J, et al. Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial. Lancet. 2011;378:498-506.
4. Sullivan KM, Goldmuntz EA, Keyes-Elstein L, McSweeney PA, Pinckney A, Welch B, et al. Myeloablative autologous stem-cell transplantation for severe scleroderma. N Engl J Med. 2018;378:35-47.
5. Sullivan K, Keyes-Elstein L, McSweeney P, Pinckney A, Welch B, Mayes M, et al. Myeloablative autologous transplantation of CD34+ selected hematopoietic stem cells versus monthly intravenous cyclophosphamide for severe scleroderma with internal organ involvement: outcomes of a randomized North American clinical trial. Biol Blood Marrow Transplant. 2017;23:S118-S91.
6. Sullivan K, Keyes-Elstein L, McSweeney P, Pinckney A, Welch B, Mayes MD, et al. Myeloablative autologous transplantation of CD34+-selected hematopoietic stem cells versus monthly intravenous cyclophosphamide for severe scleroderma with internal organ involvement. Arthritis Rheumatol. 2016;68(Suppl 10):S21.
7. Abdallah NA, Wang M, Lansiaux P, Puyade M, Berthier S, Terriou L, et al. Long-term outcomes of the French ASTIS systemic sclerosis cohort using the global rank composite score. Bone Marrow Transplant. 2021;56:2259-2267.
8. Keever-Taylor CA, Heimfeld S, Steinmiller KC, et al. Manufacture of autologous CD34+ selected grafts in the NIAID-sponsored HALT-MS and SCOT multicenter clinical trials for autoimmune diseases. Biol Blood Marrow Transplant. 2017;23:1463-1472.

9. Franks J, Martyanov V, Wood TA, Crofford L, Keyes-Elstein L, Furst DE. Machine learning classification of peripheral blood gene expression identifies a subset of patients with systemic sclerosis most likely to show clinical improvement in response to hematopoietic stem cell transplant. Arthritis Rheumatol. 2018;70(Suppl 9):S2091-S3. [Uncited reference-please verify]
10. Goldin J, Keyes-Elstein L, Crofford L, Furst DE, Goldmuntz E, Mayes MD, et al. Changes in quantitative scleroderma lung CT measures in patients treated with cyclophosphamide or transplantation. Arthritis Rheumatol. 2018;70(Suppl 9):S1005-S6. [Uncited reference-please verify]
11. ClinicalTrials.gov. Scleroderma: Cyclophosphamide or transplantation (SCOT). Identifier: NCT00114530. [Reference details need to be completed by author] [Uncited reference-please verify]
12. Assassi S, Mayes MD, Pedroza C, Chang JT, Furst DE, Crofford LJ, et al. Immunoablation followed by autologous stem cell transplantation in systemic sclerosis patients decreases significantly the interferon signature. 2015 ACR/ARHP Annual Meeting; 2015 Nov 6-11; San Francisco, CA. [Reference details need to be completed by author] [Uncited reference-please verify]
13. Assassi S, Wallace P, Ying J, Keyes-Elstein L, Goldmuntz E, Turner J. Treatment with myeloablation followed by autologous stem cell transplantation normalizes the systemic sclerosis molecular signature. J Scleroderma Relat Disord. 2018;3:S272-S273. [Uncited reference-please verify]
14. Assassi S, Wang X, Keyes-Elstein L, Goldmuntz E, Turner J, Zheng W. Changes in the systemic sclerosis molecular signatures after myeloablation followed by autologous hematopoietic stem cell transplantation and their clinical correlates. Arthritis Rheumatol. 2018;70(Suppl 9):S1002-S3.
15. Bellocchi C, Ying J, Goldmuntz E, Keyes-Elstein L, Varga J, Hinchcliff M, et al. Systemic sclerosis has a distinct serum protein profile that correlates with its clinical manifestations. Arthritis Rheumatol. 2018;70(Suppl 9):S1213-S4.