THE EFFECTIVENESS OF AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION IN THE TREATMENT OF DIFFUSE SYSTEMIC SCLEROSIS

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ABSTRACT

Rapidly progressive diffuse systemic sclerosis (dSSc) is a life-threatening condition characterized by increased mortality with few effective therapies, typically only helpful in stabilizing disease. Autologous hematopoietic stem cell transplantation (AHSCT) is the only treatment that has demonstrated improved survival. Despite promising results from three randomized controlled trials (RCTs), best practice use of AHSCT in the real-world setting is not well established. The primary objective of this thesis was to summarize the clinical efficacy, limitations and utilization of AHSCT in the management of rapidly progressive dSSc. Specifically, we conducted (1) a systematic review to describe the efficacy of AHSCT in dSSc as well as practice variation in patient selection and treatment regimens; and (2) a multicenter retrospective cohort study to compare outcomes for subjects who received AHSCT in France compared to those who received conventional care in Canada. There was important variability in the criteria for patient selection and treatment protocols. While AHSCT is associated with improved overall survival, skin fibrosis and lung function, further studies are needed to understand its potential for expanded eligibility and effects on other disease manifestations.

EXECUTIVE SUMMARY

Rapidly progressive diffuse systemic sclerosis (dSSc) is a chronic, severe multisystem disease with limited treatment options. The primary objective of this thesis was to evaluate the efficacy and clinical utilization of autologous hematopoietic stem cell transplantation (AHSCT) in the management of rapidly progressive dSSc.

Systematic literature review methodology was used to summarize clinical efficacy, protocols and patient selection for AHSCT in dSSc. Twelve included studies (3 randomized controlled trials, 2 observational cohorts and seven case series) demonstrated clinically important benefit in survival, skin fibrosis and lung function. Patient selection and treatment regimens varied widely.

A multicentre retrospective cohort study was performed comparing subjects who received AHSCT compared to those who received conventional care. Forty-one subjects who received AHSCT were compared to 85 subjects who received conventional care. Statistical methodology including multiple imputation and propensity scoring using inverse probability of treatment weights were used to account for missing data and potential confounders respectively. In summary, results suggest that AHSCT may be associated with improved overall survival, skin fibrosis and lung function.

This thesis adds complementary real-world data to support the use of AHSCT for rapidly progressive dSSc. We identified foci for future research including exploring AHSCT efficacy for other disease manifestations and establishing consistent treatment algorithms.

CONTRIBUTION OF THE AUTHORS

Two manuscripts were prepared as part of this thesis. All were led by Nancy Maltez and were co-authored by thesis supervisor (Peter Tugwell) and members of the thesis advisory committee (George A Wells, Marie Hudson). Nancy Maltez was responsible for study design with guidance from the thesis advisory committee and Dominique Farge. She participated in data collection and led the statistical analysis, interpretation and manuscript writing. As such, she is first author on both manuscripts.

George A Wells, Marie Hudson, Mianbo Wang and Pauline Lansiaux provided assistance with data management and statistical analysis. Marie Hudson, Dominique Farge and Peter Tugwell provided input on interpretation of findings. Marie Hudson, Murray Baron, Zora Marjanovic and Dominique Farge contributed to data collection (in collaboration with study networks: Canadian Scleroderma Research Group (CSRG) and Maladies Auto-Immunes et Thérapie Cellulaire (MATHEC)). All manuscripts were reviewed by Marie Hudson, Peter Tugwell and George A Wells. The manuscripts have not been published.

REQUIRED ETHICS APPROVAL

- **Manuscript:** "Autologous hematopoietic stem cell transplantation for the treatment of systemic sclerosis: A systematic review of the literature"
    - **Required approval:** None.

- **Manuscript:** "Improvement in Overall Survival, Skin Fibrosis and Lung Function with Autologous Hematopoietic Stem Cell Transplantation in Systemic Sclerosis".
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Chapter 1 - Introduction

1.1 Rationale

Rapidly progressive diffuse systemic sclerosis (dSSc) is a chronic, severe multisystem disease with limited treatment options. As such, further evaluation of the effectiveness of autologous hematopoietic stem cell transplantation (AHSCT) in routine clinical practice for the management of dSSc is needed to inform clinicians and patients of the harms and benefits of the procedure, aid in the future development of clinical practice guidelines and eventually establish more consistent treatment protocols.

1.2 Objectives

The primary objective of this thesis was to evaluate the effectiveness and clinical utilization of AHSCT for rapidly progressive dSSc. This is accomplished in the following manner:

1. A systematic review to describe the effectiveness of AHSCT in dSSc as well as practice variation in patient selection and treatment regimens.
2. A multicentre retrospective cohort study to compare outcomes for subjects who received AHSCT in France compared to those who received conventional care in Canada.
3. A summary of the available evidence for the use of AHSCT in dSSc taking into account clinical priorities and methodological limitations.

1.3 Overview of thesis and included manuscripts

Chapter 2 – Background

This chapter provides an overview of systemic sclerosis (SSc) disease subtypes, classification criteria and the wide spectrum of potential disease manifestations. A general approach to traditional management strategies is presented followed by a description of the rationale and history behind the use of AHSCT as a treatment for dSSc. Finally, a review of challenges in the study and treatment of SSc is delineated including disease-specific characteristics and limitations of currently available outcome measures.

Chapter 3 - Systematic Review of AHSCT in Systemic Sclerosis

A systematic review exploring the role of AHSCT in the management of SSc is presented in Chapter 3. This includes a summary of the variability in patient selection criteria and procedure protocols. We incorporated the manuscript "Autologous hematopoietic stem cell transplantation for the treatment of systemic sclerosis: A systematic review of the literature". This systematic review describes the measures of benefits, harms and protocol variations for the use of AHSCT in the treatment of SSc.

Chapter 4 – Effectiveness of AHSCT in SSc

In Chapter 4, we present the findings of an observational cohort study evaluating the use of AHSCT in the treatment of SSc as compared to real-world conventional care. This multicentre study compares patients in France who received AHSCT to patients in Canada who received conventional care as guided by their treating rheumatologists. This includes the

manuscript “Improvement in Overall Survival, Skin Fibrosis and Lung Function with Autologous Hematopoietic Stem Cell Transplantation in Systemic Sclerosis”.

Chapter 5 - Discussion

This chapter provides a review of key findings of this thesis including strengths, and limitations. This thesis adds important complementary real-world data to support the use of AHSCT for rapidly progressive dSSc and identifies important foci for research.

Chapter 2 – Background

2.1 Systemic sclerosis: Disease subtypes and evolution

Systemic sclerosis (SSc) is a rare chronic disease characterized by vasculopathy, inflammation and fibrosis affecting approximately 1 in 10,000 people worldwide. [1] There are two disease subtypes: limited and diffuse cutaneous SSc. The diffuse form (dSSc) is characterized by skin involvement extending proximal to the elbows and/or trunk and is typically associated with more severe organ involvement. Early diagnosis and risk stratification for complications of this uncommon disease poses a challenge for primary care providers and expert centres. Early symptoms, including Raynaud's phenomenon, gastroesophageal reflux and fatigue can be rather non-specific and therefore easily overlooked. [2] A definite diagnosis is typically described as fulfillment of the 2013 European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) classification criteria. These require a total of 9 points from the following criteria: proximal skin involvement (9 points), puffy fingers (2 points) or sclerodactyly of the fingers (4 points), digital tip ulcers (2 points), fingertip pitting scars (3 points), telangiectasia (2 points), abnormal nailfold capillaries (2 points), pulmonary arterial hypertension (2 points), interstitial lung disease (2 points), Raynaud's phenomenon (3 points), and SSc specific antibodies, namely anti-centromere autoantibodies, anti-topoisomerase autoantibodies and anti-RNA polymerase III autoantibodies (3 points). However, these are meant for classification rather than for diagnosis and therefore experts worry that a patient with early disease or atypical presentations such as scleroderma renal crisis or scleromyositis may be missed by these relatively specific criteria. [3] [4] [5]

Disease manifestations of SSc represent a spectrum of multi-organ involvement. Early disease is most commonly associated with Raynaud's phenomenon, puffy fingers, skin tightness affecting the fingers, pruritis and gastroesophageal reflux. Other symptoms may include weight loss, fatigue, weakness, joint pain and shortness of breath. Most organ involvement occurs early in the disease and may include lung fibrosis, pulmonary arterial hypertension, renal crisis, arrhythmia, inflammatory arthritis and myositis, small intestinal bacterial overgrowth, constipation, fecal incontinence, neuropathies and digital ulcerations, among others. [6]

Patients with SSc have increased rates of mortality. In particular, those with rapidly progressive diffuse skin involvement have a 5-year survival rate of ≤ 30%. [7] [8] Despite substantial recent progress in the treatment-associated prognosis in other types of life-limiting diseases such as cancer, mortality rates in SSc have remained high throughout the last several decades. Early recognition and evidence-based risk stratification are critical in order to create patient-specific treatment plans and optimize outcomes. [9] [10]

2.2 Management of systemic sclerosis

Initiation of a prompt, multi-faceted approach is crucial for the management of rapidly progressive dSSc. Baseline diagnostic investigations allow for the early identification of organ-specific manifestations and inform the required treatment goals. Clinicians may refer to the EULAR recommendations for management of scleroderma to guide initial work-up which should also include referral to an expert centre when severe organ involvement is suspected. [11]

Most recommended treatments target specific disease-related symptoms such as Raynaud's phenomenon, digital ulcerations, gastric dysmotility or pulmonary arterial hypertension. Immunosuppressive medications are typically reserved for those with specific and severe inflammatory manifestations including lung fibrosis, rapidly progressive skin thickening, arthritis and myositis. [11] Agents that are commonly recommended include methotrexate, cyclophosphamide, mycophenolate mofetil and rituximab all of which have only shown modest effects on stabilizing disease progression. [6] Unfortunately, none have demonstrated improvement in long-term survival. [12] Thus, rheumatologists have limited pharmacological options to treat rapidly progressive disease. The only treatment that has been shown to have disease-modifying properties, including improvement in skin and lung fibrosis and improvement in long-term overall survival, is autologous hematopoietic stem cell transplantation (AHSCT). [13-15]

2.3 Autologous hematopoietic stem cell transplantation (AHSCT)

AHSCT was first reported as a potential treatment for patients with dSSc in the 1990s. [16] [17] This treatment involves mobilization of stem cells from the patient's own bone marrow using cyclophosphamide (2 to 4g/m^2) and granulocyte colony stimulating factor (G-CSF) and collection via cytapheresis. Thereafter, immunosuppressive or myeloablative chemotherapy with or without anti-lymphocyte globulin for the conditioning regimen eliminates autoreactive T cells and B cells from the host. Autologous stem cells are then re-infused into the patient. [18] [19] It has been shown that after profound depletion of immune

cells, a new and naive immune system reconstituted from the stem cell graft will re-establish immune tolerance through thymic-derived naive T cell production. [20] [21] This also results in expansion of regulatory T and B cells and reprogramming of non-depleted autoimmune cells to auto-tolerant phenotypes. [22] The result is a more tolerant immune system and mitigation of immune-mediated disease progression. In addition, regression of skin and lung fibrosis (high resolution computed tomography disease scores) and remodeling of vasculature has also been observed in SSc after AHSCT. [23] [24] [25]

Enrolment for ASSIST (Autologous non-myeloablative hematopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis), the first randomized controlled trial (RCT) of AHSCT in SSc began in 2006 (10 participants received AHSCT vs 9 received cyclophosphamide). The observed improvement in skin (mean mRSS 29 (standard deviation (SD) 13.7) vs 12 (SD 8.4)) and pulmonary function (mean FVC 62% (SD 16.4) vs 74% (SD 19.8)) over 2 years in transplanted patients set a premise for a decade of further refined studies. [13] In 2014, the ASTIS (Autologous hematopoietic stem cell transplantation vs intravenous cyclophosphamide in diffuse cutaneous systemic sclerosis) RCT demonstrated the statistically significant long-term overall and event-free survival benefits of AHSCT (time varying hazard ratio (HR) for death or major organ failure: 0.34 (p=0.006) at 4 years) (79 participants received AHSCT vs 77 received cyclophosphamide). [14] However, ASTIS treatment-related mortality was 10%, raising potential concerns about the benefit to harm ratio of AHSCT for SSc. In early 2018, the SCOT (Myeloablative autologous stem-cell transplantation for severe scleroderma) RCT provided evidence to support long term benefits of AHSCT in SSc

including improvement in event-free survival (rate 79% vs 50% p=0.02) (36 participants received AHSCT vs 39 received cyclophosphamide). [15] In addition, SCOT treatment-related mortality was reported to be only 3% at 54 months. Both the ASTIS and SCOT trials required over a decade of patient recruitment given the disease incidence and strict inclusion criteria. The valuable long-term efficacy and safety data from these studies inform the evidence base for AHSCT. In summary, AHSCT is the first treatment in SSc demonstrating improvement in a number of clinically important metrics including (1) short- and long-term event-free and overall survival, (2) severity of skin and pulmonary fibrosis and (3) health-related quality of life. [26] [27]

However, not all patients with SSc may be appropriate candidates for AHSCT. Clinical experts have highlighted the importance of patient selection and individualized, patient-specific treatment regimens, especially in regards to cardiopulmonary evaluation and optimization of conditioning regimens to improve outcomes post-AHSCT. [28] For example, in the SCOT trial, a lower dose of cyclophosphamide was utilized than in earlier trials in order to minimize cardiac-related toxicity and improve treatment tolerance for patients. [15] On the other hand, it has been suggested that a more thorough and restrictive cardiac screening program may improve tolerability of more intense dosing regimens of cyclophosphamide for a more targeted patient population. While the core guiding principles for AHSCT treatment are generally accepted worldwide, there remains important clinical heterogeneity related to philosophical differences in approaches to patient selection and design of real-world treatment protocols for AHSCT. Whether these differences in protocol translate to outcome variability remains uncertain.

