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Evidence Summary SCT-10

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Autologous hematopoietic cell transplantation for autoimmune diseases

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An assessment conducted in February 2024 deferred the review of Evidence Summary (ES) SCT-10. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

You can access ES SCT-10 here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/59296

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Evidence Summary

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

INTRODUCTION

Hematopoietic cell transplantation (HCT), formerly known as stem cell transplantation, is a treatment for patients with malignant diseases such as lymphoma, leukemia, and myeloma, and for other acquired and genetic non-malignant hematological (blood), immunological, and storage disorders. Transplantation involves administration of high-dose chemotherapy, sometimes accompanied by total body radiation, to destroy the diseased cells. Because this destroys the patient's bone marrow, hematopoietic stem cells are infused to regenerate the marrow and to produce healthy blood and immune cells. Allogeneic HCT uses a donor as the source of these bone marrow-derived stem cells. Autologous HCT (aHCT) involves harvesting the patient's own hematopoietic stem cells before treatment then transplanting the stem cells back into the patient after the course of high-dose chemotherapy.

The goal of the conditioning regimen and the agents used (radiation, chemotherapy, and cytotoxic antibodies such as anti-thymocyte globulin [ATG]) vary based upon the type of transplant (allogeneic or autologous) and the indication for HCT. These goals may include one or more of the following:

- Eliminating malignant cells;
- Eliminating the recipient immune system (to prevent graft rejection, to treat a genetic disease of the immune system such as severe combined immunodeficiency, or to treat an autoimmune disease such as aplastic anemia and others);
- Eliminating diseased recipient stem cells (to treat a genetic disease of the stem cells such as sickle cell disease, thalassemia, and others); and/or
- Supplying healthy stem cells that provide enzymes or other factors that may be missing in certain genetic diseases (storage diseases such as mucopolysaccharidosis, Krabbe disease, adrenoleukodystrophy, and others).

Less commonly, aHCT has been used to treat a number of rare and severe autoimmune diseases. Indeed, autoimmune diseases are the fastest growing indication for aHCT reported to the European Society for Blood and Marrow Transplantation (EBMT) registry (https://www.ebmt.org). The most common autoimmune indications reported to the registry are multiple sclerosis (MS), scleroderma (SSc), and inflammatory bowel disease (IBD). Despite newer and more effective agents being developed for the treatment of autoimmune diseases, these drugs are not fully able to curb the inflammatory component of the disease for some patients; for these patients, HCT is a treatment that may be capable of halting the disease process.

This evidence summary addresses the use of aHCT for MS, SSc, and IBD and was undertaken by the PEBC at the request of CCO's Specialized Services Oversight (SSO) Program and the Stem Cell Transplant (SCT) Advisory Committee.

RESEARCH QUESTIONS

The following three research questions were developed to direct the search for available evidence on aHCT for the specified autoimmune diseases:

1. In patients with MS, is aHCT more effective than alternative therapies in halting disease progression?
2. In patients with SSc, is aHCT more effective than alternative therapies in halting disease progression?
3. In patients with IBD, is aHCT more effective than alternative therapies in halting disease progression?

TARGET POPULATION

All adult patients with MS, SSc, or IBD receiving aHCT were included.

INTENDED PURPOSE

The purpose of the evidence summary is as follows:

- To provide direction as to appropriate non-hematologic autoimmune indications for aHCT, focusing on three selected autoimmune diseases **(**MS, SSc, IBD),
- To potentially identify specialized resources, in addition to (or instead of) what is provided in the cancer system, to enable safe and effective aHCT for the three selected autoimmune diseases,
- To provide evidence to support programmatic decision making regarding indications for the three selected autoimmune disease.

INTENDED USERS

This evidence summary is targeted for:

- The SSO and SCT Advisory Committee to inform planning of services for HCT delivery in Ontario.

METHODS

This evidence summary was developed by a Working Group consisting of three hematologists and one health research methodologist at the request of the SSO and SCT Advisory Committee.

The Working Group was responsible for reviewing the identified evidence and drafting the summary. Conflict of interest declarations for all authors are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

This evidence review was conducted in two planned stages, including a search for systematic reviews (SR) followed by a search for primary literature. These stages are described in subsequent sections.

Search for Systematic Reviews

Relevant SRs were identified by searches of MEDLINE (2013 – January 2019 week 3), EMBASE (2013 – 2019 week 3), and the Cochrane Library (2013 - 2019). The reference lists of eligible trials were searched for relevant articles, and the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp) was searched for existing evidence-based practice guidelines. Expert colleagues were also asked to identify any relevant unpublished or published trials not otherwise identified. Along with the inclusion criteria indicated for primary studies

listed below (under study selection criteria and process), SRs were included if they contained at least one randomized controlled trial (RCT) with sensitivity analysis performed on randomized trials separately. The complete MEDLINE and EMBASE search strategies are detailed in Appendix 2.

Search for Primary Literature

For each of the three questions of interest, if no SR was identified, then a search for primary literature was conducted. For any included SR, an updated search for primary literature was performed. If any included SR was limited in scope, then a search for primary literature to address the limitation in scope was conducted.

Literature Search Strategy

The literature was searched using MEDLINE (2005 through January, 2019), EMBASE (2005 through January, 2019), PubMed (2005 – January 2019), the Cochrane Central Register of Controlled Trials (OVID CCTR: January 2019), and the Database of Abstracts of Reviews of Effects (OVID DARE: 1st quarter 2019). Reference lists of studies deemed eligible for inclusion were scanned for additional citations. The literature search of the electronic databases combined disease-specific terms (MS, SSc, IBD) and treatment-specific terms (hematopoietic transplantation, stem cell transplantation, autologous, etc.) for RCTs and SRs (Appendix 2).

Study Selection Criteria and Process

Articles were included if they were:

- Published full-report articles or abstracts of phase II and phase III RCTs evaluating the use of aHCT for treatment or management of MS, SSc, or IBD;
- Studies reporting on at least one of the outcomes of interest, namely, complete response, progression-free survival, overall survival, quality of life, toxicities; and
- Studies conducted in adult populations (≥18 years of age) with MS, SSc, or IBD.

Articles were excluded if they were:

- Letters, case reports, comments, books, notes, or editorial publication types; and/or
- Articles published in a language other than English due to unavailability of translation services.

A review of the titles and abstracts was conducted by JB. For studies that warranted full-text review, JB reviewed each study independently or, if in doubt, in collaboration with a second reviewer (either HA, CB, or TK).

Data Extraction and Quality Assessment

All included primary studies underwent data extraction by JB, with all extracted data and information subsequently audited by an independent auditor.

Risk of bias per outcome for each included study was assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [1]. For relevant SRs, the completeness of reporting of the SRs was analyzed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool [2].

Synthesizing the Evidence

When clinically homogeneous results from two or more trials were available, a meta-analysis was conducted using the Review Manager software (RevMan 5.1) provided by the Cochrane Collaboration [3]. For time-to-event outcomes, hazard ratios (HR), rather than the number of events at a specific time, were the preferred statistic for meta-analysis, and were used as reported. If the HR and/or its standard error were not reported, they were derived

from other information reported in the study, using the methods described by Parmar et al. [4]. For all outcomes, the generic inverse variance model with random effects, or other appropriate random effects models were used.

Statistical heterogeneity was calculated using the x^2 test and a probability level for the x^2 statistic less than or equal to 10% ($p \leq 0.10$) was considered indicative of statistical heterogeneity. If heterogeneity was detected, the I^2 index was used to quantify the percentage of the variability in the effect estimates that was due to heterogeneity. I^2 greater than 50% was considered indicative of statistical heterogeneity.

RESULTS

Systematic Reviews Search Results

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram summarizing this information is provided in Appendix 3.

Three SRs were considered for inclusion at full-text level [5-7]. Of the three SRs, only the one by Shouval et al. [7] performed sensitivity analysis separating RCTs from other study designs, and thus is the only SR included in this report (see Appendix 4).

Primary Literature Search Results

Articles were retrieved from the MEDLINE (n=1742) and EMBASE (n=957) databases, and additional records identified through other sources (n=25). After duplicates were removed from the combined search results, 1990 articles were assessed by title and abstract for possible inclusion in the evidence summary. Of these, 1759 articles were rejected at the title level and the remaining (n=231) were assessed at the level of full text. Of these, 226 were excluded at full text resulting in six RCTs meeting inclusion criteria. See PRISMA diagram in Appendix 3.

Two of the RCTs evaluated MS [8,9], three examined SSc [10-12], and one examined IBD (hereby referred to as Crohn's disease [CD]/IBD – a major category of IBD) [13].

The three RCTs examining SSc [10-12], previously pooled in the SR by Shouval et al. [7], were combined for the current report using RevMan 5.1 [3]. The two RCTs that examined MS were not combined because the treatments given to each of the control groups were not comparable (mitoxantrone [Mitox] vs. various disease-modifying therapies [DMTs]).

Study Quality

The results of the original AMSTAR [2] assessment for the SR included in this report is available in Appendix 5. The review by Shouval et al. [7] was rated as "yes" on 10 of the 11 quality assessment areas.

Overall, all six RCTs were rated as high risk of bias on at least one of the seven risk of bias assessments (Appendix 5). Four studies were determined to be at low risk of bias for selection bias for random sequence generation and allocation concealment since randomization was computer generated [9,11-13]; it was unclear whether sequence generation was random or if allocation was concealed in the other two studies [8,10]. It was unclear whether participants were blinded (performance bias) in one study [8]; the five remaining studies were rated as high risk for performance bias due to lack of participant blinding to the study intervention. In three of the studies [10-12], assessment personnel were not blinded to the study intervention and, thus, these studies were rated as high for risk of bias on this domain; the remaining studies were rated as low for risk of bias on this domain. It was unclear in one of the RCTs [8] whether there was attrition bias; the remaining five studies were rated as "low" on this domain. All of the six studies were rated as low risk of bias on selective reporting (reporting bias) and three of the studies were rated as high risk for other bias because of small sample size (less than 30) [8,11,13].

Study Characteristics

Appendix 4 shows the study characteristics of the included SR [14] . Shouval et al. [14] evaluated the efficacy and safety of aHCT in SSc searching the literatures from 1966 to January 2018. Four studies met inclusion criteria (3 RCTs [11,12,15] and 1 retrospective cohort study [16]). The comparison group was monthly cyclophosphamide (CYC) in all of the three RCTs.

Table 1-1 reports the characteristics of the six included RCTs. Of the two studies examining MS, one study was a phase II [8] and the other was a phase III trial [9]. Both MS studies (MIST and ASTIMS) were multi-centred [8,9]. Mean age of study participants was 36 years in both trials. Comparison treatments included approved immunosuppressant drugs, with the MS studies comparing aHCT with Mitox and to the treating physicians' preferred DMT (defined in Table 1-1). In the MIST trial, follow-up times were two years, with sample sizes of 52 (aHCT) and 51 (control) [9]. Follow-up time in the ASTIMS trial was 48 months, with samples sizes of 9 (aHCT) and 11 (control).

Of the three RCTs examining SSc, two were multi-centred (SCOT and ASTIS) [12,15] and one was single-centred (ASSIST) [11]. One study was phase II [11] and the other two were phase III trials [12,15]. Mean age of study participants was approximately 44 years in two of the trials [11,12], and mean age was not reported in one [12]. All three SSc studies compared aHCT with CYC. Follow-up times ranged from 12 months [11] to 4.5 years [15]. Sample sizes ranged from 10 [11] to 79 [12] for aHCT groups and from nine [11] to 77 [12] for control groups.

The single study (ASTIC) assessing CD/IBD was multi-centred and did not indicate the phase of the trial [13]. Mean age of study participants was 34 years and the comparison treatment was delayed treatment of aHCT by one year . The median follow-up time was 39 months and samples size were 23 and 22 for the aHCT and delayed treatment groups, respectively [13].

Table 1-1. Study characteristics of randomized controlled trials examining autologous hematopoietic cell transplantation for MS, SSc, and CD

Study	Population	Treatment	Follow-up/outcomes
Multiple Sclerosis			
Burt, 2019 [9] Multiple Sclerosis International Stem Cell Transplant **(MIST)** Phase III, multi-centre	**Population:** Patients with stable DMT with >2 relapses within the prior 12 mo. and an EDSS score of 2.0 to 6.0 enrolled between 2009 and January 2018 **Med. age yrs. (SD)** 36 (8.6) **Inclusion:** relapse-remitting MS according to McDonald criteria, age 18 to 55 years, 2 or more clinical relapses or 1 relapse and MRI gadolinium-enhancing lesion(s) at a separate time within the previous 12 months despite receiving treatment with DMT, and an EDSS score between 2.0 and 6.0. **Exclusion:** primary or secondary progressive MS; hereditary neurologic diseases; pregnancy; pulmonary, cardiac, renal, or liver dysfunction; abnormal platelet or white blood cell counts; active infection; prior treatment with alemtuzumab or Mitox; or use of natalizumab within the prior 6 months, fingolimod within 3 months, or, for teriflunomide (which undergoes extensive enterohepatic recycling), failure of oral cholestyramine to decrease teriflunomide to a plasma concentration of less than 0.02 µg/mL.	aHCT* (n=52) vs. most appropriate DMT (n=51) as judged by treating neurologist (such as interferons, glatiramer acetate, fingolimod, natalizumab, or dimethyl fumarate).	Med. 2 yrs. / Increase in EDSS
Mancardi, 2015 [8] Autologous hematopoietic Stem cell Transplantation In MS (**ASTIMS**) Phase II, multi-centred)	**Population:** Patients with secondary progressive or relapsing-remitting MS, recruited for 2 yrs. beginning in May 2004. **Med. age yrs. (range):** 35.7 (16-53) **Inclusion:** clinically defined MS, a secondary progressive or relapsing remitting form that accumulates disability between relapses, with a documented worsening during the last year (1 step of EDSS, or 0.5 when EDSS is between 5.5 and 6.5), in spite of conventional therapy (interferon-b or glatiramer acetate or immunosuppressive therapy), and presence of one or more gadolinium (Gd)-enhancing areas on MRI. EDSS score between 3.5 and 6.5. **Exclusions:** NR	aHCT* (n=9) vs. mitox IV (infusion of 20 mg plus methylprednisolone 1 g diluted in 250 mL 0.9 saline once every mo. for 6 mo.) (n=11)	Med. 48.3 mo. (0.8-126)/ cumulative number of new T2 lesions, cumulative number of Gd1 lesions, relapse rate, disability progression.
Systemic Sclerosis			

Table 1-1. Study characteristics of randomized controlled trials examining autologous hematopoietic cell transplantation for MS, SSc, and CD

Study	Population	Treatment	Follow-up/outcomes
Sullivan, 2018 [15], Sullivan, 2017 [10] Scleroderma: CYC or Transplantation (**SCOT**) (open-label, multi-centred [26 sites] controlled phase III trial)	**Population:** Adults (18 to 69 years of age) with scleroderma (American College of Rheumatology 1995 criteria) recruited between 2005 and Sept. 2011. **Mean age yrs. (SD):** NR **Inclusion:** SSc for ≤5 years with pulmonary or renal involvement, required active interstitial lung disease (as determined by bronchoalveolar cell composition or ground-glass opacities on computed tomography of the chest) plus either a FVC or a DL_{CO} <70% of predicted value. Renal involvement required previous scleroderma-related renal disease. **Exclusions:** active gastric antral vascular ectasia, DL_{CO} <40% of the predicted value, an FVC of <45% of predicted value, LVEF <50%, a creatinine clearance <40 mL per minute, pulmonary arterial hypertension, or more than 6 mo. of previous treatment with CYC.	aHCT* (n=36) vs. intravenous CYC (dose of 500 mg/m^2 of body-surface area followed by 11 monthly infusions of 750 mg/m^2 with mesna prophylaxis) (n=39)	4.5 yrs./ changes GRCS-(a global rank composite score) accounting for multiple disease manifestations (analytic tool that reflects how participants compare with one another on the basis of a hierarchy of ordered outcomes: death, event-free survival, etc).
van Laar, 2014 [12] The Autologous Stem Cell Transplantation International Scleroderma (**ASTIS**) trial (phase III, open-label, parallel-group, multi-centred, 10 countries at 29 centres)	**Population:** Patients with early diffuse cutaneous SSc , 18 to 85 yrs. old, recruited from March 2001 to October 2009 **Mean age yrs. (SD):** 43.8 (11.3) **Inclusions:** Patients with diffuse cutaneous SSc according to ARA criteria, with maximum disease duration of 4 years (2 yrs. after 2004 if mRSS at least 20 and an erythrocyte sedimentation rate greater than 25 mm in the first hour and/or hemoglobin less than 11 g/dL not explained by causes other than active scleroderma) mRSS of 15 (range, 0-51) and Involvement of heart, lungs, or kidneys. Prior treatment with CYC was allowed up to a cumulative dose of 5 g intravenously or up to 2mg/kg body weight orally for 3 mo. **Exclusions:** Patients with severe major organ involvement including severe PAH (mean >50 mmHg) or serious comorbidities.	aHCT* (n=79) vs. 12 monthly intravenous pulses of CYC (750 mg/m^2) (n=77).	24 mo., med. 5.8 yrs./event-free survival (defined as days from randomization until occurrence of death due to any cause or the development of persistent major organ failure – heart, lung or kidney)

Table 1-1. Study characteristics of randomized controlled trials examining autologous hematopoietic cell transplantation for MS, SSc, and CD

Study	Population	Treatment	Follow-up/outcomes
Burt, 2011 [11] Autologous non-myeloablative hemopoietic stem-cell transplantation compared with pulse CYC once per mo. for systemic sclerosis American Scleroderma Stem Cell versus Immune Suppression Trial (**ASSIST**) (open-label, phase II trial, single centre USA)	**Population:** Patients with diffuse SSc ≤ 60 yrs. old recruited between January 2006 and November 2009 **Mean age yrs. (SD):** 45 (32-58), 44 (26-54) **Inclusions:** mRSS > 14, and internal-organ involvement (at least one: DL_{CO} < 80% or decline in FVC by 10% or more in the previous 12 mo.; pulmonary fibrosis or ground-glass appearance on high-resolution chest CT; abnormal ECG; or gastrointestinal tract involvement). Patients with restricted skin involvement (mRSS <14) were eligible only if they had coexistent pulmonary involvement. **Exclusions:** Patients receiving >6 previous intravenous injections of CYC, a total lung capacity <45% of predicted volume, LVEF of < 40%, symptomatic cardiac disease, duration of SSc of > 4 years from diagnosis, HIV-positive status, positivity for hepatitis B surface antigen, renal insufficiency (creatinine >177 µmol/L), pregnancy, tricuspid annular plane systolic excursion <1.8 cm, pulmonary artery systolic pressure of >40 mm Hg, or mean pulmonary artery pressure >25 mm Hg.	aHCT* (n=10) vs. 6 cycles intravenous pulses of CYC (1.0 g/m^2 per mo.) (n=9).	12 mo. / decrease in mRSS, or increase in FVC
Inflammatory Bowel Disease – Crohn's disease			
Hawkey, 2015 [13] the Autologous Stem Cell Transplantation International Crohn's Disease (**ASTIC**) trial Parallel-group randomized clinical trial conducted in 11 centres in 6 European transplant units	**Population:** Patients followed from July 2007 to September 2011, with follow-up through March 2013. Patients aged 18 to 50 years with impaired QofL from refractory CD. **Mean age yrs. (SD):** 34.1 (26.1-41.2), 30.6 (24.0-37.6) **Inclusions:** Patients with continuing refractory disease not amenable to surgery with impaired QofL (defined as IBDQ score <170, EQ-VAS Index <85, or KPI <80) despite having tried at least 3 immunosuppressive or biological agents in addition to corticosteroids. **Exclusions:** Patients with organ failure or other severe comorbidities; active infection; infectious risk, including a history of tuberculosis; malnutrition; or if pregnant or unwilling to use contraception during the study.	aHCT* immediately (n=23), aHCT after a delay of 1 yr. (n=22).	Med. 369 dys. (346-391)/ Sustained disease remission (composite outcome), individual components of composite outcome, QofL.
*details of aHCT treatment available in Appendix 7.			