Despite increasing evidence, the uptake of AHSCT in clinical practice has been slow in Canada. There are two academic centres (Ottawa and Calgary) performing AHSCT for SSc. Logistics surrounding travel, caregiver availability and need for long-term monitoring result in accessibility challenges for some patients. In addition, the multi-disciplinary care requirements can be resource intensive. As such, health-advocacy groups will play a crucial role in making this resource more widely available to Canadians living with SSc. [29]

Studies evaluating the cost-effectiveness of AHSCT vs conventional care in SSc are lacking. However, in other chronic autoimmune diseases such as multiple sclerosis, the higher upfront costs of AHSCT and post-AHSCT care are recouped in 3.9 years compared to other drug therapies. [30] Similarly, AHSCT is more cost-effective than intravenous immunoglobulin (IVIg) in the long-term treatment of chronic inflammatory demyelinating polyradiculoneuropathy. [31] As such, despite the resource intensity up front, there are potential long-term cost savings for the use of AHSCT as compared to other standard therapies in autoimmune diseases.

2.4 Systemic sclerosis: Challenges in study design and outcome measures

Research for SSc is challenging as it is an orphan disease characterized by high unmet clinical needs. It is a rare disease with a wide spectrum of clinical manifestations which leads to (1) patient population heterogeneity and (2) difficulty in establishing patient-centered outcomes sufficiently comprehensive and reliable for clinical trials.

Patient Population Heterogeneity

SSc represents a spectrum of disease manifestations ranging from mild skin and musculoskeletal symptoms to severe, life-threatening end organ damage. This reflects the complex pathophysiology of interplay between fibrosis, inflammation and vasculopathy, which results in unique combinations of disease manifestations for each patient. [6] Thus, the identification of a target population for clinical study requires well-defined and reproducible eligibility criteria. However, given the rarity of SSc, realistic sample size considerations and recruitment ability (especially for RCTs) remain important limitations. In addition, given the wide-ranging disease manifestations, overly restrictive enrolment criteria lead to concerns regarding external generalizability of study results to a real-world setting.

Therefore, well-conducted observational studies are often relied upon as an important evidence base in the study of SSc. These studies often must rely on complex statistical modeling to account for confounding from population heterogeneity, most commonly in the form of regression modeling adjusting for confounding covariates or propensity scoring.

A propensity score is a conditional probability that a participant will receive a certain treatment given a specific set of relevant covariates. The score serves to balance these covariates between participants in each study group. Propensity scores are determined by creating a logistic regression model in which relevant covariates are used as predictors of treatment assignment. [32] Once propensity scores have been determined, study groups can be established by propensity score matching. These techniques allow for pairing of observations in

study groups with similar values in propensity scores. However, matching procedures are not ideal for studies with smaller sample sizes since not all observations may be paired. In these cases, more inverse probability of treatment weighting (IPTW) can be used to adjust for potential confounding variables. Balance between groups is achieved by weighting each observation by the inverse probability of being allocated to a study group as determined by the propensity score. Balance in characteristics between groups can be verified via further analyses including computing standardized mean differences. If there are concerns regarding the extreme weights, weight stabilization can be considered. [33]

Defining Appropriate Outcome Measures

Another major obstacle in studying management strategies in SSc is the lack of feasible and discriminatory outcome measures [34] to compare treatment safety and efficacy. The spectrum of disease manifestations makes it difficult to translate patient experience into quantifiable and holistic clinical outcomes. Consequently, studies most often rely on well-established measures targeting specific manifestations individually such as skin thickening, lung fibrosis, cardiac function, functional status and health-related quality of life.

Skin involvement is assessed using the modified Rodnan skin score (mRSS), which evaluates a patient's skin thickness rated by clinical palpation, and ranges from 0 (no involvement) to 3 (severe thickening), in 17 anatomic sites (total score range 0–51). It has been validated [35] and is commonly used as a primary outcome measure in clinical trials of SSc. [36] [37]

Lung disease is evaluated using quantitative pulmonary function tests, namely forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DLCO) (%predicted corrected for hemoglobin). These measures have been validated [38] as surrogate markers of SSc-associated lung disease and are often used as primary outcomes in clinical trials. [39] [40] [41]

Clinical signs and symptoms of heart disease are determined in accordance with the New York Heart Association Classification (NYHA). This clinical assessment tool classifies subjects in classes I (no objective evidence of cardiovascular disease) to IV (objective evidence of severe cardiovascular disease). [42] Pulmonary hypertension is determined by echocardiogram and confirmed by measuring mean pulmonary artery pressure with a right heart catheterization. Left ventricular function is measured by echocardiogram.

Functional status is typically assessed with the Health Assessment Questionnaire (HAQ). [43] [44] [45] The HAQ is a self-administered questionnaire developed to assess physical functional ability in patients with rheumatoid arthritis. Health-related quality of life is measured with the Medical Outcomes Short Form-36 (SF-36) survey. This self-reported questionnaire is composed of 36 questions covering 8 domains: physical function, bodily pain, role physical, general health, social function, mental health, vitality and role emotional. [46]

Two composite outcome measures have been developed for the evaluation of SSc. The Composite Response Index in Diffuse Cutaneous Systemic Sclerosis (CRISS) is a two-step

composite measure specifically designed for use in clinical trials of SSc. It consists of 5 core set items: mRSS, FVC, HAQ, and patient global assessment and physician global assessment. It also takes into account internal organ worsening (renal and cardiopulmonary). [36] The Global Rank Composite Score (GRCS) is an analytic tool used as the primary outcome in the SCOT trial, which assessed the efficacy of AHSCT compared to cyclophosphamide in SSc. The score is generated by the following hierarchy of outcomes: death, event-free survival (survival without respiratory, renal, or cardiac failure), FVC, HAQ and mRSS. [15] The use of these measures is limited by lack of extensive validation in truth, discrimination, responsiveness, sensitivity and feasibility. [34] Clinicians have additional concerns regarding generalizability and applicability of these in the context of individualized patient care given the potential differences in clinical manifestation, patient values and spectrum of organ involvement outside of inclusion criteria for RCTs.

The tightly controlled RCT protocols and eligibility criteria result in high internal validity. However, stakeholders are also interested in the external validity of study results; in other words, how this may perform in the 'real-world'. [47] Although there remains variability in the definition of what constitutes real-world data, most interpretations describe it as data collected in a non-RCT setting. [48] Health-care professionals, patients and regulatory bodies must consider complementary data to compensate for the described "efficacy-effectiveness" gap [49] in order to appropriately extrapolate findings to the greater patient population.

In summary, there is an urgent need to better understand the role of AHSCT in the treatment of SSc, outside of stringent RCT protocols. We hypothesized that while important

clinical heterogeneity with regard to patient selection and specific treatment protocols exist, the benefits translate to routine clinical practice and that real world (non-RCT setting) findings will support its use in patients with rapidly progressive dSSc.

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Chapter 3 – Systematic Literature Review of AHSCT for the Treatment of SSc

SECTION OVERVIEW

In this chapter a systematic review of the literature for the use of AHSCT in the management of SSc is presented. It includes the manuscript titled: "Autologous hematopoietic stem cell transplantation for the treatment of systemic sclerosis: A systematic review of the literature"

MANUSCRIPT STATUS

This manuscript has not been published.

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PROTOCOL REGISTRATION

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NM, PT, GW and MH contributed to the study design and conception. NM completed screening and data extraction. NM conducted the analysis. NM, MH contributed to data interpretation. NM drafted the manuscript which was revised by all authors.

"Autologous hematopoietic stem cell transplantation for the treatment of systemic sclerosis: A systematic review of the literature"

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Abstract

Background

Rapidly progressive systemic sclerosis (SSc) is a life-threatening disease with potential for early multi-organ involvement. Rheumatologists have few options for disease modifying therapies to stabilize manifestations. Autologous hematopoietic stem cell transplantation (AHSCT) is a promising treatment with benefits in survival, skin fibrosis and lung function.

Objective

The primary objective of this systematic review is to summarize existing literature pertaining to the benefits and harms of AHSCT in the management of SSc.

Methods

Embase, MEDLINE and Cochrane Central Register of Controlled Trials were searched for randomized control trials (RCTs), cohorts and large case series. The Health Canada registry, clinicaltrials.gov and the World Health Organization (WHO) international clinical trials registry were searched for grey literature. Studies pertaining to patients with SSc were included. The main intervention of interest was AHSCT with no limitation on procedure protocol. Comparators were any other standard disease modifying agents, open-label, standard of care or placebo. The outcome of interest was overall mortality. Descriptive statistics were applied to synthesize available data.

Results

The electronic search identified 1315 records after removal of duplicates, of which 147 full-text studies were screened for inclusion. Twelve studies involving 539 patients who received AHSCT and 171 patients who received other treatments were included in the qualitative synthesis. Three RCTs reported overall mortality in the AHSCT groups of 24% at 5.8 years, 0% at 2.6 years and 17% at 6 years, respectively. The remaining studies described overall mortality rates ranging between 11 and 36% over follow-up times ranging between 1 and 15 years. All studies demonstrated some improvement in skin involvement, most commonly reported as a change in mRSS. Five of 12 studies reported an improvement in forced vital capacity (FVC) in AHSCT patients, whereas 3 of 12 studies reported no improvement. Few studies (n=3) reported total lung capacity (TLC) as a measure of lung function. The majority of studies (n=11) reported diffusion capacity of the lungs for carbon monoxide (DLCO), with only 2 reporting an improvement over time. We identified heterogeneity in study design, outcome measures, eligibility criteria and AHSCT-specific protocols amongst the included studies.

Conclusion

This systematic review describes the measures of benefits, harms and protocol variations for the use of AHSCT in the treatment of SSc. Narrative synthesis suggested clinically important benefits in survival, skin fibrosis and lung function. We highlight the need for the development of standardized algorithms pertaining to treatment protocols and patient selection to better inform evidence-based care.

Description of the condition

Systemic sclerosis (SSc) is a chronic disease characterized by vasculopathy, inflammation and fibrosis. Disease manifestations include progressive multi-organ dysfunction involving primarily the skin, lungs, heart, gastro-intestinal tract and kidneys, resulting in high rates of mortality that have not improved over the last several decades. [1] [2] In particular, patients with rapidly progressive diffuse skin involvement have a 5-year survival rate of ≤ 50%. [3] [4]

Despite a multidisciplinary approach, there is an unmet medical need for disease modifying therapy for SSc. Physicians have limited options to treat rapidly progressive disease and continue to resort to cyclophosphamide, despite no association with improved survival. [5]

Description of the intervention / How the intervention might work

Autologous hematopoietic stem cell transplantation (AHSCT) was first reported as a potential treatment for patients with SSc in the 1990s. [6, 7] More recently, 3 randomized controlled studies (RCTs) of AHSCT in SSc have shown promising improvement in survival, skin fibrosis and lung function as compared to cyclophosphamide alone. [8-10] Although the exact mechanism remains unknown, it has been postulated that the re-constitution of a new self-tolerant immune system plays a role. [8] As this therapy is thought to be mainly anti-inflammatory, it was to the surprise of investigators that regression of fibrosis and remodeling of vasculature was also observed. However, due to concerns for treatment toxicity [11] and durability of effect, clinical uptake has been slow. AHSCT requires mobilization of hematopoietic cells into peripheral blood followed by collection and cryopreservation. Ablation

of the immune system is induced by a conditioning regimen after which hematopoietic stem cells are re-infused. They engraft and lead to reconstitution of a self-tolerant immune system. [12]

Why it is important to do this review

There is currently no widely accepted protocol for patient selection and/or administration of AHSCT in SSc. In addition, there is significant variability in the mobilization and conditioning protocols used. The development of an evidence-based protocol endorsed by primary stakeholders offers the potential to maximize clinical uptake and utility. However, a comprehensive summary of existing clinical practice variations and outcomes is first required to support this endeavor. This review is intended to address this critical knowledge gap.

Therefore, the primary objective of this review was to describe the efficacy and safety outcomes of AHSCT in SSc. A second objective was to describe protocol differences with regards to patient selection, mobilization and conditioning.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. [13] The study protocol was registered with the Register of Systematic Reviews (PROSPERO) (CRD42018086851).

Study Selection Criteria

Studies were selected according to the following PICOS (population, intervention, comparator, outcomes, study design) structure.

Population

Studies enrolling patients with a clinical diagnosis of SSc were included. There was no limitation by age, nor by classification criteria. Given the lack of gold standard for diagnosis, author's ascertainment of SSc was used (as the physician gold standard). Animal studies, pre-clinical studies, and patients with overlap syndrome (i.e. SSc and another rheumatological condition) were excluded.

Interventions

All studies providing AHSCT as a treatment for SSc were included. There was no specific limitation on mobilization or conditioning regimens or whether participants had previously been exposed to other disease modifying agents.

Comparators

Included studies were not required to have a comparator intervention. Where available, comparators were defined as any other standard disease modifying agent, open-label, standard of care or placebo.

Outcomes

The primary outcome was overall mortality, though included studies were not required to report it. Secondary outcomes included: extent of skin fibrosis measured by the modified Rodnan skin score (mRSS), which has been validated [14] as a measure of skin fibrosis in SSc, [15, 16] pulmonary function (forced vital capacity, total lung capacity and diffusion capacity), event-free survival and any measure of safety as defined by the study authors.

Study Design

Randomized control trials (RCTs) (including cluster RCTs) and prospective and retrospective cohorts and case series with a minimum of 10 participants were included. Case reports, quasi-randomized studies, case-control studies, controlled before-after studies and case series of < 10 participants were excluded. Commentaries and editorials were also excluded.

Report Characteristics

Articles that were only available in abstract form were excluded. Attempts to locate published results of abstracts were made through citation searching and keyword searching. There were no limitations on publication date or language. A list of articles published in languages other than English and French was kept, and the reviewer endeavoured to find a translator. Where translation was not feasible, the article was excluded during full-text screening. Articles were not excluded based on publication status (published or in progress).

Search Strategy

A literature search strategy was developed using medical subject headings (MeSH), keywords, truncation and symbols. This search strategy was peer-reviewed by an academic librarian and was adapted for use in the following databases: Medline (OVID interface, 1946 onwards), EMBASE (OVID interface, 1947 onwards) and the Cochrane Central Register of Controlled Trials (OVID interface). The search was performed in 2019 and updated in April 2021. The electronic database search was supplemented by searching the Health Canada registry, clinicaltrials.gov, and the World Health Organization (WHO) international clinical trials registry. Finally, reference list of included studies were reviewed to identify any missing studies.