Table 1-1. Study characteristics of randomized controlled trials examining autologous hematopoietic cell transplantation for MS, SSc, and CD

Study	Population	Treatment	Follow-up/outcomes
ARA = American Rheumatism Association; aHCT = autologous hematopoietic cell transplantation; ASTIMS = Autologous Hematopoietic Stem Cell Transplantation Trial in MS; ASTIS = Autologous Stem cell Transplantation International Scleroderma study; CD = Crohn's disease; CT = computed tomography; CYC = cyclophosphamide; DL_{CO} = diffusing capacity of carbon monoxide; DMT = disease-modifying therapy; ECG = electrocardiogram; EDSS = Expanded Disability Status Scale; EQ-VAS European Quality of Life Visual Analogue Scale; FVC = forced vital capacity; IBDQ = inflammatory bowel disease questionnaire; LVEF = left ventricular ejection fraction; KPI = Karnofsky Performance Index; Med = median; Mitox = Mitoxantrone; MRI = magnetic resonance imaging; mRSS = modified Rodnan Skin Score; MS = multiple sclerosis; QofL = quality of life; PAH = pulmonary arterial hypertension; SSc = systemic sclerosis.			

Outcomes

Table 1-2 shows the results for each of the six included RCTs (see Appendix 6 for additional outcome data, Appendix 7 for adverse events, and Appendix 8 for mobilization and conditioning regimens for aHCT arms for each of the RCTs).

Multiple Sclerosis

The ASTIMS trial [8] assessed the effects of aHCT among nine MS patients compared with 12 MS patients receiving Mitox. The number of new T2 lesions was significantly reduced (median 2.5 vs. 8) over four years in the aHCT group, compared with the Mitox group (p< 0.001). The difference in the rate of new T2 lesions remained significant when adjusting for baseline gadolinium-enhancing (Gd+) lesions (p<0.0001). Likewise, the annualized relapse rate was significantly reduced in the aHCT group compared with the Mitox group (0.19 vs. 0.6, p=0.026). No significant differences between the groups were found for the progression of disability and the Expanded Disability Status Scale (EDSS). Serious adverse events (SAEs) occurred in the aHCT arm only and were resolved without any long-term consequences (see Appendix 7) [8]. Of note, recruitment is this study was difficult and biased as many patients did not want to enroll in case they ended up in the non-HCT arm, resulting in the trial being halted early because of poor recruitment.

The MIST trial [9] randomized patients to treatment with CYC and ATG conditioning followed by aHCT (n=52) or to continued treatment with the most appropriate DMT as judged by their treating neurologist (n=54). Disease progression occurred in three (6%) patients in the aHCT group and 34 patients (63%) in the DMT group. During the first year, mean EDSS improved in the aHCT group from 3.4 to 2.4, compared with a worsening effect from 3.3 to 4 in the DMT group (p<0.001) (See Table 1-2). Median time to progression could not be calculated in the aHCT group because of too few events and was 24 months in the DMT group. There were no deaths in either group and no aHCT patients developed non-hematopoietic grade 4 toxicities [9].

Scleroderma

Three randomized trials (ASSIST [11], ASTIS [12], and SCOT [15]) examined the efficacy and toxicity of aHCT (n=10, 79, and 36, respectively) for SSc compared with intravenous CYC (n=9, 77, and 39, respectively). Data from the three SSc RCTs were pooled in the review by Shouval et al. [14] and replicated in RevMan 5.1 in this review. There were no deaths in the ASSIST trial and two late treatment-related mortality (TRM) events were observed in the aHCT arm of the SCOT trial. However, in the ASTIS trial, TRM was higher in the aHCT arm compared with the CYC group (8 of 79 vs. 0 of 77). Pooled estimates show TRM odds were significantly higher in the aHCT groups compared with the CYC group (odds ratio [OR],10.81; 95% CI, 1.36 to 85.70; p=0.02) (see Figure 1). Follow-up times varied among the studies (12, 24, and 54 months follow-up in the ASSIST, ASTIS, and SCOT trials, respectively). Figure 2 shows that all-cause mortality at the end of follow-up for all three RCTs examining SSc was reduced in the aHCT group, compared with the CYC group (risk ratio, 0.61; 95% confidence interval (CI), 0.40 to 0.93; p=0.02).

Individual results in the SCOT trial [15] showed global rank composite scores (analytic tool that reflects how participants compare with one another on the basis of a hierarchy of ordered outcomes: death, event-free survival, etc) at 48 months (68% favoured aHCT and 32% favoured CYC, p=0.008) and 54 months (67% favoured aHCT and 33% favoured CYC, p=0.01) to be superior in the intention-to-treat population. In the per-protocol population, the percent favouring aHCT on the global rank composite score was 70% versus 30% at 54 months (p=0.004) and 71% versus 29% at 48 months (p=0.003). Over 72 months, SAEs were lower in the CYC group, compared with the aHCT group (51% vs. 74%). However, the difference was not significant (rate ratio , 0.74; p=0.08) (see Appendix 7) [15].

Individual results from the ASTIS trial show time-varying hazard ratios for event-free survival were 0.35 (95% CI, 0.16 to 0.74) at two years and 0.34 (95% CI, 0.16 to 0.74) at four years [12]. There were more adverse events at the first year following treatment in the aHCT group (13 events [16.5%], including 8 treatment-related deaths) than in the CYC group (8 events [10.4%], with no treatment-related deaths). Fourteen events (17.7%) had occurred cumulatively by year 2 in the aHCT group, compared with 14 events (18.2%) in the CYC group; by year 4, there were 15 events (19%) in the aHCT group, compared with 20 events (26%) in the CYC group. Grade 3 or 4 adverse events occurred in 63% of patients in the aHCT group and in 37% of the CYC group (p=0.02) (see Appendix 7) [12].

In the ASSIST trial [11] all 10 aHCT patients showed improvement (defined as a decrease in modified Rodnan Skin Score [mRSS] [>25% for those with initial mRSS >14] or an increase in forced vital capacity [FVC] by more than 10%) on at or before 12 months' follow-up, compared with none of the nine randomized to CYC (OR, 110; 95% CI, -14.04 to 22.6; p=0.00001). Eight of nine CYC patients experienced disease progression (without interval improvement) compared with none of the aHCT patients (p=0.0001), and seven of the CYC patients crossed over to aHCT. Compared with baseline, data for 11 aHCT patients with follow-up to two years, showed improvements in the mRSS (p<0.0001) and FVC (p<0.03).

Inflammatory bowel disease/Crohn's disease

In the study by Hawkey et al. [13], 23 patients were randomized to aHCT (early aHCT) and 22 received standard CD/IBD treatment followed by aHCT one year after randomization (delayed aHCT). At one year, two patients undergoing early aHCT (intervention) (8.7%) achieved sustained disease remission compared with one control patient in the delayed aHCT (ie, before they underwent aHCT) group (4.5%) (absolute difference [AD], 4.2%, 95% CI, 14.2% to 22.6%; p=0.60). Fourteen early aHCT patients (61%) had discontinued immunosuppressive or biologic agents or corticosteroids for at least three months, compared with five of the delayed aHCT patients (AD, 38.1%, 95% CI, 9.3% to 59.3%; p=0.01). Ten patients in the early aHCT group had a CD/IBD Activity Index (CDAI) less than 150 (remission) at the final evaluation, compared to two in the delayed aHCT group. Likewise, eight (34.8%) patients in the early aHCT group and two (9.1%) in the delayed aHCT group had a CDAI of less than 150 for three or more months (difference, 25.7%; 95% CI, 1.1% to 47.1%; p=0.052). Eight (34.8%) early aHCT patients and two (9.1%) delayed aHCT patients were adjudicated free of active disease on endoscopy and radiology at final assessment (AD 25.7%; 95% CI, 1.1% to 47.1%; p =0.054). There were 76 SAEs in patients undergoing aHCT in the early aHCT arm compared with 38 before aHCT in the delayed aHCT arm. One patient died undergoing aHCT [13] (see Appendix 7).

Table 1-2. Study outcomes of randomized controlled trials examining autologous hematopoietic cell transplantation for MS, SSc, and CD

Multiple Sclerosis					
Burt, 2019 [9]		**aHCT % (N)**	**DMT % (N)**	**Hazard Ratio (95% CI)**	**P-value**
MIST	Med. 2 yr. Disease progression (EDSS change ≥1)	6% (3/52)	63% (34/54)		
	Median time to progression	Not reached (too few events)	24 mo. (IR 18-48)	0.07 (0.02-0.24) DMT	<0.001
aHCT (n=50) appropriate DMT (n=52)		**aHCT % (95% CI)**	**DMT (95% CI)**		
	Patients with disease progression (1 yr.)	1.92% (0.27-12.9)	24.5% (14.7-39.1)		
	Patients with disease progression (5 yrs.)	9.71% (3.0-28.8)	75.3% (60.4-87.8)		
		aHCT (mean change)	**DMT (mean change)**	**Between-group diff. (95%CI)**	**P=value**
	Pre-HCT to 1 yr. EDSS improvement/deterioration (negative mean change indicates improvement)	3.38 to 2.36 (-1.02)	3.31 to 3.98 (+0.67)	-1.7 (-2.03 to -1.29)	<0.001
Mancardi, 2015 [8]		**aHCT Med., Mean (range)**	**Mitox Med., Mean (range)**	**Rate Ratio (95% CI)**	**P-value**
ASTIMS	Number of T2 lesions (over 4 yrs.)	2.5, 2.75 (0-8)	8, 12.75 (2-34)	0.21 (0.10 to 0.48)	0.00016
aHCT (n=9) vs. Mitox (n=12)	T2 lesions adjusted for baseline Gd+ lesions			0.19 (0.09 to 0.41)	<0.00001
		aHCT Mean(SD)/%	**Mitox Mean (SD)/%**	**Rate Ratio (95% CI)**	**P-value**
	ARR	0.19	0.6	0.36 (0.15 to 0.88)	0.026
Systemic Sclerosis					
Sullivan, 2017, [10]	***ITT***	**aHCT**	**CYC**		**P-value**
SCOT	54 mo. GRCS ¥ Med.(range)	17.0 (-58 to 52)	-6.0 (-58 to 52)		0.01
	54 mo. GRCS ¥ %	67%	33%		0.01
	48 mo. GRCS ¥ Med.(range)	20.0 (-58 to 55)	-8.0 (-58 to 55)		0.008
aHCT (n=36) vs. CYC (n=39)	48 mo. GRCS ¥ %	68%	32%		0.008
	PPP	**aHCT**	**CYC**		**P-value**
	54 mo. GRCS ¥ Med.(range)	16.0 (-56 to 46)	-11.0 (-56 to 46)		0.004
	54 mo. GRCS ¥ %	70%	30%		0.0004
	48 mo. GRCS ¥ Med.(range)	17.0 (-56 to 49)	-13.0 (-56 to 49)		0.003
	48 mo. GRCS ¥ %	71%	29%		0.003
van Laar, 2014	**All patients**	**aHCT**	**CYC n**	**Ratios (95% CI)**	**P-value**

Table 1-2. Study outcomes of randomized controlled trials examining autologous hematopoietic cell transplantation for MS, SSc, and CD

ASTIS [12] aHCT (n=79) vs. CYC (n=77)	1 yr. n(%) Events	13 (16.5%)	8(10.4%)	RR = 1.59 (0.7 to 4.4)	
	1-yr. death or major organ failure			HR = 0.52 (0.28 to 0.96)	0.04
	1-yr. Mortality	13.9%	9.1%	RR = 1.53 (0.4 to 5.4) HR = 0.48 (0.25 to 0.91)	0.02
	2 yr. n(%) Events	14 (17.7%)	14(18.2%)	RR = 0.97 (0.5 to 2.0)	
	2-yr. death or major organ failure			HR = 0.35 (0.16 to 0.74)	0.006
	2-yr. Mortality	15.2%	16.9%	RR = 0.90 (0.4 to 1.8) HR = 0.29 (0.13 to 0.65)	0.002
	4 yr. n(%) Events	15 (19.0%)	20(26.0%)	RR = 0.73 (0.4 to 1.43)	
	4-yr. death or major organ failure			HR = 0.34 (0.16 to 0.74)	0.006
	4-yr. Mortality	16.5%	26.0%	RR = 0.64 (0.3 to 1.1) HR = 0.29 (0.13 to 0.64)	0.002
	10-yr. OS	19/79	30/77	RR = 0.62 (0.38 to 1.00) HR = 3-10 yr. follow-up = 0.29 (0.13 to 0.64)	0.002
Burt, 2011 [11] **ASSIST** aHCT (n=10) vs. CYC (n=9)	**All patients**	**aHCT n**	**CYC n**	**Odds ratio (95% CI)**	**P-value**
	Improvement at 12 mo. (decrease in mRSS [>25% for those with initial mRSS >14])	10/10	0/9	110 (14.04 to NE)	0.00001
	Disease progression	0/10	8/9 (7 switched to HCT at mean of 14 mo.)		0.0001
	aHCT only compared to baseline data Improved mRSS				<0.001
	mRSS mean (SD) change baseline to 2 yrs.	-19.9 (10.2)	-8.8 (12.0)	Diff,11.1 (7.3 to 15.0)	<0.001
	FVC mean (SD) change baseline to 2 yrs. % predicted	6.3% (18.3)	-2.8% (17.2)	Diff,-9.1 (-14.7 to -2.5)	0.004
Inflammatory Bowel Disease – Crohn's disease					
	All Patients	**HCT n (%)**	**Control n (%)**	**% med. diff. (95% CI)**	**P value**

Table 1-2. Study outcomes of randomized controlled trials examining autologous hematopoietic cell transplantation for MS, SSc, and CD

Hawkey, 2015 [13] **ASTIC** HCT (n=23) vs. treatment deferred for 1 yr. (n=22)	**Sustained disease remission (SDR)**		2 (8.7%)	1 (4.5%)	4.2 (-14.2 to 22.6)	0.60
	Components of SDR	No active treatment	14 (60.9)	5 (22.7)	38.1 (9.3 to 59.3)	0.01
		CDAI <150 last 3 mo.	8 (34.8)	2 (9.1)	25.7 (1.08 to 47.1)	0.052
		Free of active disease on imaging	8 (34.8)	2 (9.1)	25.7 (1.08 to 47.1)	0.054

*details of aHCT treatment available in Appendix 7; ¥ comparing participants with each other on the basis of hierarchy of disease features assessed at 54 mo.;

aHCT = autologous hematopoietic cell transplantation; ARR = annualized relapse rate; ASTIMS = Autologous Hematopoietic Stem Cell Transplantation Trial in MS; ASTIS = autologous stem cell transplantation international scleroderma study; CDAI = Crohn's disease activity index; CI = confidence interval; CYC = Cyclophosphamide; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; FVC = forced vital capacity; GRCS = Global rank composite score; HR = hazard ratio; IR = interquartile range; ITT = intention to treat; Med. = median; Mitox = Mitoxantrone; mRSS = modified Rodnan Skin Score; MS = multiple sclerosis; OS = overall survival; PPP = per protocol population; RR = Risk Ratio; SSc = systemic sclerosis

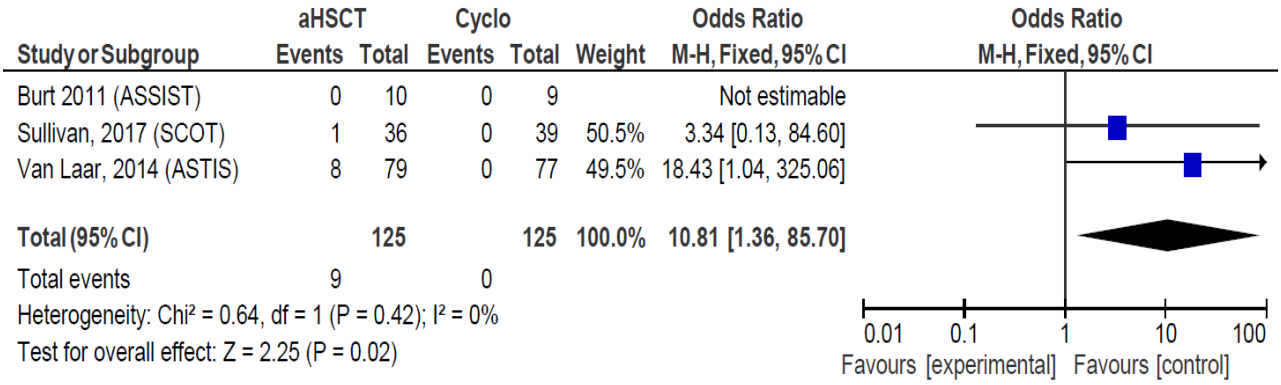

Figure 1: Treatment-related mortality results from RCTs examining systemic sclerosis

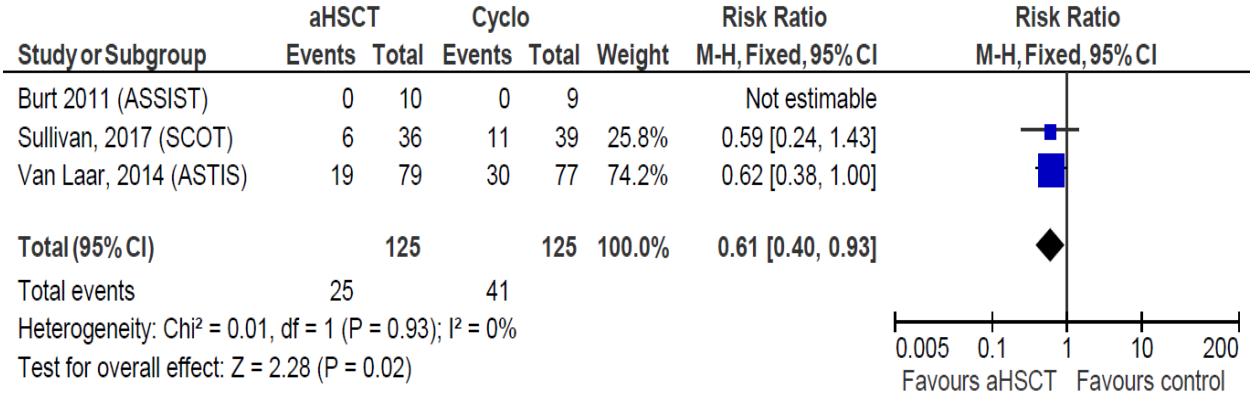

Figure 2: All-cause mortality results from RCTs examining systemic sclerosis

Ongoing, Unpublished, or Incomplete Studies

Table 1-3 includes ongoing studies and studies that have reported an interim analysis, but are not yet complete. Studies that have closed, but have not yet been published, are also included.