Study Records/Data Management

Literature review sources were uploaded to Covidence, an internet-based software program designed for citation management and duplicates were removed. Screening questions for title and abstract screening (level one) and full-text screening (level two) were developed, and integrated into Covidence. Full text articles were uploaded prior to level two screening. A PRISMA diagram was produced to document the selection flow.

Selection Process

One review author (NM) completed independent and duplicate screening for both stages of screening (i.e. title/abstract and full text). Full texts were retrieved for any articles with title/abstract that appeared to meet the inclusion criteria, or where there was ambiguity.

Data Collection Process

Standardized data extraction forms were developed (in Excel) by review authors. One review author (NM) extracted data.

Data Items

Extracted data points included study characteristics, methods, demographics, intervention and outcomes. Study characteristics included: the date of publication, publication status (published or in progress), journal or publishing format, authors, reported conflicts of interest and funding sources. The study author's definition or diagnostic criteria for systemic sclerosis was also extracted. Methods included: study design, randomization (if applicable), group allocation (if applicable), duration of the study, study setting, and date of study.

Recorded intervention characteristics included: conditioning regimen and use of CD34 selection. The comparator (and its dose, duration, route, and concomitant medication if applicable) was also extracted. Demographics and clinical characteristics included: age, sex/gender, disease duration (from onset of Raynaud's phenomenon and from onset of the first non-Raynaud's disease manifestation), mRSS and pulmonary involvement (FVC, TLC, DLCO).

The primary outcome was overall mortality. Secondary outcomes included extent of skin fibrosis, pulmonary function, event-free survival and safety outcomes. Skin fibrosis was defined using the mRSS and includes an evaluation of a patient's skin thickness rated by clinical palpation, which ranges from 0 (no involvement) to 3 (severe thickening) in 17 anatomic sites (total score range 0–51). [14-16] Safety outcomes were recorded if they occurred during the period of AHSCT or during study follow-up. Safety outcomes included: all-cause mortality; death

occurring after intervention and definitely or probably resulting from treatment as determined by reporting authors; and treatment-related toxicities (i.e. undesirable complications resulting from treatment regimen). Treatment related toxicities were determined as reported by study authors. They included but were not limited to: serious adverse events such as life-threatening events and hospitalizations; infections (author's definition and severity were recorded); secondary autoimmune diseases; and secondary malignancies.

Quality Assessment of Individual Studies

Study quality was determined for the primary outcome (overall mortality). All assessments were performed by one reviewer (NM). The Study Quality Assessment Tools developed by the National Heart, Lung, and Blood Institute (NIHBI) were applied accordingly to RCTs, observational cohorts and case series. [17] All studies were included despite risk of bias. Sensitivity analyses based on study quality could not be performed due to paucity of data.

Data Synthesis

Feasability of performing meta-analysis was assessed by evaluating outcome reporting variability and clinical heterogeneity among included studies. Narrative synthesis was undertaken where applicable.

Results

The electronic search identified 1315 records after removal of duplicates, of which 147 full-text studies were screened (Figure 1). Twelve studies involving 539 patients who received AHSCT and 171 patients who received other treatments were included.

Study selection and characteristics

Study characteristics are summarized in Table 1. We included 3 RCTs, 2 observational cohorts and 7 case series, all conducted between 2009 and 2021. Total number of participants varied between 16 and 156. We included 539 SSc patients receiving AHSCT. Five studies had comparator arms incorporating 160 participants who received cyclophosphamide and 11 others who received alternative pharmacologic treatments.

Primary outcomes used to assess overall response to treatment varied widely, namely, overall survival (n=3), event-free survival (n=2), progression-free survival (n=1), disease improvement (n=1), disease response (n=1), nailfold videocapillaroscopy (n=1) and global rank composite score (GRCS) (n=1).

Participant characteristics are presented in Table 2. Patients were mostly women with an average age between 39 and 48.5 years. Mean disease duration ranged from 13.6 to 70.5 months and mean baseline mRSS from 18.1 to 32. Mean lung function as measured by FVC and DLCO ranged from 62% to 85% and from 49.5% to 75%, respectively.

Inclusion criteria

There was no consistent definition for participant inclusion and exclusion criteria. Each study included patients based on varying criteria that incorporated age, extent of skin fibrosis and internal organ involvement (Table 3). Five studies limited inclusion according to disease duration. Seven studies required that participants demonstrate a minimum mRSS (range 14 to 20). Criteria for lung function included: bronchoalveolar lavage cell composition, presence of ground glass opacities on HRCT, decrease in FVC and decrease in DLCO. Other than lung function, internal organ involvement was also defined as abnormalities on electrocardiogram, previous renal abnormalities attributable to SSc and gastrointestinal tract involvement.

Exclusion criteria also differed between studies (Table 3) and encompassed markers of disease severity such as: lung function, previous use of high doses of cyclophosphamide, active/chronic infection, pregnancy, significant renal or hepatic impairment and severe gastrointestinal involvement. The presence of pulmonary arterial hypertension was a stated exclusion criteria in several studies (n=8), although cut-off measures varied.

Characteristics of AHSCT

The conditioning regimens used in each trial are listed in Table 4. The vast majority of trials utilized cyclophosphamide (200 mg/kg (n=8) and/or 100-120 mg/kg (n=5)) in combination with antithymocyte globulin (ATG) (rabbit (n=8), horse (n=2) or unspecified (n=2)). Total body irradiation was used in 2 studies and the combination of fludarabine and rituximab in one study. CD34+ selection was performed strictly in 7 studies and was variable in 2 studies.

Overall and treatment-related mortality

Overall and treatment-related mortality were reported in 11 of 12 included studies. Results are summarized in Table 5. The ASTIS, ASSIST and SCOT (Autologous hematopoietic stem cell transplantation vs intravenous cyclophosphamide in diffuse cutaneous systemic sclerosis; Autologous non-myeloablative hematopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis; Myeloablative autologous stem-cell transplantation for severe scleroderma) trials reported overall mortality in the AHSCT vs Cyclophosphamide groups of 21% vs 37% at 6 years, 0% vs 0% at 2.6 years and 17% vs 36% at 6 years, respectively. The remaining studies described overall mortality rates ranging between 11 and 36% over follow-up times ranging between 1 and 15 years. Rates of treatment-related mortality in ASTIS, ASSIST and SCOT were 10% at 5.8 years, 0% at 2.6 years and 6% at 6 years, respectively. In other studies, treatment-related mortality rates ranged between 2 and 23% over study periods between 1 and 15 years.

Skin involvement

All studies demonstrated some improvement in skin involvement, most commonly reported as a change in mRSS (Table 6). Post-treatment mRSS values were reported in 11 studies (Table 5). The ASTIS trial demonstrated a decrease in mRSS after 2 years of follow-up with a mean difference from baseline of -19.9 (SD 10.2) in the AHSCT group compared to -8.8 (SD 12.0) in the Cyclophosphamide group. In the ASSIST trial, there was a decrease from baseline to post-treatment mRSS in the AHSCT group (28 (SD 13.6) to 15 (SD 7.9)) as compared to the Cyclophosphamide group (19 (SD 13.7) to 22 (SD 14.2)) at 1 year. In the SCOT trial, at 54

months, those who received AHSCT were more likely to have demonstrated an improvement in mRSS as compared to those who received Cyclophosphamide (100% vs 82%). Del Pappa et al reported a significant decrease in mRSS with AHSCT as compared to baseline at 2 and 5 years independently of the European Scleroderma Study Group (ESSG) disease activity score and demonstrated that the probability that the score would fall below 14 was >90% in the AHSCT group as compared to 60% in the conventional care group. Maniati et al described a decrease in the AHSCT group ($p=0.02$ at 1 year and $p=0.00$ at 2 years) as opposed to no difference in the Cyclophosphamide group ($p=0.367$ at 1 year and $p=0.425$ at 2 years). Burt et al reported improvements in mRSS at 1, 2, 3 and 4 years ($p<0.0003$) as compared to baseline values with AHSCT. Similarly, Henes, Nash, Vonk, Burt, and Bijnen et al reported improvements in mRSS from baseline at follow-up varying between 1 and 8 years.

Lung function

Five studies reported an improvement in FVC in AHSCT patients, whereas 3 of 12 studies reported no improvement. Effects on lung function are shown in Table 7. Seven studies reported FVC at baseline and after treatment. Two RCTs, ASTIS and ASSIST, described significant increases in FVC with AHSCT (area under the curve (AUC), mean 6.3% (standard deviation (SD) 18.3) vs -2.8% (SD 17.2) at 2 years and increase from mean, 62% (SD 15.0) to 74% (SD 15.7) vs 67% (SD 17.0) to 61% (SD19.8) at 1 year, respectively. In the SCOT trial, at 54 months, the proportion of patients experiencing an improvement of >10% in FVC was similar in both treatment groups ($p=0.3$). Burt et al reported an increase in FVC post-AHSCT in the first 3 years of follow-up ($p=0.009$, $p=0.02$, $p=0.004$) with stabilization after 4 and 5 years ($p=0.11$, $p=0.26$).

Nash et al described a mean difference (MD) of 10.36 (CI: 3.52, 17.2) at 5-8 years post-AHSCT. Burt, Bijnen, and Henes et al reported modest or no increases in FVC at time ascertainments varying between 0.5 and 5 years.

Three studies reported TLC as a measure of lung function. ASTIS and ASSIST reported an increase in TLC (mean, AUC -5.1 (SD 17.5) vs -1.3 (SD 13.9)) at 2 years and from mean, 76% (SD 14.6) to 80% (SD 17.9) vs 83% (SD 14.8) to 74% (SD 18.7) at 1 year, respectively, after AHSCT.

Eleven studies reported DLCO, with only 2 reporting an improvement over time. Results of ASSIST were consistent with an increase in DLCO from 58% (SD 21.8) to 69% (SD 18.6) with AHSCT vs 75% (SD 27.5) to 74% (SD 37.0) with Cyclophosphamide at 1 year. Del Pappa et al estimated the probability that DLCO would fall under 50% of the predicted value at 5 years was below 20% in the AHSCT group. The lack of improvement in DLCO was consistent despite ESSG score. ASTIS reported a MD of 0.6 (95% CI -4.9 to 6.0) after AHSCT vs Cyclophosphamide. In the SCOT trial, a similar proportion of both treatment groups experienced an improvement of $\geq$10 points in DLCO (p-value: 0.6). Similarly, Burt, Henes, Nash, Vonk, and Bijnen et al did not show improvement in measures of DLCO spanning follow-up times from 1 to 5 years.

Data synthesis

Given significant outcome reporting variability and clinical heterogeneity among included studies, a meta-analysis could not be performed. Narrative synthesis was reported.

Study quality assessment

Quality assessments for RCTs are presented in **Figure 2**. All three studies were rated as good overall quality for the primary outcome of overall mortality. All included case series were deemed to have an overall good rating (Figure 3). The included observational studies were determined to have good and fair overall ratings (Figure 4).

Discussion

This systematic review describes the measures of efficacy and safety as well as protocol variations for the use of AHSCT in the treatment of SSc. We describe study characteristics, participant inclusion criteria, treatment protocols as well as efficacy of AHSCT on survival, skin involvement and pulmonary manifestations. Taken together, this review summarizes the best existing evidence and clinical practice variation for the use of AHSCT in the treatment of SSc.

Baseline characteristics were similar across studies (Table 2). Patients were typically between 40 and 50 years old with a female predominance characteristic of SSc. [18] Baseline mRSS scores are compatible with diffuse disease subtype in the context of relatively short disease duration. Despite significant variability in inclusion criteria (Table 3), there was a trend for inclusion of new, rapidly progressive disease with extensive skin fibrosis in young patients with either pulmonary, cardiac or renal involvement. It has been hypothesized that early in disease, immune alterations in response to microvascular endothelial cell injury play a key role in the pathogenesis of SSc.[19] In fact, Brkic et al demonstrated the presence of a prominent type I interferon signature in early SSc even before overt fibrosis, which correlated with B-cell activating factor (BAFF) mRNA expression and serum type III procollagen N-terminal propeptide

(PIIINP) levels. Such immune dysregulation is thought to play a key role in early disease pathogenesis and prognosis. [20, 21] Whether the benefits of AHSCT relate to the development of immunological tolerance or are related to intense immunosuppression [22], the procedure ultimately targets immunological disruption and is therefore more likely to be advantageous in the early stages of SSc. In fact, it has been demonstrated that AHSCT has a favorable impact on disease-associated molecular signatures as compared to other conventional studies. [23] More studies are needed to clarify the role of AHSCT in later phases of disease.

This review highlights the variability in protocols utilized in AHSCT for SSc (Table 4). Most protocols utilized CD34 selection and therefore we were unable to determine whether this may have had an effect on outcomes. However, all participants received a combination of cyclophosphamide and ATG for conditioning. The extent of cardiac involvement in early SSc is often underrecognized and has been described as a key prognostic factor in post-transplant survival. [24] Many suspect that this is directly associated with the well-known dose-limiting toxic effect of cyclophosphamide. As such, several studies have explored other modalities in an attempt to minimize this exposure. [9, 25] In SCOT, Sullivan et al used total body irradiation in combination with a lower dose of cyclophosphamide and ATG as an alternative approach. This may have contributed to the lower rate of treatment-related mortality. However, the efficacy of that regimen is difficult to compare with those using higher doses of cyclophosphamide as specific data on mRSS and lung function were not reported in SCOT.

This study corroborates results of previous systematic reviews supporting the role of AHSCT in the management of SSc. [26, 27] This review additionally includes recent evidence pertaining to emerging regimens developed to target specific cardiac toxicities and offers a

comprehensive overview by including smaller case series. Although there is heterogeneity in clinical outcomes reported, length of follow-up and treatment protocols, most studies consistently reported an improvement in survival, skin fibrosis and lung function. Watchful interpretation of comprehensive endpoints is necessary in SSc given its multifaceted manifestations with potential mixed response in individual components. Strategies for patient selection have evolved over time with the goal of mitigating treatment-related mortality. These concepts are further reflected in the treatment recommendations set forth by the European Alliance of Associations for Rheumatology (EULAR) in 2017. [28]

Strengths and Limitations

Strengths of this review include the conduct of a comprehensive search, adherence to recommendations for conduct and reporting of systematic reviews [13], and pragmatic approach to data collection and synthesis in the setting of anticipated paucity. However, this review also has limitations including selection and extraction by single reviewer. While we pragmatically included studies with differing protocols and outcome measures to maximize utility, our interpretation of results is therefore limited by meaningful heterogeneity that precluded meta-analysis. Specifically, there were meaningful differences with regards to inclusion criteria, conditioning regimens and definition of clinically important outcome measures. While this review suggested clinical benefits pertaining to survival, skin fibrosis and lung function, little is reported regarding other important disease manifestations including vascular and gastrointestinal involvement. Finally, although risk of bias for observational studies was determined to be low for the primary outcome of survival, careful consideration must be

given to the interpretation of other clinical outcomes including mRSS that could have been influenced by the evaluator's knowledge of intervention received.

Conclusion and implications

This systematic review describes the measures of efficacy and safety as well as protocol variations for the use of AHSCT in the treatment of SSc. The clinical heterogeneity of our findings precluded meta-analysis, and we therefore narratively described results of 12 studies involving 539 AHSCT patients and 171 who received other treatments. These findings suggested improved outcomes for survival, skin fibrosis and lung function. We identified heterogeneity in study design, outcome measures, eligibility criteria and AHSCT-specific protocols amongst the included studies. This review serves as a comprehensive summary of existing clinical practice variations and outcomes among patients receiving AHSCT for SSc. We highlight the need for the development of standardized algorithms pertaining to treatment protocols and patient selection to better inform evidence-based care.

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Table 1. Characteristics of included studies

Study	Study design	n AHSCT	n (Comparator)	Primary outcome
Sullivan 2018 [9]	RCT	36	39 (CYC)	GRCS
Van Laar 2014 [10]	RCT	79	77 (CYC)	Event-free survival
Burt 2011 [8]	RCT	10	9 (CYC)	Disease improvement
Del Pappa 2017 [29]	Observational cohort	18	25 (CYC) 11 (Other)	Overall survival
Maniati 2009 [30]	Observational cohort	6	10 (CYC)	Nail fold videocapillaroscopy
Henes 2012 [31]	Case series	26	N/A	Disease response at 6 months
Burt 2013 [24]	Case series	90	N/A	Treatment-related mortality
Nash 2007 [32]	Case series	34	N/A	Progression-free survival
Vonk 2008 [33]	Case series	26	N/A	Overall survival
Bijnen 2020 [34]	Case series	92	N/A	Event-free survival
Burt 2021 [25]	Case series	42	N/A	Overall survival
Henes 2021 [35]	Case series	80	N/A	Progression-free survival

AHSCT: Autologous hematopoietic stem cell transplantation
RCT: Randomized controlled trial
CYC: Cyclophosphamide
N/A: Not applicable
GRCS: Global Rank Composite Score

Table 2. Baseline characteristics of subjects in included studies

Study	Intervention (n)	Age	Sex (% female) (n)	Disease duration	mRSS	FVC (% predicted)	DLCO (% predicted)
Sullivan 2018 [9]	AHSCT (36)	44.9 (10.9)	53 (19)	25.1 mo (12.9)	28.5 (8.7)	74.5 (14.8)	53.9 (7.6)
	CYC (39)	46.9 (10.4)	74 (29)	29.0 mo (16.0)	30.8 (10.5)	73.8 (17.0)	52.7 (8.2)
Van Laar 2014 [10]	AHSCT (79)	44.2 (11.1)	54.4 (43)	1.4 y (1.2)	24.8 (8.1)	81.7 (19.3)	59.3 (14.3)
	CYC (77)	43.3 (11.5)	63.6 (49)	1.5 y (1.4)	25.8 (7.9)	81.1 (17.6)	57.7 (14.0) (n=76)
Burt 2011 [8]	AHSCT (10)	45 (32-58)	90 (9)	13.6 mo (2-33)	28 (6-48)	62 (53-70)	58 (29-82)
	CYC (9)	44 (26-54)	89 (8)	18 mo (6-36)	19 (4-45)	67 (43-84)	75 (29-111)
Del Pappa 2017 [29]	AHSCT (18)	41 (20-64)	72 (13)	24.0 mo (10-48)	20.0 (15-32)	NR	68 (51-100)
	Conventional (36)	44 (19-62)	72 (26)	24.2 mo (6-48)	19.5 (14-32)	NR	67 (53-98)
Maniati 2009 [30]	AHSCT (6)	48.5 (36-64)	NR	28 mo (18-48)	NR	NR	48
	CYC (10)	47.2 (28-61)	NR	32 mo (12-42)	NR	NR	NR
Henes 2012 [31]	AHSCT (26)	39 (19-65)	69 (18)	2.25 y (1-17)	18.2 (2-32)	NR	58 (32-104)
Burt 2013 [24]	AHSCT (90)	42 (16-71)	81 (73)	25 mo (2-156)	24 (3-47)	67 (31-103)	64 (19-123)
Nash 2007 [32]	AHSCT (34)	41 (23-61)	76 (26)	21 mo (4-51)	30 (3-48)	71 (27-103)	61 (40-83)
Vonk 2008 [33]	AHSCT (26)	42 (16-65)	73 (19)	2.0 y (0.8-13)	32 (9-51)	NR	65% (17) had <70% predicted
Bijnen 2020 [34]	AHSCT (92)	46 (10)	43 (47)	1.5 y (IQR 0.9-3.0)	26.0 (10.1)	85 (23)	55 (16)
Burt 2021 [25]	AHSCT (42)	46.3 (11.9)	64 (27)	70.5 mo (59)	18.1 (12)	62.5 (16)	49.4 (16.4)
Henes 2021 [35]	AHSCT (80)	43 (20-62)	71.3 (57)	23.8 mo (5.3-103.7)	24 (2-49)	72 (43-132)	59 (34.3-120)

AHSCT: Autologous hematopoietic stem cell transplantation
CYC: Cyclophosphamide
NR: Not reported
mRSS: Modified Rodnan skin score
FVC: Forced vital capacity
DLCO: Diffusion capacity of the lung for carbon monoxide

Table 3. Inclusion and exclusion criteria applied in included studies

Study	Inclusion Criteria				Exclusion Criteria
	Age	mRSS	Internal organ involvement	Other	
Sullivan 2018 [9]	18-69	>16	Pulmonary involvement (bronchoalveolar cell composition or ground-glass opacities or HRCT and either FVC or DLCO <70%) or renal involvement (previous scleroderma-related renal disease)	DD <5 y	GAVE, DLCO <40%, FVC <45%, LVEF <50%, CrCl <40 ml/min, PAH, >6 months of previous treatment with CYC
Van Laar 2014 [10]	18-65	>15 <20 if ESR >25 mm or Hgb <11g/dL	Involvement of heart, lung or kidneys	DD <4 y	Cumulative CYC >5 g IV or up to 2 mg/kg body weight orally for 3 months, PAP >50 mmHg, serious comorbidities
Burt 2011 [8]	<60	>14 or <14 with coexistent pulmonary involvement	DLCO <80% or decline in FVC by 10% or more in the previous 12 months or pulmonary fibrosis or ground-glass on HRCT or abnormal electrocardiogram or gastrointestinal tract involvement	DD <4 y	More than 6 months of CYC IV, TLC <45%, LVEF <40%, symptomatic cardiac disease, HIV or hepatitis B surface antigen seropositivity, Cr >177 umol/L, pregnancy, PASP >40 mmHg, mPAP >25 mmHg
Del Pappa 2017 [29]	NR	>14		Any patient with rp-SSc whose response to conventional therapies were nil or very unsatisfactory, clinical activity score (ESSG) of at least 3 and DD <4y	PAH confirmed by RHC, SRC, DLCO <50%, LVEF <45%
Maniati 2009 [30]	NR	NR	NR	NR	NR
Burt 2013 [24]	NR	>14 or <14 with coexistent pulmonary involvement	Pulmonary fibrosis or ground glass on HRCT, abnormal electrocardiograph or gastrointestinal trac involvement		TLC <45%; LVEF <40%, PAP >42mmHg, HIV or hepatitis B surface antigen seropositivity For a subset of patients: age >55 or DD >4 years
Henes 2012 [31]				Inefficacy of CYC or rp-SSc with strong indicators for bad prognosis: positive Scl-70 antibodies, rapid progression of skin/organ manifestations, male sex, alveolitis, early PAH	Karnofsky index <70%, PAP >50 mmHg, DLCO <40%

Nash 2007 [32]	<65	>16	Significant visceral organ involvement or with decrease in FVC or DLCO of >15% in the previous 6 months	DD <4 y; patients with an estimated mortality risk of 50% at 5 years with conventional treatment	NR
Vonk 2008 [33]	<66		If DD <2 y: mRSS >20 and ESR >25 mm or Hgb <11g/dL If DD >2 y: progression of mRSS (>20%) plus either: 1.VC/DLCO <70% or mean PAP >40mmHg 2. Serum albumin <25 g/L or weight loss >10% in last 12 months 3. 24h urinary protein >0.5 g or serum creatinine >120 umol/L		Uncontrolled arrhythmia, LVEF <50%, mean PAP >50 mmHg, DLCO <45%, CrCl <20 ml/min, platelets <80 000/mm3, hemorrhagic cystitis, HIV or HTLV1 seropositivity, malignancy, pregnancy, cardiac or vascular prosthesis, no vascular access
Burt 2021 [25]		>14 or <14 with coexistent pulmonary involvement	DLCO <80% or decline in FVC by 10% or more in the previous 12 months or pulmonary fibrosis or ground-glass on HRCT or abnormal electrocardiogram or gastrointestinal tract involvement	PASP on RHC >40mmHg at rest or >45 mmHg with fluid challenge or mPAP >25 mmHg at rest or >30 mmHg with fluid challenge or diastolic interventricular septal flattening or septal bounce on cardiac MRI	Cardiac tamponade, CrCl <80 ml/min, malignancies, transaminases >2x ULN, platelet count <100 000/ul, hepatitis B or C or HIV seropositivity or active infection
Bijnen 2020 [34]	NR	NR	NR	NR	NR
Henes 2021 [35]	18-65	NR	NR	Severe progressive SSc	NR

NR: Not reported
DD: Disease duration
CYC: Cyclophosphamide
mRSS: Modified Rodnan skin score
FVC: Forced vital capacity
DLCO: Diffusion capacity of the lung for carbon monoxide
TLC: Total lung capacity
HRCT: High-resolution computed tomography
LVEF: Left ventricular ejection fraction
PAP: Pulmonary artery pressure
GAVE: Gastric antral vascular ectasia
PAH: Pulmonary artery hypertension
ESR: Erythrocyte sedimentation rate
IV: Intravenous
CrCl: Creatinine clearance

Table 4. Conditioning regimens used in included studies

Study	Conditioning regimen	CD34 Selection
Sullivan 2018 [9]	CYC 120 mg/kg + Horse ATG + Total body irradiation	Yes
Van Laar 2014 [10]	CYC 200 mg/kg + Rabbit ATG	Yes
Burt 2011 [8]	CYC 200 mg/kg + Rabbit ATG	No
Del Pappa 2017 [29]	CYC 200 mg/kg + Rabbit ATG	Yes
Maniati 2009 [30]	Variable: • CYC 100 mg/kg + Thiotepa + Rabbit ATG • CYC 200 mg/kg + Rabbit ATG	Yes
Burt 2013 [24]	CYC 200 mg/kg + Rabbit ATG	No
Henes 2012 [31]	CYC 200 mg/kg + Rabbit ATG	Yes
Nash 2007 [32]	CYC 120 mg/kg + Horse ATG + Total body irradiation	Yes
Vonk 2008 [33]	CYC 120 mg/kg + ATG (Unspecified)	Variable
Burt 2021 [25]	Variable: • Fludarabine 120 mg/m2, ATG, CYC 60 mg/kg • Fludarabine 120 mg/m2, ATG, CYC 60 mg/kg, Rituximab 1000 mg • Fludarabine 120 mg/m2, ATG, CYC 60 mg/kg, Rituximab 500 mg	No
Bijnen 2020 [34]	CYC 200 mg/kg + Rabbit ATG	Yes
Henes 2021 [35]	Variable (at participating centre's discretion): • CYC 200 mg/kg or "other dose" + Rabbit ATG • CYC 100 mg/kg + Thiotepa + Rabbit ATG	Variable

CYC: Cyclophosphamide
ATG: Anti-thymocyte globulin

Table 5. Reported overall survival and treatment-related mortality after AHSCT or comparators in included studies

Study	Intervention (n)	Overall mortality (%)	Treatment-related mortality (%)	Follow-up time (years)
Sullivan 2018 [9]	AHSCT (36)	17	6	6
	CYC (39)	36	0	
Van Laar 2014 [10]	AHSCT (79)	21	10	6
	CYC (77)	37	0	
Burt 2011 [8]	AHSCT (10)	0	0	2.6 (R:1-5)
	CYC (9)	0	0	
Del Pappa 2017 [29]	AHSCT (18)	11	5.6	5
	Conventional (36)	61	0	
Maniati 2009 [30]	AHSCT (6)	NR	NR	
	CYC (10)	NR	NR	
Burt 2013 [24]	AHSCT (90)	22	6	5
Henes 2012 [31]	AHSCT (26)	27	4	3
Nash 2007 [32]	AHSCT (34)	36	23	5
Vonk 2008 [33]	AHSCT (26)	15	4	7
Burt 2021 [25]	AHSCT (42)	10	2	1
Bijnen 2020 [34]	AHSCT (92)	22	11	15
Henes 2021 [35]	AHSCT (80)	10	6.25	2