Table 1-3. Ongoing Studies

Protocol ID(s)	Title and details of study
NCT03342638	**Official title:** Maximizing Outcome of Multiple Sclerosis Transplantation: "MOST" Trial **Study type:** RCT **Treatment groups:** aHCT vs. aHCT (comparing conditioning regimes) **Estimated enrolment:** 200 **Start date:** Nov. 8, 2017 **Date trial summary last modified:** Jun. 7, 2018 **Estimated primary completion date:** Jan. 1, 2023 **Status:** Recruiting **Primary results reported:** No
NCT00273364	**Official title:** Hematopoietic Stem Cell Therapy for Patients With Inflammatory Multiple Sclerosis Failing Alternate Approved Therapy: A Randomized Study **Study type:** RCT **Treatment groups:** aHCT vs. standard drug treatment **Estimated enrolment:** 110 **Start date:** Nov. 16, 2005 **Date trial summary last modified:** Jul. 16, 2018 **Estimated primary completion date:** Feb. 2018 **Status:** Active, not recruiting **Primary results reported:** No
NCT03477500	**Official title:** Randomized Autologous Hematopoietic Stem Cell Transplantation Versus Alemtuzumab for Patients With Relapsing Remitting Multiple Sclerosis **Study type:** RCT/ Phase III **Treatment groups:** aHCT vs. Alemtuzumab **Estimated enrolment:** 100 **Start date:** Mar. 21, 2018 **Date trial summary last modified:** May 9, 2018 **Estimated primary completion date:** Mar. 21, 2022 **Status:** Recruiting **Primary results reported: No**
NCT02516124	**Official title:** Autologous Stem Cell Transplantation for Progressive Systemic Sclerosis: a Prospective Non-Interventional Approach Across Europe (NISSC) for the Autoimmune Diseases Working Party of the EBMT Study type: Observational (single group) **Treatment groups:** Autologous HCT **Estimated enrolment:** 82 **Start date:** Dec. 2012 **Date trial summary last modified:** May 1, 2018 **Estimated primary completion date:** Jan. 2018 **Status:** Recruitment completed **Primary results reported:** No
NCT03113162	**Official title:** Evaluation of the Safety and Efficacy of Reduced-intensity Immunoablation and Autologous Hematopoietic Stem Cell Transplantation (aHCT) in Multiple Sclerosis **Study type:** Phase I, single arm **Treatment groups:** aHCT **Estimated enrolment:** 15 **Start date:** May 29, 2015 **Date trial summary last modified:** May 5, 2017 **Estimated primary completion date:** May 29, 2020 **Status:** Recruiting **Primary results reported:** No
NCT03630211	**Official title:** Autologous Stem Cell Transplantation With CD34-Selected Peripheral Blood Stem Cells (PBSC) in Patients With Treatment Resistant Systemic Sclerosis (SSc) **Study type:** Phase II, single arm

	Treatment groups: aHCT **Estimated enrolment:** 8 **Start date:** Jul. 21, 2018 **Date trial summary last modified:** Aug. 27, 2018 **Estimated primary completion date:** Aug. 1, 2023 **Status:** Recruiting **Primary results reported:** No

DISCUSSION

This document summarizes the available RCT evidence for the use of aHCT for MS, SSC, and CD/IBD compared with standard treatments. The overall strengths of the RCTs include the high level of follow-up in these cohorts, the prospective study design, blinded evaluators, the detailed multidimensional objective outcomes measured, and the multi-centred nature of many of the trials. Furthermore, the meta-analysis by Shouval et al. [14] was the first (and only) review to include the three RCTs examining SSc; the study populations were relatively homogeneous and the mechanistic aspects of stem cell mobilization and transplantation were similar among the studies.

For MS, there is evidence from two trials [8,9] that aHCT resulted in better outcomes such as EDSS and a reduction in new T2 lesions compared to other treatment options (DMT, Mitox). In the ASTIMS trial, the reduction in T2 lesions remained significant when adjusting for baseline Gd+ lesions ($p<0.00001$). The MIST trial reported improved EDSS in the first year following aHCT, compared with a worsening effect in the DMT group ($P<0.001$), showing that neurological recovery can occur following aHCT, which is rare following most standard agents. There were no long-term SAEs noted in either study.

As previously mentioned, it is important to note that recruitment was difficult and biased in the ASTIMS trial as many MS patients did not want to enrol in case they ended up in the non-HCT arm, resulting in the trial being halted early because of poor recruitment. Likewise, in the MIST trial there was an absence of treatment with newer conventional agents in the control arm, limiting conclusions as to aHCT's effectiveness compared with contemporary therapies. Regardless, sample sizes are small, particularly in the ASTIMS trial, and conclusions based on these two RCTs are limited. However, it should be noted that, based on eight retrospective studies, eight clinical trials, and three SRs, a recent position statement by the American Society for Blood and Marrow Transplantation recommended aHCT be considered "a standard of care available" for patients with treatment-refractory relapsing MS with high risk of future disability [17].

It should be noted that the use of the terms "relapse" and "progression" differ than the definitions commonly used in hemato-oncology. An MS relapse refers to the acute development of a neurological symptom or sign related to active central nervous system inflammation, while MS progression refers to the sustained accumulation of disability. The former may or may not improve or resolve over the course of a few weeks (a remission) while the latter are long-lasting and generally considered to be permanent and progressive.

For SSc, the pooled estimate from three trials of aHCT showed benefit of aHCT compared with standard therapy for the treatment of SSc, with aHCT showing a reduction in risk of all-cause mortality ($p=0.02$), compared with CYC. However, pooled estimates for the risk of TRM were significantly higher in the aHCT group compared with the CYC group ($p=0.02$). The differences in TRM between the three trials may be due to experience of the treating centre, patient selection factors, and the protocolization of the treatment and its complications. The TRM of aHCT was not surprisingly greater than standard doses of monthly CYC in the ASTIS trial [12] but this may be a function of the factors outlined above. The SCOT trial [15], arguably using a more intense conditioning regimen, did not show a difference in one-year TRM. In the ASTIS trial, grade 3 or higher adverse events were more significant in the aHCT group than in

the CYC group (p=0.02). The rate of serious SAEs was not significant in the SCOT trial and SAEs were not graded in the ASSIST trial. As with studies examining treatment of MS with aHCT, the limited number of RCTs, with a relatively low number of patients and events, and wide confidence internals for some of the outcomes, limit definitive conclusions based on these trials. However, these are some of the best transplant studies available for rare diseases, and all three showed some benefit of aHCT in a population with otherwise limited treatment options.

The single RCT assessing CD/IBD found aHCT not superior at sustaining disease remission compared with standard therapy for patients with refractory CD/IBD not amenable to surgery with impaired function or quality of life. Although more patients in the aHCT group discontinued all immunosuppressive therapy, as compared to the standard therapy group, the differences were not statistically significant. The authors suggest that more patients in the aHCT group may have been in clinical remission and free of active disease on imaging in the months prior to assessment [13].

In general, there were some limitations inherent in the RCTs assessing aHCT for MS, SSc, and CD/IBD. Most studies were rated as "high" for risk of bias on the domain of blinding of study participants in this report (one study did not disclose whether they blinded participants). Participant and personnel blinding is not possible in transplantation studies and thus detection bias is an issue. Many of the trials started more than a decade ago and, especially for MS, patients in the control arm did not have access to the newer disease-modifying agents. All trials had a very long enrolment period due to the rarity of the illness and recruitment was slow for some. Furthermore, the results of aHCT may not be generalizable to the entire population of those affected with an autoimmune disease. It should be noted that given the risks of aHCT, studies for MS or CD/IBD focused on patients that experienced treatment failure or that had aggressive forms of the disease. Similarly, patient selection is critical in selecting scleroderma patients whose illness is severe enough but do not have critical cardiopulmonary involvement.

This review included only RCTs and pooled data from SRs. As indicated previously, other non-randomized studies and data have been published. Findings from these other types of studies provide other clues for the role of aHCT. For example, MS clinical relapses and new magnetic resonance imaging (MRI) activity in some case series studies [18-20] were lower than the best of the new drugs (a non-randomized comparison). In the Canadian trial [19], they reported an absence of MS activity (ie, relapse, MRI, progression of disability) over a prolonged follow-up period (median 6.7 years), a change in outcome of MS that is unique among studies of MS. Other researchers have used EBMT registry data [21] to summarize trends and identify outcomes for patients receiving autologous and allogeneic HCT as an intervention for various autoimmune diseases (eg, MS, connective tissue disorders, inflammatory arthritis, vasculitis, IBD, hematological immune cytopenia, and insulin-dependent diabetes). Improved relapse/progression, and non-relapse mortality were reported with the use of aHCT. Health care expenditure was also associated with the improved outcomes in SSc and MS. In multivariate analysis, focusing on adults undergoing aHCT for MS, SSC, and CD/IBD, better outcomes were associated with greater centre experience in providing care for patients with these autoimmune diseases (≥23 transplants for AD, p=0.001), greater learning (time from first aHCT for AD ≥6 years, p=0.01), and for care provided at centers accredited by the Joint Accreditation Committee of the International Society for Cellular Therapy and EBMT (p=0.02). However, an a priori decision was made by the PEBC to solely examine the data from RCT, so observational, retrospective, and single-arm interventional trials were not considered in this analysis.

CONCLUSIONS

Research findings suggest that aHCT improves long-term benefits for patients with MS and SSc, compared with standard drug therapies. Toxicity appears acceptable and lower in MS than SSc. However, more well-designed RCTs with larger samples sizes are warranted to more

definitely assess aHCT's effectiveness compared with contemporary established treatment. Thus, while established as an acceptable form of care for selected patients, further research is needed to refine patient selection and timing of aHCT for patients with MS and SSc.

The RCT findings did not support the widespread use of aHCT for patients with refractory CD/IBD. For patients with CD/IBD, continued development at specialized centres and more clinical trials are needed for patients with CD/IBD.

In general, the small samples sizes and the scarcity of RCTs assessing aHCT treatment for MS, SSc, and CD/IBD makes more robust research in the field necessary.

INTERNAL REVIEW

The evidence summary was reviewed by internally by the PEBC. The Working Group was responsible for ensuring any necessary changes were made.

Acceptance by the SSO and SCT Advisory Committee

After internal review, the report was presented to the SSO and SCT Advisory Committee. The SSO and SCT Advisory Committee reviewed and formally accepted the document on April 25, 2019.

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- Sarah Deshpande for conducting a data audit.
- Sara Miller for copy editing.

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Appendix 1. Working Group Affliations and Conflict of Interest Declarations

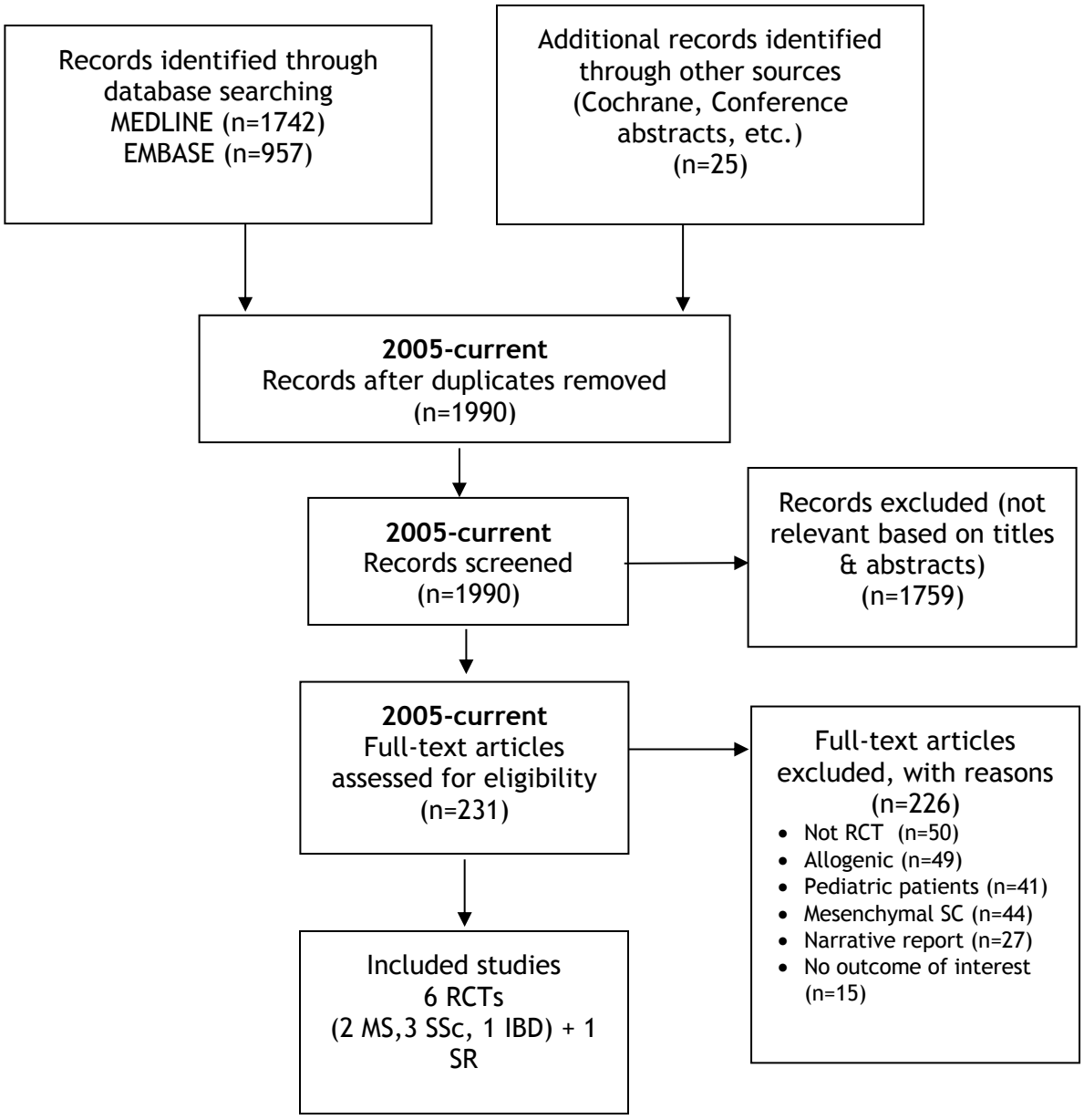
Name	Specialty	Location	COI declared
Harry Atkins	Hematologist	The Ottawa Hospital 501 Smyth Rd.	• Work as a hematopoietic stem cell physician with a special interest in stem cell transplants for MS and other autoimmune diseases. • Clinical practice is constituted as a medical professional corporation. • Trial of stem cell transplantation in multiple sclerosis (MSBMT) and in allorejection in liver transplantation (ASCOTT). • Review articles in this field. Has submitted an editorial regarding an article in this field.
Christopher Bredeson	Hematologist	The Ottawa Hospital Central Campus	• Potentially the number of referrals could increase as the data are disseminated RE the effectiveness of stem cell transplantation for these diseases. We are already seeing and caring for these patients as the data is available in the literature already.
Tom Kouroukis	Hematologist	Juravinski Cancer Centre	None declared
Judy Brown	Health Research Methodologist	Program in Evidence-based Care McMaster University	None declared

Appendix 2. Literature Search Strategy

Below is the search used in OVID MEDLINE. A similar search was conducted in EMBASE (2017 through November, 2018), the Cochrane Central Register of Controlled Trials (OVID CCTR: November 2018), and the Database of Abstracts of Reviews of Effects (OVID DARE: 4th quarter 2018).

Section A: Disease and/or population	1a	Multiple sclerosis or disseminated sclerosis or encephalomyelitis disseminata or clinically isolated syndrome or clinically isolated syndromes or demyelinat*
	1b	Systemic sclerosis or systemic sclerosis limited or systemic sclerosis diffuse or scleroderma systemic or scleroderma diffuse or scleroderma limited
	1c	inflammatory bowel disease or crohn's disease or PI-IBD or IBD OR functional GI disorder or spastic colon *or* inflammatory colon or functional *adj5* bowel
Section B: Intervention or diagnostic test	2	exp Bone Marrow Transplantation/ or hematopoietic transplantation or exp Stem Cell Transplantation or (bone marrow transplantation or stem cell transplantation or peripheral stem cell transplantation).mp.
Section C: Study design (this example only focuses on RCTs and Phase II, III, IV trials)	3	exp Clinical Trial/ or exp Clinical Study/ or exp Controlled Clinical Trial/ or exp Multicenter Study/ or exp Phase I Clinical Trial/ or exp Phase II Clinical Trial/ or exp Phase III Clinical Trial/ or exp Phase IV Clinical Trial/ or exp Clinical trial, controlled/ or exp Clinical trial, Phase I/ or Clinical trial, Phase II/ or exp Clinical trial, Phase III/ or exp Clinical trial, Phase IV/ or exp Clinical trial, Phase I/ or Clinical trial, Phase II/ or Clinical trial, Phase III/ or exp Clinical trial, Phase IV/ or exp Comparative studies/ or exp Prospective Studies/
	4	(((Clinical Trial$ or random$) adj3 trial$) or Comparative Study).mp.
	5	(Systematic Review or Pooled Analysis or Meta-analysis or systematic overview or Health Technology Assessment or Practice Guideline).mp.
	6	exp Evidence Based Medicine/ or exp Practice Guideline/
	7	or/3-6
Section D: Exclusion strategy	8	(Case Report$ or Editorial$ or Comment$ or Letter$).pt.
	9	Animal/ not Human/
	10	or/8-9
Combining Section A, B, C, D	11	(1 and 2 and 7) not 10
Limiting the final search by date and language	12	Limit 11 to (yr="2005 - Current")

Appendix 3. PRISMA Flow Diagram

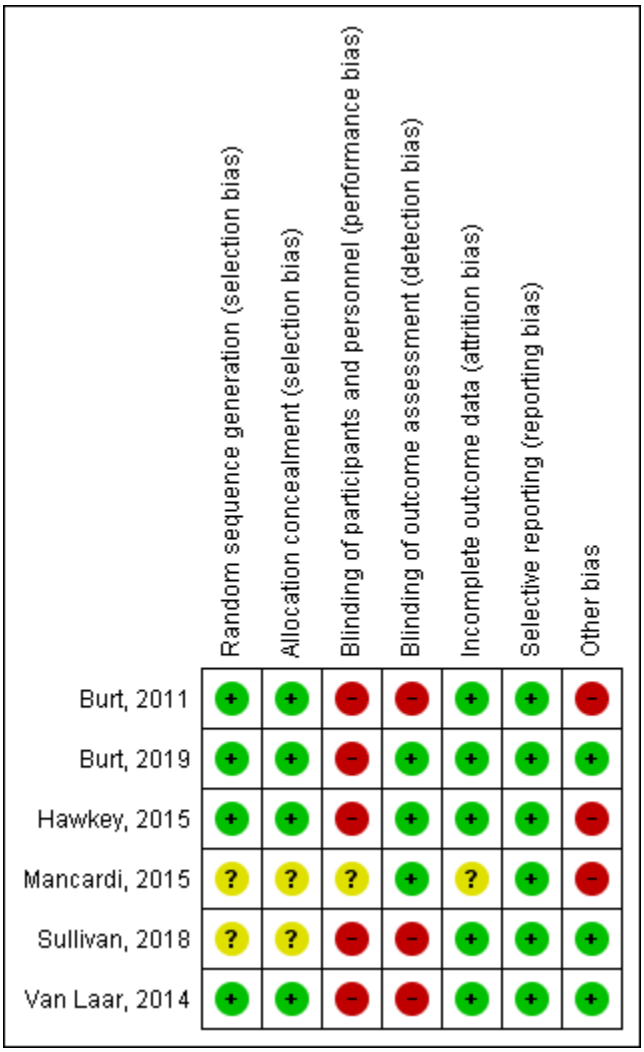


Appendix 4. Systematic Reviews (published within the last 5 years)

Study Details	Study Characteristics	Study Design	Results
Author: Shouval, 2018 **Title:** Autologous Hematopoietic Stem Cell Transplantation for Systemic Sclerosis: A Systematic Review and Meta-Analysis **Search dates:** Earliest – Jan. 2018 **Note:** Meta-analysis performed on 3 RCTs separate from cohort study.	**Inclusion:** all comparative studies: RCTs and retrospective trials, comparing aHCT versus standard care for the treatment of SSc. **Treatment:** Peripheral stem cells mobilized with CYC and granulocyte colony-stimulating factor in all studies except SCOT (Scleroderma: CYC or Transplantation) trial, where only granulocyte colony-stimulating factor used **Controls:** monthly CYC in all the RCTs and the majority of patients in the retrospective analysis (69%).	**4 studies included (n=306):** 3 RCTs (SCOT, ASTIS, ASSIST) and 1 retrospective cohort (Del Papa, 2017)	aHCT vs. control: • Reduced ACM RR 0.5 (95% CI, 0.33 to 0.75) • Improved skin thickness (mRSS) (MD 10.62 [95% CI, -14.21 to 7.03]), FVC (MD, 9.58 [95% CI, 3.89 to 15.18]), total lung capacity (MD, 6.36 [95% CI, 1.23 to 11.49]), and quality of life (physical 36-Item Short Form Health Survey [MD, 6.99 [95% CI, 2.79 to 11.18]). • Treatment-related mortality considerably varied between trials but was overall higher with aHCT (RR, 9.00 [95% CI, 1.57 to 51.69]).