AHSCT: Autologous hematopoietic stem cell transplantation
CYC: Cyclophosphamide

Table 6. Reported change in mRSS after AHSCT or comparators in included studies

Study	Intervention (n)	mRSS		Time ascertainment (years)
		Baseline	After treatment	
Sullivan 2018 [9]	AHSCT (36)	28.5 (SD: 8.7)	NR	
	CYC (39)	30.8 (SD: 10.5)		
Van Laar 2014 [10]	AHSCT (79)	24.8 (SD: 8.1)	Mean difference: -19.9 (SD: 10.2)	2
	CYC (77)	25.8 (SD: 7.9)	Mean difference: -8.8 (SD: 12.0)	2
Burt 2011 [8]	AHSCT (10)	28 (SD: 13.6)	15 (SD: 7.9)	1
	CYC (9)	19 (SD: 13.7)	22 (SD: 14.2)	1
Del Pappa 2017 [29]	AHSCT (18)	ESSG≥6: 22.0 (CI: 18.7-25.3)	ESSG≥6 : 4.0 (CI: 1.9-6.2)	2
			ESSG≥6 : 3.9 (CI: 1.8-5.9)	5
		ESSG<6 : 21.7 (CI: 17.6-25.9)	ESSG<6 : 4.1 (CI: 2.2-6.0)	2
			ESSG<6 : 3.0 (CI: 1.7-4.2)	5
	Conventional (36)	19.5 (R:14-32)	NR*	
Maniati 2009 [30]	AHSCT (6)		p=0.02	1
			P=0.00	2
	CYC (10)		p=0.367	1
			p=0.425	2
Burt 2013 [24]	AHSCT (90)	24 (R: 3-47)	12.9 (p<0.0001)	1
			12.2 (p<0.0001)	2
			11.1 (p<0.0001)	3
			10.3 (p=0.0001)	4
			8.9 (p=0.0003)	5
Henes 2012 [31]	AHSCT (26)	18.2 (SD: 7.9)	9.3 (SD: 6.5)	1
Nash 2007 [32]	AHSCT (34)	30 (R: 3-48)	Mean difference: -17.56 (CI: -20.72;14.40)	1-2
			Mean difference: -21.24 (CI: -25.42;-17.52)	3-4
			Mean difference -21.82 (CI: -25.88;-17.74)	5-8
Vonk 2008 [33]	AHSCT (26)	32 (R: 9-51)	19 (R: 3-51)	1
			12 (R: 0-49)	2
			7 (R: 3-43)	3
			4 (R: 0-35)	4
			4 (R: 0-34)	5
			5 (R: 0-19)	6
			3 (R: 2-10)	7
Burt 2021 [25]	AHSCT (42)	18 (SD: 12)	Flu/CYC/ATG: 6.1 (SD: 3.6)	1
			Flu/CYC/ATG/RTX/IVIg: 8.5 (SD: 10.1)	1
Bijnen 2020 [34]	AHSCT (92)	26 (IQR 18-32)	6 (IQR 2-7)	5
Henes 2021 [35]	AHSCT (80)	23.9 (SD: 9.7)	14.2 (SD: 9.2)	1
			12.6 (SD: 8.3)	2

*Probability that the score would fall below 14 was >90% in the AHSCT group vs >60% in the conventional group

AHSCT: Autologous hematopoietic stem cell transplant
CYC: Cyclophosphamide
ATG: Anti-thymocyte globulin
Flu: Fludarabine
RTX: Rituximab
IVIg: Intravenous imune globulin
ESSG: European Scleroderma Study Group Disease Activity Score

Table 7. Reported change in FVC, TLC, DLCO after AHSCT or comparators in included studies

Study	Intervention (n)	FVC (mean % predicted)		TLC (% mean predicted)		DLCO (% mean predicted)		Time ascertainment (years)
		Baseline	After treatment	Baseline	After treatment	Baseline	After treatment	
Sullivan 2018 [9]	AHSCT (36)	74.5 (SD: 14.8)	NR			53.9 (SD: 7.6)	NR	
	CYC (39)	73.8 (SD: 17.0)				52.7 (SD: 8.2)		
Van Laar 2014 [10]	AHSCT (79)	81.7 (SD: 19.3)	MD: 6.3 (SD: 18.3)	81.0 (SD: 17.1)	MD: 5.1 (SD: 17.5)	59.3 (SD: 14.3)	MD: -4.7 (SD: 13.7)	2
	CYC (77)	81.1 (SD: 17.6)	MD: -2.8 (SD: 17.2)	80.5 (SD: 16.5)	MD: -1.3 (SD: 13.9)	57.7 (SD: 14.0)	MD: -4.1 (SD: 17.6)	2
Burt 2011 [8]	AHSCT (10)	62 (SD: 15.0)	74 (SD: 15.7)	76 (SD: 14.6)	80 (SD: 17.9)	58 (SD: 21.8)	69 (SD: 18.6)	1
	CYC (9)	67 (SD: 17.0)	61 (SD: 19.8)	83 (SD: 14.8)	74 (SD: 18.7)	75 (SD: 27.5)	74 (SD: 37.0)	1
Del Pappa 2017 [29]	AHSCT (18)					*ESSG≥6 : 67.6 (CI: 57.6;77.5)	ESSG≥6 : 57.2 (CI: 48.7;65.7)	2
							*ESSG≥6 : 56.7 (CI: 49.8;63.6)	5
						*ESSG<6 : 70.5 (CI: 55.1;85.9)	ESSG<6 : 72.3 (CI: 50.6;94.1)	2
							*ESSG<6 : 72.0 (CI: 50.0;94.0)	5
	Conventional (36)						NR	
Maniati 2009 [30]	AHSCT (6)					48	59	2
	CYC (10)						NR	
Burt 2013 [24]	AHSCT (90)	66.2	71.1 (p=0.009)			68.2	66.5 (p=0.56)	1
			72.6 (p=0.02)				72.8 (p=0.82)	2
			76.1 (p=0.004)				68.3 (p=0.27)	3
			73.4 (p=0.11)				64.5 (p=0.48)	4
			73.0 (p=0.26)				64.5 (p=0.67)	5
Henes 2012 [31]	AHSCT (26)					58.3 (SD: 20.6)	61.4 (SD: 13)	1
Nash 2007 [32]	AHSCT (34)	71 (R: 27-103)	Mean difference: 4.48 (CI: 0.14;9.10)			61 (R: 40-83)	Mean difference: -1.37 (CI: -5.64;4.98)	1-2
			Mean difference: 2.09 (CI: -5.17;9.34)				Mean difference: -3.70 (CI: -9.68;4.9)	3-4
			Mean difference: 10.36 (CI: 3.52;17.2)				Mean difference: -2.27 (CI: -9.69;5.15)	5-8
Vonk 2008 [33]	AHSCT (26)					55 (R: 21-100)	52 (R: 26-100)	1
							58 (R: 21-100)	2
							58 (R: 15-94)	3
							50 (R: 16-85)	4
							52 (R: 17-75)	5
							62 (R: 11-74)	6
							75 (R: 18-76)	7
Burt 2021 [25]	AHSCT (42)	62.5 (SD: 16)	Flu/CYC/ATG: 62.3 (SD: 13.3)	70 (SD: 16.5)	Flu/CYC/ATG: 71.4 (SD: 13.8)	49.4 (SD: 16.4)	Flu/CYC/ATG: 37.8 (SD: 12.4)	0.5
			Flu/CYC/ATG/RTX/IVIg: 69.9 (SD: 17.5)		Flu/CYC/ATG/RTX/IVIg: 77.7 (SD: 15.9)		Flu/CYC/ATG/RTX/IVIg : 51.8 (SD: 11.9)	0.5
Bijnen 2020 [34]	AHSCT (92)	84% (IQR 68-102)	94% (IQR 81-107)			65% (IQR 42-67)	61% (IQR 53-73)	5
Henes 2021 [35]	AHSCT (80)	73.6 (SD: 16.9)	79.5 (SD: 16.9)			60.2 (SD: 19.3)	59.7 (SD: 17.7)	1
			80.6 (SD: 19.1)				60.4 (SD: 19.1)	2

* The estimated probability that DLCO fell to under 50% of the predicted value at 5 years was below 20% in the AHSCT group and over 60% in both the whole control group and the CYC-treated subgroup at 5 years

AHSCT: Autologous hematopoietic stem cell transplant, CYC: Cyclophosphamide, ATG: Anti-thymocyte globulin, Flu: Fludarabine, RTX: Rituximab, IVIg: Intravenous immune globulin, ESSG: European Scleroderma Study Group, FVC: Forced vital capacity, TLC: Total lung capacity, DLCO: Diffusion capacity of the lung for carbon monoxide

Figure 1. PRISMA flow diagram

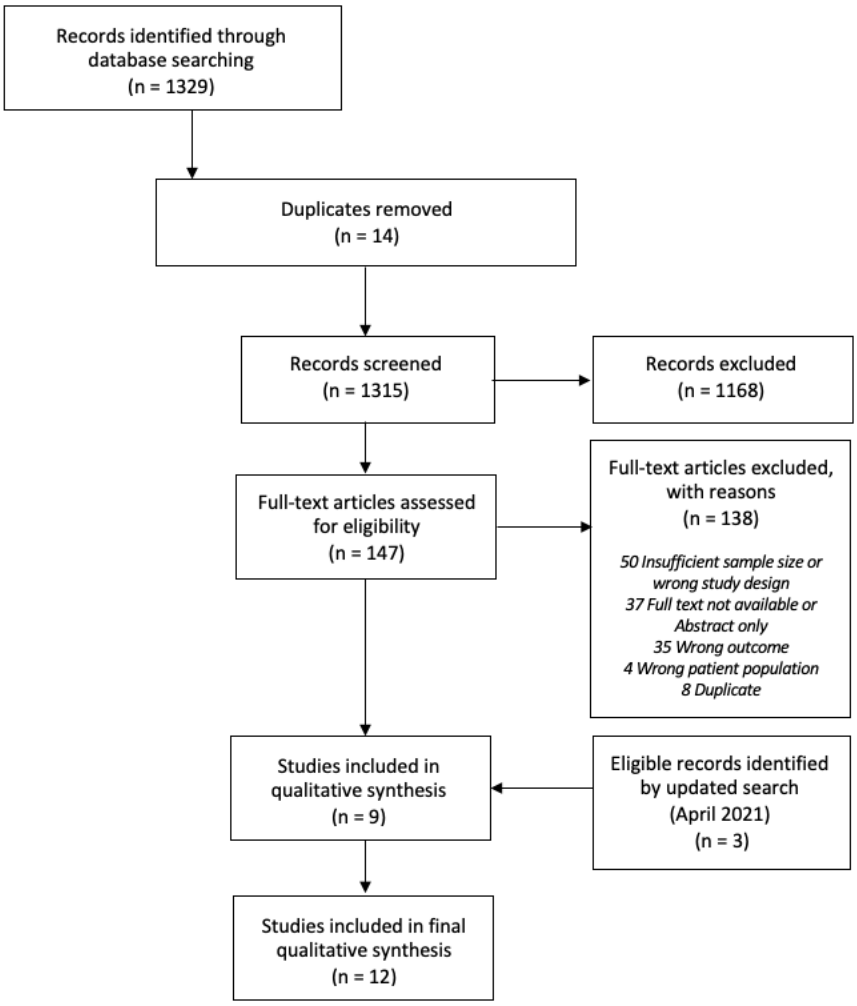

Figure 2 – NIH Quality Assessment Tool – Controlled Intervention Studies

NIH Quality Assessment Tool – Controlled Intervention Studies			
	Burt 2011	**Van Laar 2014**	**Sullivan 2018**
1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?	Yes	Yes	Yes
2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?	Yes	Yes	Yes
3. Was the treatment allocation concealed (so that assignments could not be predicted)?	Yes	Yes	Yes
4. Were study participants and providers blinded to treatment group assignment?	No	No	No
5. Were the people assessing the outcomes blinded to the participants' group assignments?	No	No	No
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?	Yes	Yes	Yes
7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	Yes	Yes	Yes
8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	Yes	Yes	Yes
9. Was there high adherence to the intervention protocols for each treatment group?	Yes	Yes	Yes
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?	Cannot determine	Cannot determine	Cannot determine
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Yes	Yes	Yes
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?	Yes	No	Yes
13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?	Yes	Yes	Yes
14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?	Yes	Yes	Yes
Quality Rating (Good, Fair, Poor)	**Good**	**Good**	**Good**

Figure 3 – NIH Quality Assessment Tool – Case Series Studies

NIH Quality Assessment Tool – Case Series Studies							
	Burt 2013	**Henes 2012**	**Nash 2007**	**Vonk 2008**	**Burt 2021**	**Bijnen 2020**	**Henes 2021**
1. Was the study question or objective clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly and fully described, including a case definition?	Yes	No	Yes	Yes	Yes	Yes	Yes
3. Were the cases consecutive?	Yes	Yes	Yes	Cannot determine	Cannot determine	Yes	Yes
4. Were the subjects comparable?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Was the intervention clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Was the length of follow-up adequate?	Yes	No	Yes	Yes	Yes	Yes	Yes
8. Were the statistical methods well-described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Were the results well-described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Quality Rating (Good, Fair, Poor)	**Good**	**Fair**	**Good**	**Good**	**Good**	**Good**	**Good**

Figure 4 – NIH Quality Assessment Tool – Observational Cohorts

NIH Quality Assessment Tool – Observational Cohort		
	Del Pappa 2017	**Maniati 2009**
1. Was the research question or objective in this paper clearly stated?	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Cannot determine
3. Was the participation rate of eligible persons at least 50%?	Cannot determine	Cannot determine
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	Cannot determine
5. Was a sample size justification, power description, or variance and effect estimates provided?	Yes	Yes
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	Yes
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	Yes
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Not applicable	Not applicable
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Not applicable	Not applicable
10. Was the exposure(s) assessed more than once over time?	Not applicable	Not applicable
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes
12. Were the outcome assessors blinded to the exposure status of participants?	No	No
13. Was loss to follow-up after baseline 20% or less?	Yes	Yes
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Yes	Yes
Overall Rating (Good, Fair, Poor)	**Good**	**Fair**

Supplementary Material:

Search Strategy

1 exp Scleroderma, Systemic
2 Systemic sclerosis.tw,kw.
3 scleroderma.tw,kw.
4 crest syndrome*.tw,kw.
5 or/1-4 (66281)
6 Hematopoietic Stem Cell Transplantation
7 ((h?ematopoietic adj3 transplant*) or hsct*).tw. or ahsct.tw,kw.
8 peripheral blood cell transplant*.tw,kw.
9 Bone Marrow Transplantation
10 bone marrow transplant*.tw,kw.
11 stem cell transplantation
12 stem cell transplant*.tw,kw.
13 stem cell therap*.tw,kw.
14 peripheral blood stem cell transplantation
15 or/6-14 (315753)
16 5 and 15
17 exp animals/ not humans/
18 16 not 17
20 remove duplicates from 18
21 20 use medall Medline
22 20 use emczd (702) Embase
23 20 use cctr (11) Cochrane

Chapter 4 – The Effectiveness of AHSCT for the Treatment of SSc

SECTION OVERVIEW

This chapter describes the analysis and interpretation of a retrospective study pertaining to the efficacy of AHSCT in the management of SSc. It includes the manuscript "Improvement in Overall Survival, Skin Fibrosis and Lung Function with Autologous Hematopoietic Stem Cell Transplantation in Systemic Sclerosis"

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NM, DF, MH, PT and GW contributed to the study design and conception. NM, MP, PL, ZM, CC, MB, IC, MH, DF contributed to data collection. NM conducted the statistical analysis under the supervision of MW, MH, RS and GW. NM, DF, MH contributed to data interpretation. NM drafted the manuscript which was revised by MH, GW and PT.