ACM =all-cause mortality; aHCT = autologous hematopoietic cell transplantation; ASSIST = American Scleroderma Stem Cell versus Immune Suppression Trial; ASTIS = Autologous Stem cell Transplantation International Scleroderma study; CI = confidence interval; CYC = Cyclophosphamide; FVC = forced vital capacity; MD = mean difference; mRSS = modified Rodnan Skin Score; RR = Risk Ratio; SCOT = Scleroderma: CYC or Transplantation; SSc = systemic sclerosis.

Appendix 5: Study Quality Assessment



Risk of Bias Assessments for RCTs

AMSTAR Ratings for Shouval, 2018	Rating
1. Was an 'a priori' design provided?	Yes
2. Was there duplicate study selection and data extraction?	Yes
3. Was a comprehensive literature search performed?	Yes
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?	Yes
5. Was a list of studies (included and excluded) provided?	Yes
6. Were the characteristics of the included studies provided?	Yes
7. Was the scientific quality of the included studies assessed and documented?	Yes
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes
9. Were the methods used to combine the findings of the studies appropriate?	Yes
10. Was the likelihood of publication bias assessed?	No
11. Was the conflict of interest stated?	Yes
TOTAL AMSTAR POINTS	**10/11**

Appendix 6: Secondary Study Outcomes

Multiple Sclerosis					
Burt, 2019		**aHCT N**	**DMT N**		
	Death	0	0		
		aHCT Mean (SD)	**DMT Mean (SD)**	**BGD baseline to 1 yr**	**P-value**
	NRS score (baseline to 1 yr)	79.5 (10.2) to 88.3 (9.15)	81.1 (10.9) to 79.5 (11.8)	11.2 (8.08 t0 14.29)	0.001
	MRI T2-weighted lesion volume % (baseline to 1 yr)	100 to 68.3 (20.7)	100 to 134.3 (45.6)	-66 (-70.6 to -61.3)	<0.001
	Time 25-ft walk, s (baseline to 1 yr)	6.5 (3.16) to 6 (4.5)	5.6 (1.7) to 8 (6.2)	-2.85 (-3.92 to -1.77)	<0.001
	9-Hole Peg Test s (baseline to 1 yr)	30.8 (23.2) to 24 (9.5)	24.7 (6.3) to 25.6 (8.2)	-8.03 (-11.3 to -4.76)	<0.001
	PASAT, % (baseline to 1 yr)	67.4 (20.9) to 77.8 (21.1)	65.2 (21.5) to 75.4 (22.5)	0.22 (-72.4 to 72.9)	0.61
	SF36 QofL score (baseline to 1 yr)	50.5 (20.1) to 70 (21.3)	49.5 (18) to 46.1 (22.5)	23 (17.6 to 28.9)	<0.001
Mancardi, 2015	***Secondary outcome(s):***	**aHCT Mean (SD)/%**	**Mitox Mean(SD)/%**	**Rate Ratio**	**P-value**
	Annualized relapse rate:	0.19 (0.17)	0.6 (0.44)	0.36 (0.15-0.88)	0.026
	48 mo. time to progression of disability	57%	48%		log rank test p=0.50
	EDSS change at year 1, 2, 3, 4				NSD
Systemic Sclerosis (RCTs)					
Sullivan, 2018	***ITT Patients***	**aHCT N (%)**	**CYC N (%)**		**P-value**
	54 mo. Death (or resp, renal, card fail.)	10 (28)	20 (51)		0.06
	48 mo. Death (or resp, renal, card fail.)	10 (28)	20 (51)		0.06
	54 mo. Death (any cause)	6 (17)	11 (28)		0.28
	48 mo. Death (any cause)	6 (17)	11 (28)		0.28
	54 mo. Treatment-related death	1 (3)	0		0.48
	48 mo. Treatment-related death	1 (3)	0		0.48
	PPP Patients	**aHCT N (%)**	**CYC N (%)**		**P-value**
	54 mo. Death (or resp, renal, card. Fail.)	7 (21)	17 (50)		0.02
	48 mo. Death (or resp, renal, card. Fail.)	7 (21)	17 (50)		0.02
	54 mo. Death (any cause)	3 (9)	8 (24)		0.19
	48 mo. Death (any cause)	3 (9)	8 (24)		0.19
	54 mo. Treatment-related death	1 (3)	0		0.49
	48 mo. Treatment-related death	1 (3)	0		0.49

van Laar, 2014 **ASTIS**	**All Patients**	**aHCT Mean SD**	**CYC Mean (SD)**	**Difference**	**P-value**
	mRSS mean (SD) change baseline to 2 yrs.)	-19.9 (10.2)	-8.8 (12.0)	Diff, 11.1 (7.3 to 15.0)	<0.001
	Creatinine clearance, mL/min	-12.1 (29.7)	-1.2 (24.1)	10.9 (1.5 to 20.3)	0.02
	LVEF, % by cardiac echocardiography mean (sd) change baseline to 2 yrs.)	-2.2 (14.7)	-1.9 (13.8)	Diff, 0.3 (-4.7 to 5.2)	0.91
	Forced vital capacity mean (SD) change baseline to 2 yrs.) % predicted	6.3% (18.3)	-2.8% (17.2)	Diff, -9.1 (-14.7 to -2.5)	0.004
	Total lung capacity mean (SD) change baseline to 2 yrs.) % predicted	5.1% (17.5)	-1.3% (13.9)	Diff,-6.4 (-11.9 to -0.9)	0.02
	Residual volume mean (SD) change baseline to 2 yrs.) % predicted	-4.8 (33.7)	-2.1 (26.9)	Diff, 2.7 (-7.9 to -13.2)	0.62
	DL_{CO} mean (SD) change baseline to 2 yrs.) % predicted	-4.7 (13.7)	-4.1 (17.6)	0.6 (-4.9 to 6.0)	0.84
	HAQ-DI mean (SD) change baseline to 2 yrs.)	-0.58 (1.14)	-0.19 (0.79)	Diff, 0.39 (0.51 to 0.73)	0.02
	Physical component SF-36 mean (SD) change baseline to 2 yrs.)	10.1 (15.8)	4.0 (11.2)	Diff, -6.1(-10.9 to -1.4)	0.01
	Mental component SF-36 mean (SD) change baseline to 2 yrs.)	3.1 (16.0)	3.4 (17.1)	0.3 (-5.41 to 6.07)	0.91
	EQ-SD utility score mean (SD) change baseline to 2 yrs.)	0.31 (0.50)	0.03 (0.44)	Diff, -0.29 (-0.45 to -0.12)	<0.001
	VAS score mean (SD) change baseline to 2 yrs.)	16.9 (44.5)	10.2 (39.7)	-6.7 (-21.33 to 7.87)	0.36

Burt et al., 2011 systemic sclerosis **ASSIST**	**Before switch to transplantation**	**aHCT Mean (SD) Baseline, 1 yr.**		**CYC Mean (SD) Baseline , 1 yr.**	**P-value**
	Predicted forced vital capacity (%)	62% (15.0), 74% (15.7)		67% (17.0), 61% (19.8)	0.04
	Predicted total lung capacity (%)	76% (14.6), 80% (17.9)		83% (14.8), 74% (18.7)	0.05
	Predicted DL_{CO} corrected for hemoglobin (%)	58% (21.8), 69% (18.6)		75% (27.5), 74% (37.0)	0.36
	Volume diseased lung (mL)	823 (268.9), 551 (277.1)		877 (240.6), 985 (277.1)	0.001
	mRSS	28 (13.6), 15(7.9)		19 (13.7), 22 (14.2)	0.0004
	After switch to transplantation (All)	**Baseline**	**12 mo.**	**24 mo.**	**P-value**
	Predicted forced vital capacity (%)	62% (16.4)	75% (18.5),	74% (19.8)	0.029

	Predicted total lung capacity (%)	77% (14.1)	83% (16.6)	82% (17.9)	0.14
	Predicted DL_{CO} corrected for hemoglobin (%)	68% (31.0)	68% (19.1)	64% (19.8)	0.82
	Volume diseased lung (mL)	840(250.9)	567(271.0)	499 (293.9)	0.003
	mRSS	29 (13.7)	15 (7.4)	12 (8.4)	0.0001
	Quality of Life Before aHCT	**Before HCT**	**1-yr. after HCT**	**Diff. (SD)**	**p-value**
	Physical function	28	60	32 (29.6)	0.002
	Physical role limitation	17	44	27 (38.9)	0.095
	Body pain	34	55	21 (23.0)	0.023
	General health perception	38	44	6 (27.4)	0.662
	Vitality energy fatigue	33	46	13 (21.5)	0.079
	Social function	38	60	22 (31.5)	0.078
	Emotional role limitation	59	67	8 (45.8)	0.707
	Mental health	64	73	9 (15.7)	0.118
	Physical health dimension	30	50	20 (22.1)	0.007
	Mental health dimension	46	58	12 (12.0)	0.076
	SF-36 score total	39	56	17 (20.6)	0.003
	Quality of Life Before CYC	**Before HCT**	**1-yr. after HCT**	**Diff. (SD)**	**p-value**
	Physical function	44	37	7 (31.5)	0.347
	Physical role limitation	15	22	7 (34.8)	0.451
	Body pain	59	53	-6 (21.8)	0.570
	General health perception	35	12	-23 (27.2)	0.182
	Vitality energy fatigue	34	36	2 (26.5)	0.853
	Social function	53	41	-12 (28.3)	0.387
	Emotional role limitation	87	46	-41 (43.9)	0.028
	Mental health	70	75	5 (13.8)	0.305
	Physical health dimension	38	32	-6 (22.0)	0.327
	Mental health dimension	56	42	-14 (17.2)	0.043
	SF-36 score total	50	40	-10 (18.0)	0.042
	Quality of Life	**CYC before switch to HCT**	**CYC after switch to HCT**	**Diff. (SD)**	**p-value**
	Physical function	31	67	36 (35.7)	0.085
	Physical role limitation	30	80	50 (49.7)	0.089
	Body pain	56	85	29 (25.3)	0.189
	General health perception	8	67	59 (41.8)	0.062
	Vitality energy fatigue	46	72	26 (25.9)	0.212
	Social function	35	85	50 (45.9)	0.071