"Improvement in Overall Survival, Skin Fibrosis and Lung Function with Autologous Hematopoietic Stem Cell Transplantation in Systemic Sclerosis"

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Keywords: Systemic sclerosis, autologous stem cell transplant, propensity score, inverse probability treatment weights

Abstract

Background:

Systemic sclerosis (SSc) is a chronic disease characterized by vasculopathy, inflammation and fibrosis with limited treatment options for progressive disease. There is an important unmet medical need for disease modifying therapy for patients with SSc. Autologous hematopoietic stem cell transplantation (AHSCT) has been shown in randomized trials to be an effective treatment for rapidly progressive SSc. However, little is known about its performance as compared to real-world (non-randomized controlled trial setting) clinical care. The objective of this study was to evaluate the effectiveness of AHSCT for SSc compared to conventional clinical practice.

Methods:

SSc patients from France who underwent AHSCT were compared to similar patients from Canada who met criteria for AHSCT (as defined in the ASTIS trial) but received conventional care. The primary outcome was overall survival. Secondary outcomes included modified Rodnan skin score (mRSS), forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DLCO). Overall survival for both groups was estimated by Kaplan-Meier survival curves. Measures of mRSS, FVC and DLCO were compared using linear regression models. Analyses were adjusted for baseline scores and incorporated stabilized inverse probability of treatment weights to account for confounding by indication. Propensity scores were estimated using logistic regression.

Results:

Forty-one AHSCT patients and 85 conventional care patients were compared. Mean mRSS was 25.0 (10.5) in the AHSCT group and 27.0 (8.0) in the conventional care group. Mean FVC and DLCO were 78.9 (17.5) and 55.2 (15.5) in the AHSCT group and 79.0 (20.2) and 62.0 (19.6) in the conventional care group, respectively. AHSCT was associated with improvement in overall survival (log-rank p=0.115; Figure 1). In follow-up, the mRSS was lower with AHSCT compared to conventional care: between group difference of 8.81; p=<0.0001 at 12 months and 11.28; p=0.011 at 60 months. There was no significant difference in FVC between groups at 12 months but at 24 months, AHSCT was associated with a higher FVC (between group difference of 10.53 (p=0.05)) but a lower DLCO (between group difference of -3.43 (p=0.002)).

Conclusion:

This study demonstrates with real-world long-term data that compared with conventional care, treatment with AHSCT may offer superior outcomes for SSc patients.

Systemic sclerosis is a multi-system disease with known poor prognosis. [1, 2] Despite improved understanding of pathophysiologic mechanisms including autoimmunity, fibrosis and vasculopathy, there are few options for the treatment of rapidly progressive, diffuse, severe disease. Autologous hematopoietic stem cell transplantation (AHSCT) was first reported as a potential treatment for patients with SSc in the 1990s. [3, 4] More recently, 3 randomized controlled studies (RCTs) of AHSCT in SSc have shown promising results relating to survival, skin fibrosis and lung function as compared to the use of cyclophosphamide alone. [5-7] However, clinical uptake has been limited by concerns about treatment-related toxicities.

This study sought to evaluate the role AHSCT in the management of SSc outside of the strict RCT follow-up protocols. Specifically, we describe differences in overall survival, skin fibrosis and lung function in SSc patients who received AHSCT versus conventional care.

The Maladies Auto-Immunes et Thérapie Cellulaire (MATHEC) (www.mathec.com) is a French network of reference with a mission to improve clinical practice and advance research in the use of cellular therapies for autoimmune diseases, including SSc. The Canadian Scleroderma Research Group (CSRG) has followed up a large cohort of adult patients with SSc from multiple participating academic centres in Canada longitudinally since 2004. As AHSCT is less commonly performed in Canada, we leveraged complementary expertise and datasets from French and Canadian scleroderma research teams to compare treatment strategies. Specifically, we compared SSc patients treated with AHSCT in France compared to Canadian patients who would have met transplantation criteria but instead received conventional care as per their

treating physician. We hypothesized that treatment with AHSCT would demonstrate improved overall survival as compared to conventional care.

Patients and methods

Ethics considerations

Ethics committee approval for this study was obtained from the Jewish General Hospital in Montreal (approval no. REB 2023-3503). Informed consent was obtained from all patients in accordance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice.

Study population

Subjects with a clinical diagnosis of SSc who underwent AHSCT in the MATHEC cohort were included. The comparator group included patients enrolled in the CSRG cohort who fulfilled the eligibility criteria for AHSCT in the ASTIS trial [7]: age>18 years, diffuse cutaneous SSc according to the American College of Rheumatology 1980 classification criteria for SSc **AND** maximum duration of disease of 4 years since first non-Raynaud's symptoms AND minimum modified Rodnan skin thickness score (mRSS) of 15 **AND** involvement of heart, lungs or kidneys **OR** disease duration of <2 years with no major organ involvement but with a mRSS of at least 20 and erythrocyte sedimentation rate (ESR) of >25 mm/hour and/or hemoglobin level of <110 g/L) but who received standard of care.

Data collection

Patient characteristics were recorded within each cohort. Disease duration was determined by the participating physicians and defined as time since first non-Raynaud's phenomenon symptom. Age, sex and smoking history were self-reported. Skin involvement was assessed using the mRSS. [8] This score consists of an evaluation of a patient's skin thickness rated by clinical palpation, which ranges from 0 (no involvement) to 3 (severe thickening) in 17 anatomic sites (total score range 0–51). It has been validated and is commonly used as a primary outcome measure in SSc clinical trials. [9, 10] Participating clinicians also recorded history of scleroderma renal crisis (SRC), need for parenteral nutrition and body mass index. Laboratory testing included serum antibodies, erythrocyte sedimentation rate (ESR), levels of hemoglobin, creatinine and proteinuria. The presence of interstitial lung disease (ILD) was determined using a clinical decision tool. According to this algorithm, ILD is considered present if a high resolution computed tomography (HRCT) scan of the lung is interpreted by an experienced radiologist as showing ILD or, in the case where no HRCT is available, if either a chest X-ray is reported as showing either increased interstitial markings (not thought to be due to congestive heart failure) or fibrosis, and/or if a study physician reports the presence of typical "velcro-like crackles" on physical examination. [11] Pulmonary function tests including forced vital capacity (FVC), total lung capacity (TLC) and diffusion capacity for carbon monoxide (DLCO) % predicted (and corrected for hemoglobin) were recorded. Left ventricular ejection fraction and systolic pulmonary arterial pressure were measured by cardiac echocardiogram. Mobilization and conditioning regimens for AHSCT and/or other pharmacologic agents used for the management of SSc were noted.

Outcome measures

The primary outcome was defined as overall survival. Secondary outcomes included extent of skin fibrosis as defined by mRSS, presence of lung disease (FVC, TLC, DLCO) as well as safety and treatment-related morbidity (development of scleroderma renal crisis, new malignancy, new secondary autoimmune disease and the need for placement of pacemaker). Post-transplant infections were defined as the presence of positive serologies (Epstein-Barr virus (EBV), cytomegalovirus (CMV), hepatitis B and C) or positive cultures (bacterial, fungal or viral (herpes simplex)) and need for active treatment in the 24 months post-transplant.

Statistical analysis

Descriptive statistics were used to compare baseline characteristics and safety events of cases and controls. Categorical data was presented as a number and percentage (%) and continuous data as means and standard deviations.

Overall survival was compared using a Kaplan-Meier model adjusted for clinically important variables in a propensity score (presence of ILD, presence of anti-topoisomerase auto-antibodies, sex, age, disease duration, FVC, mRSS, hemoglobin and ESR) using stabilized inverse probability of treatment weights (IPTW). Time zero was defined as date of transplantation or study visit date at which patient would have been deemed eligible for AHSCT. An adjusted Cox proportional model was fit to observe the predictive value of baseline variables on overall survival. Differences in mRSS, FVC and DLCO were compared using linear models with adjustment for a priori defined, clinically important baseline characteristics (presence of ILD, presence of anti-topoisomerase auto-antibodies, sex, age, disease duration,

hemoglobin and ESR) and IPTW. Categorization thresholds for continuous variables were determined based on clinical expertise.

IPTW was calculated as 1/propensity score for subjects who received AHSCT and 1/(1-propensity score) for controls. Propensity scores were estimated using logistic regression analyses and included the following clinically important covariates: presence of ILD, presence of anti-topoisomerase auto-antibodies, sex, age, disease duration, FVC, mRSS, hemoglobin and ESR. Multiple imputation was used to impute missing covariates based on observed values of all covariates included in the regression model. Regression coefficients and variances were estimated using ten imputed datasets. IPTW were estimated within each dataset and averaged. Standardized mean differences were computed to determine balance in baseline covariates between groups. A standardized difference of 0.1 represents meaningful balance. [12-14] Balance for all covariates improved with re-weighting (Supplemental Figure 1).

Crude incidence rates were computed for the development of SRC, need for placement of permanent pacemaker, new malignancy and new secondary autoimmune disease.

All analyses were performed using SAS version 9.4.

Results

Baseline characteristics

A total of 126 subjects were included in the analysis: 41 cases who underwent AHSCT and 85 controls who received conventional care. Of these, 65.9% and 75.3% were female in the AHSCT and control groups, respectively. Subjects in the control group were older (53.5 (11.6) vs 44.7 (13.3) years) and had shorter disease duration (19.5 (11.1) vs 30.6 (18.5) months). Baseline

mRSS were similar 25.0 (10.5) in the AHSCT and 27.0 (8.0) in the control groups. A higher proportion of those who received AHSCT were non-smokers (67.6%) as compared to the control group (43.9%), while mean measures of % predicted FVC were similar in the 2 groups (78.9% (17.5) vs 79.0% (20.2)). There were no differences in baseline systolic pulmonary artery pressure (31.0 (9.1) vs 35.0 (13.9) mmHg) and proportion of those with left ventricular ejection fraction >50% (100% vs 97.4%), respectively. Baseline creatinine levels were higher among controls (90.3 (48.1)) compared to the AHSCT group (62.4 (12.8) umol/L)). A higher proportion of controls had positive anti-centromere antibodies (13.5% vs 2.6%), while anti-topoisomerase antibodies were more common (65.0% vs 27.0%) in the AHSCT group.

Overall survival

The adjusted Kaplan-Meier survival estimates of overall survival are shown in Figure 1. AHSCT was associated with improvement in overall survival (log-rank p=0.115). Weighted survival estimates at 1.5 years were 0.88 (standard error (SE) 0.05) and 0.98 (SE 0.03), at 5 years were 0.70 (SE 0.06) and 0.84 (SE 0.08) and at 8 years were 0.48 (SE 0.10) and 0.75 (SE 0.10) for the group treated with conventional care and AHSCT respectively. Computed hazard ratios (HRs) for predictors of overall survival are listed in Table 2. Older age (>50 years) was associated with worse overall survival (HR 0.257 (p=0.080). The remainder of covariates studied including ILD (p=0.231), anti-topoisomerase antibodies (p=0.276), sex (p=0.163), mRSS (p=0.932), FVC (p=0.245), DLCO (p=0.142), disease duration (p=0.835), hemoglobin (p=0.161) and creatinine (p=0.136) were not statistically significantly associated with overall survival. Improved survival was observed with AHSCT (HR 2.34 (0.84;6.53), higher baseline FVC (HR 1.72 (0.69;4.29) and

DLCO (HR 1.90 (0.81;4.49), female sex (HR 1.83 (0.78;4.30), higher hemoglobin (HR 1.93 (0.77;4.81), lower creatinine (HR 0.53 (0.23;1.23) and absence of anti-topoisomerase antibodies (HR 0.59 (0.23;1.52) though these differences were not statistically significant.

Skin involvement

Differences in mRSS between AHSCT and control groups at annual follow-up visits are presented in Figure 2. Scores describing skin involvement were consistently improved in the AHSCT group as compared to control and this difference was maintained over time: -8.81; p=<0.0001 at 12 months and -11.28; p=0.011 at 60 months. Patterns in improvement were similar with stratification by baseline mRSS (grouped by mRSS <20 and $\geq$ 20).

Lung involvement

Differences in FVC and DLCO between AHSCT and control groups are illustrated in Figures 3 and 4. At 12 months, there was no difference between groups in FVC and DLCO of 3.51 (p=0.5) and -1.93 (p=0.642), respectively. At 24 months, there was a statistically significant difference in FVC (10.53 (p=0.05)) but not DLCO -1.62 (p=0.718) in favor of AHSCT. At 60 months, there was no statistically significant difference between AHSCT and control groups in FVC (9.45 (p=0.19)) and DLCO (0.17 (p=0.979).

Long-term complications

Crude incidence ratios for long-term disease complications are presented in Table 3. The incidence rate of SRC was lower in the AHSCT group (0.58 cases / 100 person-years) as

compared to the control group (6.02 cases / 100 person-years). The incidence rate for the need for pacemaker placement was 0.87 cases / 100 person-years and 0.29 cases / 100 person-years in the AHSCT and control groups, respectively. There was a higher incidence rate of new malignancies (3.72 vs 0.58 cases / 100 person-years) and new autoimmune diseases (6.30 vs 1.45 cases / 100 person – years) in the control group compared to AHSCT.

Infectious complications

The peri-AHSCT infectious complications are listed in Table 4. There were 18 cases of bacterial sepsis, 7 EBV reactivations, 5 CMV reactivations, 3 herpes infections and 1 viral hepatitis. There were no recorded cases of EBV or CMV primary infections.

Discussion

In this multicentre study of French and Canadian subjects, we found that AHSCT was associated with long-term improvement in overall survival as compared to conventional care. The effect on overall survival was most notable in the first 4 years of follow-up. The results also suggest that younger age, better lung function and higher hemoglobin may be associated with improved survival. Altogether, this likely reflects that early severe organ involvement commonly seen in patients with rapidly progressive SSc is an important factor and suggests that earlier AHSCT may be more effective. There was marked improvement in mRSS following AHSCT, well beyond the 3.2-5.3 points threshold for minimal clinical importance [15], and this effect was sustained over time. With regards to lung function, FVC was similar at 12 months but markedly improved in the AHSCT at 24 and 60 months. This could represent the slow recovery

and continued remodeling in the first-year post-transplant. There was also a statistically significant difference between both groups favoring AHSCT at 84, 108 and 120 months, although this may be attributable to survival bias. There was no statistically significant difference between groups in DLCO during long-term follow-up. Of note, the predictive value of DLCO in systemic sclerosis has mainly been associated with the development of pulmonary arterial hypertension in those with the limited cutaneous subtype which are patients that would not have been candidates for AHSCT. [16]

The results of this study further corroborate the benefits of AHSCT for the improvement of overall survival, skin fibrosis and lung function, functional status and health-related quality of life for patients with SSc. In ASTIS [7], at 2-year follow-up there was a difference between treatment groups in mRSS of 11.1 (7.5 ; 1.0) and FVC -9.1% predicted (-14.7 ; -2.5) favoring the use of AHSCT. However, there was similarly no difference in DLCO (0.6 (-4.9 ; 6.0)). At 54 months, a higher proportion of participants enrolled in SCOT [6] who received AHSCT had noted an improvement in mRSS and FVC as compared to those in the group that received cyclophosphamide. Both ASTIS and SCOT demonstrated benefit in long-term overall survival. However, while the ASTIS and SCOT trials were restricted to cyclophosphamide as a comparison regimen, this observational study pragmatically included a variety of comparison agents utilized in routine clinical practice. These findings demonstrate treatment effectiveness for AHSCT persists even outside tightly run RCT regimens.

Although the role of AHSCT in the management of skin fibrosis and lung function has been well established, its effect on other disease manifestations remains unclear. Interestingly, this study noted a higher incidence of scleroderma renal crisis (SRC) in the conventional care group during long term follow-up. Although the low event rates preclude a definitive conclusion, these findings allow for interesting hypotheses relating to pathogenesis. It has been hypothesized that SRC occurs secondary to endothelial dysfunction and ischemia as demonstrated by the lack of inflammatory infiltrates on renal biopsy. [17, 18] However, these results may support the alternate hypothesis that inflammatory changes and auto-immunity may in fact play a key role in endothelial activation. This corroborates evidence confirming the presence of inflammatory infiltrates in other studies assessing renal biopsies. [19] Similarly, poorly controlled auto-immunity may also contribute to development of new malignancies and secondary auto-immune diseases in the long-term in the conventional care group.

This study has several strengths, including the high-quality multicentre dataset, pragmatic inclusion of a diverse patient population, as well as methodologically rigorous approaches to address clinical heterogeneity. These considerations were undertaken to maximize external generalizability. However, this study also has limitations. Despite robust methods to address heterogeneity, there remains the possibility of residual confounding. In addition, a cluster effect cannot be excluded, as French patients were used exclusively in the intervention arm while Canadian patients were used exclusively for controls. Therefore, unaccounted geographical or system differences in health-care access and logistical obstacles may have impacted patient selection and long-term follow-up. Finally, the umbrella term of

conventional care encompassed a variety of disease-modifying agents that were chosen by the treating physician. While this consideration was intentional to maximize inclusiveness and external generalizability, we acknowledgeable trade-offs with regards to internal validity.

Conclusion

This pragmatic, multicentre study provides real-world long-term data supporting the superiority of AHSCT as compared to conventional care for patients with SSc. Specifically, we demonstrate that there is an improvement in overall survival, skin fibrosis and lung function with AHSCT as compared to conventional care. Further studies are required to assess the efficacy of AHSCT in the treatment of other disease manifestations.

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Table 1. Baseline characteristics of the subjects treated with AHSCT compared to those treated with conventional care

	AHSCT *n / mean (SD)* (n=41)	**Conventional Care** *n / mean (SD)* (n=85)	**Missing Data**	
			AHCST	Conventional Care
Sex (% female)	27 (65.9%)	64 (75.3%)	0	0
Age	44.7 (13.3)	53.5 (11.6)	0	0
Disease duration (months)	30.6 (18.5)	19.5 (11.1)	0	0
BMI (kg/m^2)	23.4 (4.0)	24.9 (5.1)	0	2
Modified Rodnan Skin Score	25.0 (10.5)	27.0 (8.0)	1	0
Smoking			4	3
Never smoker	25 (67.6%)	36 (43.9%)		
Past smoker	8 (21.6%)	39 (47.6%)		
Current smoker	4 (10.8%)	7 (8.5%)		
Interstitial lung disease (% present)	38 (92.7%)	55 (64.7)	3	7
FVC	78.9 (17.5)	79.0 (20.2)	4	5
DLCO	55.2 (15.5)	62.0 (19.6)	0	12
Pulmonary artery pressure (mmHg)	31.0 (9.1)	35.0 (13.9)	0	30
Left ventricular ejection fraction			2	11
> 50%	38 (100%)	76 (97.4%)		
45-49%	0	2 (2.6%)		
Creatinine (umol/L)	62.4 (12.8)	90.3 (48.1)	0	6
ESR (mm/h)	42.8 (24.8)	34.4 (27.8)	17	14
Hemoglobin (g/L)	126.2 (11.8)	118.2 (19.8)	0	1
Serologies				
ACA (+)	1 (2.6%)	10 (13.5%)	1	11
SCL70 (+)	26 (65.0%)	20 (27.0%)	0	10
ANA (+)	27 (65.8%)	64 (75.3%)	0	0

AHSCT: Autologous hematopoietic stem cell transplantation
BMI: Body mass index
FVC: Forced vital capacity
DLCO: Diffusion capacity of the lungs for carbon monoxide
ESR: Erythrocyte sedimentation rate
ACA: Anticentromere antibodies
SCL70: Anti-Scl70 antibodies
ANA: Antinuclear antibodies

Table 2. Cox proportional hazard ratios estimating the effect of treatment on overall survival

Parameter	REF	Hazard Ratio (95% Confidence Interval)	P value
Treatment	AHSCT/Conv Care	2.338 (0.838, 6.526)	0.1049
ILD	Yes/No	1.764 (0.697, 4.4463)	0.2311
Scl70	Positive/Negative	0.592 (0.230, 1.520)	0.2759
Sex	Female/Male	1.834 (0.782, 4.302)	0.1629
MRSS	Above 20/Below	1.050 (0.341, 3.231)	0.9320
FVC	Above 60%/Below	1.720 (0.690, 4.288)	0.2446
DLCO	Above 60%/Below	1.903 (0.806, 4.490)	0.1420
Disease Duration	Above 24mo/Below	0.912 (0.382, 2.176)	0.8349
Hemoglobin	Above 110/Below	1.925 (0.770, 4.810)	0.1612
Creatinine	Above 70/Below	0.527 (0.226, 1.225)	0.1364
Age	Above 50/Below	0.257 (0.094, 0.701)	0.0080

AHSCT: Autologous hematopoietic stem cell transplantation
ILD: Interstitial lung disease
MRSS: Modified Rodnan skin score
FVC: Forced vital capacity
DLCO: Diffusion capacity of the lungs for carbon monoxide
SCL70: Anti-Scl70 antibodies

Table 3. Crude incidence rates of long-term complications in subjects treated with SSc compared to conventional care

	Number of cases	Total person-time at risk (years)	Incidence rate (cases / 100 person-years)
Scleroderma Renal Crisis			
AHSCT	2	344.7	0.58
Conventional care	21	349.1	6.02
Need for pacemaker placement			
AHSCT	3	344.7	0.87
Conventional care	1	349.1	0.29
Development of new malignancy			
AHSCT	2	344.7	0.58
Conventional care	13	349.1	3.72
Development of new autoimmune disease			
AHSCT	5	344.7	1.45
Conventional care	22	349.1	6.30

Table 4. Post-AHSCT infectious complications

Infectious complication	Number of cases
Bacterial sepsis with positive blood cultures	18
EBV reactivation	7
EBV primoinfection	0
CMV reactivation	5
CMV primoinfection	0
Herpes infection	3
Fungal infection	2
Viral hepatitis (Hepatitis B/C)	1

Figure 1. Adjusted Kaplan-Meier survival estimates of overall survival of subjects treated with AHSCT compared to those treated with conventional care

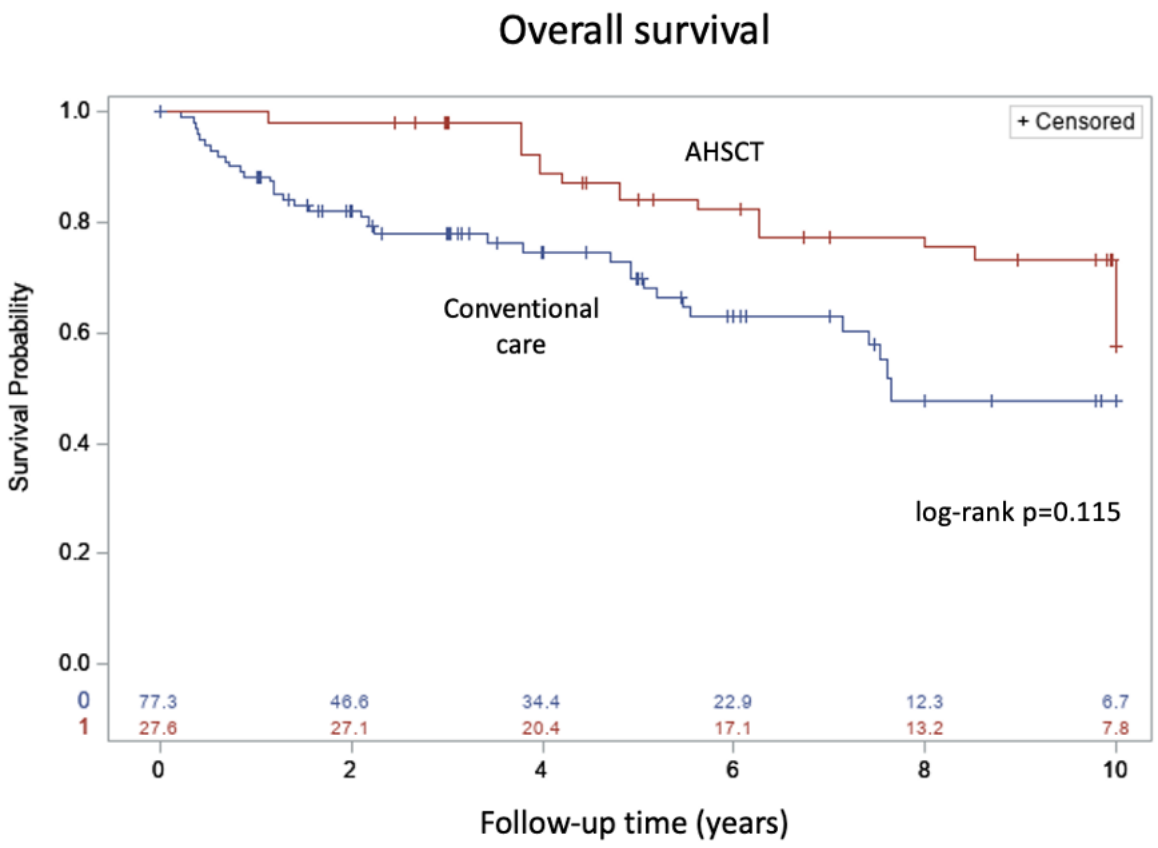


Figure 2. Difference at annual visits in mRSS between patients with SSc treated with AHSCT compared to conventional care

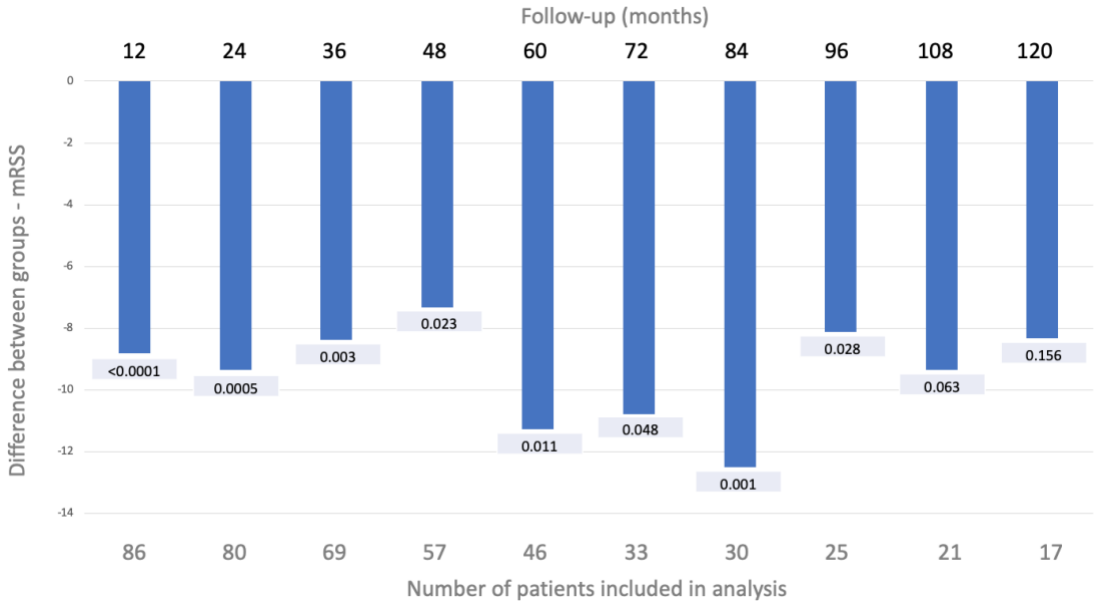


Figure 3. Difference at annual visits in FVC between patients with SSc treated with AHSCT compared to conventional care

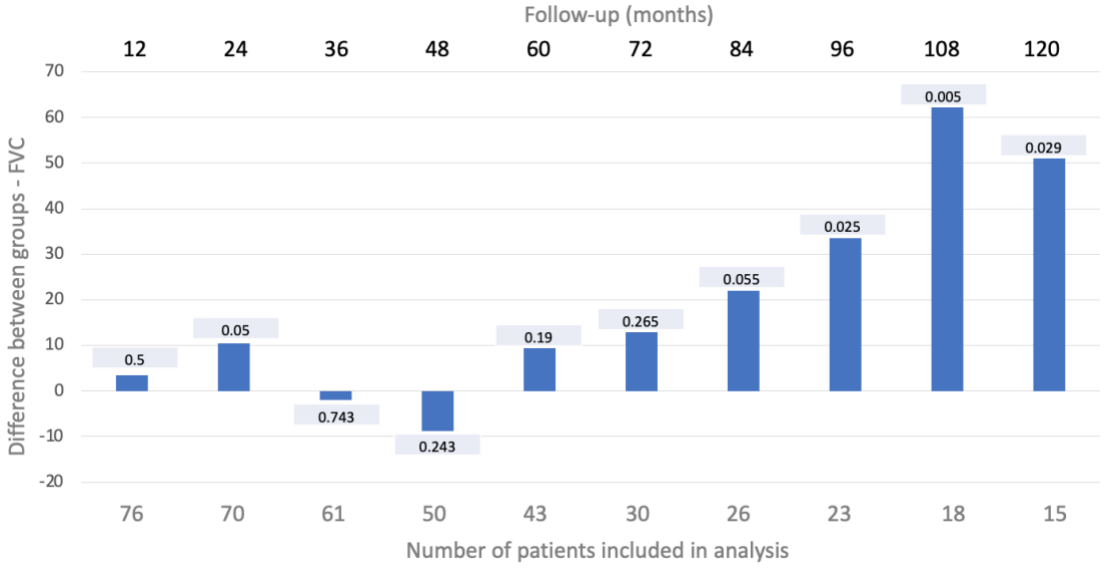
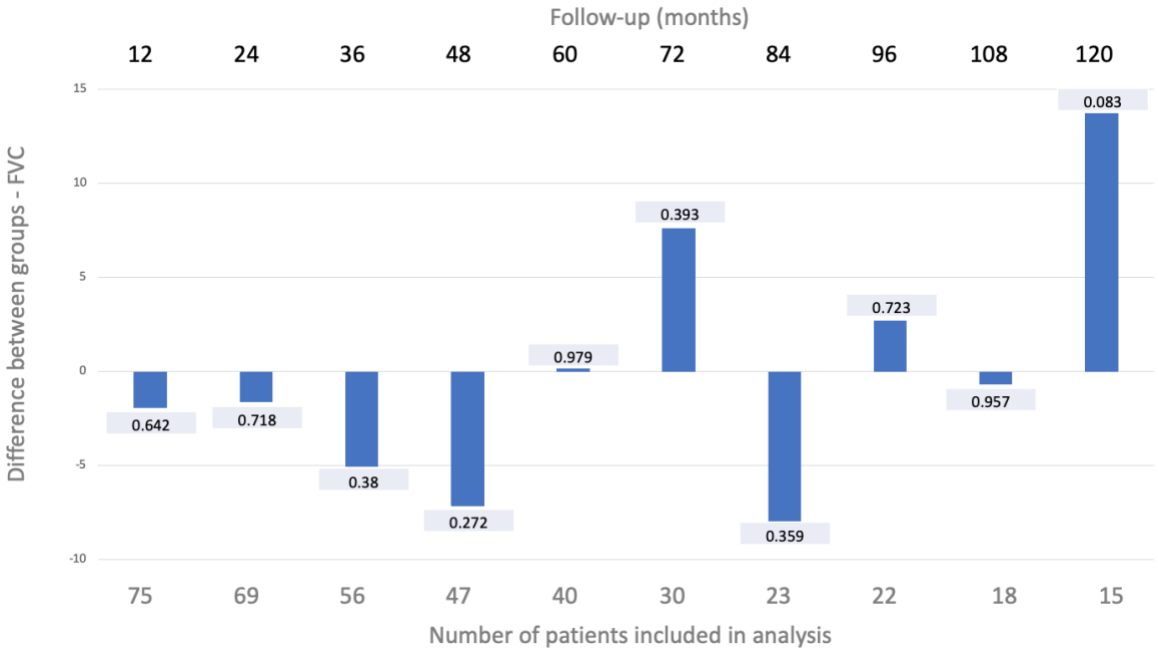
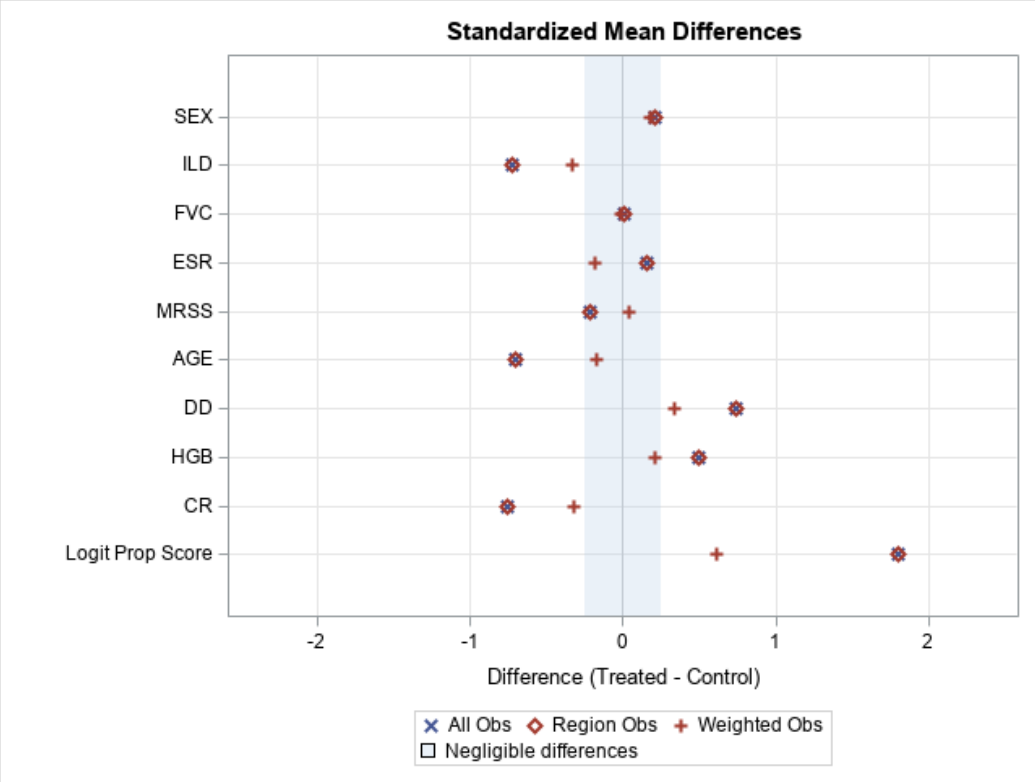


Figure 4. Difference at annual visits in DLCO between patients with SSc treated with AHSCT compared to conventional care



Supplementary Material

Figure 1. Standardized mean differences computed to determine balances in baseline covariates between groups.



Chapter 5 – Discussion

This chapter reviews key findings of this thesis including strengths, limitations and proposed foci for future research.

5.1 Summary

Rapidly progressive SSc is a rare disease with potentially severe multi-organ involvement and high mortality rates. Despite an improved understanding of the underlying pathophysiologic mechanisms linking autoimmunity, fibrosis and vasculopathy, there remains an unmet need for treatments with demonstrable efficacy for improvement of clinical outcomes. Due to its rare disease prevalence, population heterogeneity, wide spectrum of disease manifestations and limitations with existing outcome measures, SSc remains a very challenging disease to treat and study.

Our work in this thesis supports the existing literature that AHSCT represents a promising therapy with the potential to improve overall and event-free survival in patients with SSc. [1-3] However, despite this evidence base, its clinical uptake has been limited by challenges regarding accessibility for patients and perceived uncertainty with regards to indications, overall efficacy, and variability in treatment protocols.

5.2 Key findings

In this thesis, we conducted a comprehensive and evidence-based review of the use of AHSCT in the treatment of SSc. In Chapter 3, our systematic review demonstrated substantial

variability with regards to patient selection, treatment protocols and follow-up regimens between centers. However, despite this noted variability in real world application, we found consistent evidence of benefit. In Chapter 4, our multicentre cohort study of real-world application also demonstrated improvement in a variety of clinical outcomes as compared to conventional therapy – providing further evidence of external generalizability outside of a strict RCT protocol. When compared to the findings of the systematic review, we identified similar benefits pertaining to overall survival, skin fibrosis and lung function.

5.3 Importance of findings

Although uptake of AHSCT for SSc has been slower in Canada [4], there has been increasing interest among rheumatologists leading to more referrals and transplants performed over time. Local treatment protocols and patient selection criteria are largely influenced by those delineated in RCTs. However, there is growing interest in expansion beyond classical indications. These potential populations of interest include those with very early onset disease, older patients and second transplants for disease recurrence.

The evolving evidence base for AHSCT for SSc so far has been based predominantly on basic science work demonstrating biological plausibility followed by randomized trials suggesting clinical efficacy and safety. This thesis provides further evidence supporting AHSCT by focusing on the pragmatic considerations of external generalizability. Specially, we highlight that despite existing heterogeneity in adaptation and application of treatment protocols, there remains evidence of benefit and ongoing improvement in clinical uptake. These findings are methodologically and clinically meaningful – the applications of which are likely compelling to

both patients and providers. However, the notable heterogeneity suggests an opportunity for further study and potential for standardization. A foundational evidence base is set for the development of future studies to explore more nuanced research objectives including: (1) evaluation of treatment effects on other clinical disease manifestation; (2) exploration of expanded indications; and (3) refinement and standardization of treatment protocols.

5.4 Strengths and limitations

In this thesis, we explored concepts related to external generalizability of AHSCT for the treatment of SSc and the quality of our work is highlighted by several strengths. We focused on real world application using a pragmatic approach to data acquisition and emphasized findings that were most clinically relevant to patients and healthcare providers. We complemented this pragmatic approach with rigorous statistical methods to account for limitations pertaining to heterogeneous observational data. The use of propensity score and inverse probability of treatment weights allowed for balancing of baseline characteristics between study groups whilst not omitting any observations – an important consideration when studying a disease with a rare prevalence rate and limited sample size availability. In addition, our pragmatic definition of conventional care (including any form of pharmacological immunomodulation), allowed for a comparator group more reflective of clinical practice, an option otherwise not feasible within the constraints of an RCT.

Our findings also have limitations. Notably, all AHSCTs included in the multicentre cohort study were performed at a single center with well-defined local patient selection criteria and treatment protocols. Although these criteria were also applied to select the conventional

care group and robust statistical analyses were performed to minimize the impact of important patient confounders, the potential for residual confounding or clustering cannot be discounted. Similarly, the retrospective local cohort described in Chapter 4 represents AHSCTs that were performed at a tertiary care center with expertise in managing SSc patients with extensive multidisciplinary support. This may limit generalizability to other transplant centers with potentially less experience in this application of AHSCT. Furthermore, although these findings are compelling for the improvement of survival, skin fibrosis and lung function, there is limited data regarding the effects on other disease manifestations such as vascular disease (Raynaud's phenomenon, digital ulcerations) or gastrointestinal involvement (gut dysmotility, small intestinal bacterial overgrowth). Finally, we focused predominantly on external generalizability of existing evidence for AHSCT use for SSc, we acknowledge that our findings would be complemented greatly by additional endeavors focused on knowledge translation. Although we demonstrate real world effectiveness and improving clinical uptake for this promising therapy, a more nuanced understanding of barriers faced by healthcare providers and patients could dramatically improve the potential magnitude of its impact.

5.5 Conclusion and next steps

This thesis adds important complementary real-world data to support the use of AHSCT in the management of rapidly progressive dSSc. It corroborates previous findings of statiscally significant and clinically important improvement in overall survival, skin fibrosis and lung function as noted in large multicentre RCTs. There is ongoing uncertainty and resultant practice variability in terms of patient selection, treatment protocols and management of other disease

manifestations. However, despite an initial slow uptake of this procedure in Canada, the number of referrals and AHSCTs performed is increasing over time.

Future foci of research may include expanded eligibility criteria to the following patient groups: (1) patients with shorter disease duration and predictors of severe organ involvement; (2) older patients; (3) those with mild pulmonary vascular disease or (4) those with disease relapse. Furthermore, there is a need for standardized and pragmatic protocols for referral, eligibility, treatment and follow-up with the intention of improving accessibility. Well-defined follow-up procedures would also allow for improved data capture regarding other disease manifestations outside of skin and lung involvement. Finally, dedicated efforts to improve knowledge translation are needed to minimize barriers to appropriate, evidence-based clinical uptake. Taken together, it is clear that further work is urgently needed to define the ideal role of AHSCT in the overall management of dSSc which despite increased mortality, remains an orphan disease with limited options for disease modifying therapies.

1. Burt, R.K., 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.* The Lancet, 2011. **378**(9790): p. 498-506.
2. Sullivan, K.M., et al., *Myeloablative Autologous Stem-Cell Transplantation for Severe Scleroderma.* New England Journal of Medicine, 2018. **378**(1): p. 35-47.
3. van Laar, J.M., et al., *Autologous Hematopoietic Stem Cell Transplantation vs Intravenous Pulse Cyclophosphamide in Diffuse Cutaneous Systemic Sclerosis: A Randomized Clinical Trial.* JAMA, 2014. **311**(24): p. 2490-2498.
4. Storek, J., A. Daly, and S.A. LeClercq, *Autologous hematopoietic cell transplantation for systemic sclerosis - a challenge for the Canadian health care system.* Cmaj, 2017. **189**(17): p. E623-e624.