	Emotional role limitation	53	87	34 (42.9)	0.141
	Mental health	75	85	10 (13.9)	0.080
	Physical health dimension	34	74	40 (28.9)	0.046
	Mental health dimension	43	79	36 (28.4)	0.040
	SF-36 score total	42	78	36 (27.8)	0.035
	Quality of Life	**All patients before HCT**	**Longest follow-up after HCT**	**Diff. (SD)**	**p-value**
	Physical function	28	58	30 (29.7)	0.008
	Physical role limitation	17	44	27 (38.9)	0.095
	Body pain	34	61	27 (24.5)	0.002
	General health perception	38	46	8 (23.9)	0.510
	Vitality energy fatigue	33	48	15 (22.1)	0.038
	Social function	37	61	24 (29.9)	0.036
	Emotional role limitation	59	67	8 (42.6)	0.664
	Mental health	64	66	2 (16.0)	0.650
	Physical health dimension	30	51	21 (22.1)	0.007
	Mental health dimension	46	58	12 (20.1)	0.086
	SF-36 score total	39	56	17 (20.5)	0.009

Inflammatory Bowel Disease						
Hawkey e al., 2015 **ASTIC** HCT (n=23) vs. treatment deferred for 1 yr. (n=22)	***All Patients***		**Med. (IQR) [n]**	**Med. (IQR) [n]**	**Difference (95% CI)**	**P value**
	Disease activity	CDAI change from baseline	-150.7 (−62.0 to −196.3) [21]	−63.0 (34.0 to −120.8) [21]	−87.7 (−13.5 to −155.0)	0.04
		HBI change from baseline	−6 (−4 to −9) [21]	−2 (3 to −4) [21]	−4 (−1 to −9)	0.002
	Endoscopic activity	SES-CD change from baseline	−7 (−4 to −13) [21]	0 (5 to −8.5) [19]	−7 (−13 to −1)	0.03
	Quality of Life Change from baseline:	EQ-VAS	20 (−2.5 to 30) [19]	5.5 (−11.5 to 19.5) [14]	14.5 (−7.5 to 33)	0.50
		EQ-5D	0.025 (−0.022 to 0.163) [17]	0 (−0.013 to 0.093) [13]	0.025 (−0.072 to 0.163)	0.41
		IBDQ	35.5 (−6.3 to 53.8) [18]	1 (−11.3 to 23.3) [16]	34.5 (−8 to 54.5)	0.54
		Karnofsky Performance Index	10 (0 to 20) [15]	0 (0 to 10) [14]	10 (−7.5 to 20)	0.85

*details of aHCT treatment available in Appendix 7;
aHCT = autologous hematopoietic stem cell transplantation; ASTIMS = Autologous Hematopoietic Stem Cell Transplantation Trial in MS; ASTIS = autologous stem cell transplantation international scleroderma study; BGD = Between Group Differences; CDAI = Crohn disease activity index; CI

= confidence interval; CYC = Cyclophosphamide; DL_{CO} = diffusing capacity of carbon monoxide; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; EQ-VAS European Quality of Life Visual Analogue Scale; HAQ = Health Assessment Questionnaire; HBI = Harvey-Bradshaw Index; IBDQ = inflammatory bowel disease questionnaire; ITT = intention to treat; LVEF = left ventricular ejection fraction; med = median; MRI = magnetic resonance imaging; mRSS = modified Rodnan Skin Score; MS = multiple sclerosis; Mitox = mitoxantrone; NRS = neurologic rating scale; PASAT = the Paced Auditory Serial Addition Test; PPP = per protocol population; QofL = quality of life; SF-36 = 36 item short form survey; SSc = systemic sclerosis.

Appendix 7. Adverse Events

Burt, 2019	
aHCT group NCI common toxicity criteria #	**Number of patients with Grade 3 @**
Febrile neutropenia (culture negative)	13
Metabolism abnormalities	
Hypophosphatemia	17
Hypokalemia	13
Hyperglycemia	5
Hypocalcemia	1
Hyponatremia	1
Hypomagnesemia	1
Hypermagnesemia	1
Cardiovascular	
Hypertension	3
Atrial fibrillation	1
Tachycardia	1
Syncope	1
Liver	
Elevated transaminases	**5**
Infection	
Urinary tract infection - *Escherichia coli*	1
Pneumonia (culture negative)	1
Clostridium difficile diarrhea	1
Rectal surveillance culture - vancomycin-resistant enterococcus	1
Other	
Engraftment bone pain	1
Serum sickness	1
Seizure	1
Hematuria	1
Epistaxis	1
# Toxicities per NCI Common Toxicity Criteria version 2.0 @ There were no grade 4 toxicities	

Mancardi, 2015		
Adverse Events	**HCT (n=9) G=Grade**	**Mitox (n=12)**
Febrile neutropenia	G2 33%, G3 33%, G4 22%	0
Leukopenia	G2 22%, G3 33%, G4 33%	G3 17%
Diarrhea	G1 n=78%, G2 11%	0
Anemia	G1 11%, G2 33%, G3 33%, G4 11%	G1 8%
Cystitis	G2 11%	0
Herpes zoster	G1 11%	0
Platelets count decreased	G3 44%, G4 11%	0
Pneumothorax	G2 11%	0
Neutrophil count decreased	0	G3 17%, G4 8%
Lymphocyte count decreased	0	G1 17%, G3 8%
Amenorrhea	G3 33%	G3 17%
Gastrointestinal toxicity	0	G2 8%
Mucositis	G2 11%	0
Arthritis	0	G1 8%
Severe Adverse Events (by patient [n=21])	**aHCT (n=9) G=Grade**	**Mitox (n=12)**
Patient 3	Sepsis (G4)	---
Patient 6	Late engraftment (G3); prolonged hospitalization	---
Patient 15	Systemic candidiasis (G4), CMV reactivation (G4), engraftment failure (G4); life-threatening	---
Patient 19	ATG reaction (dyspnea [G2], bradycardia [G3], hypoxemia [G2]); life threatening	---
aHCT = autologous hematopoietic stem cell transplantation; ATG = anti-thymocyte globulin; CMV 5 cytomegalovirus;, Mitox = Mitoxantrone		

Sullivan, 2018			
Adverse Events (AE)	**aHCT (n=34) n(%) [Events]**	**CYC (n=37) n(%) [Events]**	**Rate Ratio, (P-value)**
Any serious AE	25 (73.5) [67]	19 (51.4) [73]	0.74, (0.08)
Treatment related serious AE	14 (41.2) [20]	3 (8.1) [5]	3.24, (0.01)
Any Grade 4 or higher	29 (85.3) [100]	19 (51.4) [33]	2.45, (<0.001)
Treatment related ≥ Grade 4	27 (79.4) [81]	4 (10.8) [6]	10.94, (<0.001)
Any Grade 3 or higher	34 (100) [356]	31 (83.8) [166]	1.74, (<0.001)
Treatment related ≥ Grade 3	34 (100) [188]	12 (32.4) [18]	8.46, (<0.001)
CYC = Cyclophosphamide; aHCT = autologous hematopoietic stem cell transplantation			

Van Laar, 2014			
Adverse Events	**aHCT (n=79)**	**CYC (n=77)**	**P-value**
Grade 3 or 4 adverse event, severe or life-threatening	51 (62.9)	30 (37.0)	.002
Any grade 3 adverse event	38 (48.1) 20	20 (26.0)	.005
Any grade 4 adverse event	29 (36.7)	21 (27.3)	.23
Adverse event with a fatal outcome	12 (15.2)	13 (16.9)	.83
Adverse event of grade 3-4			
Respiratory	15 (19.0)	6 (7.8)	.06
Cardiovascular	13 (16.5)	8 (10.4)	.35
Gastrointestinal	10 (12.7)	11 (14.3)	.82
Hematologic	10 (12.7)	1 (1.3)	.009
Renal	8 (10.1)	4 (5.2)	.37
Infection	8 (10.1)	4 (5.2)	.37
Neurologic	5 (6.3)	1 (1.3)	.21
Fever	5 (6.3)	0	.06
Musculoskeletal	3 (3.8)	2 (2.6)	>.99
Cancer	0	3 (3.9)	.12
Allergy/hypersensitivity	3 (3.8)	0	.24
Urogenital	0	2 (2.6)	.24
Sarcoidosis	1 (1.3)	0	>.99
Flushing	0	1 (1.3)	.49
Psychiatric	0	1 (1.3)	.49
CYC = Cyclophosphamide; aHCT = autologous hematopoietic stem cell transplantation			

Hawkey, 2015				
SAE	aHCT (n=23)	CYC (n=22)	Median diff. in no. of events (95% CI)	Median diff. in no. % of patients (95% CI)
Total SAEs	19 (76 events)	15 (38 events)	0 (-1 to 4), p=0.07	14.4 (10.6 to 37.7), p=0.28
Total SAEs 100 days following conditioning and HCT	13 (34 events)	5 (4 events)	1 (0 to 2), p=0.02	38.3 (10.0 to 59.2), p=0.01
Infectious SAE	11 (26 events)	7 (12 events)	0 (-1 to 2), p=0.99	16.0 (-11.9 to 40.7), p=0.27
Total infections SAE 100 days following conditioning and HCT	8 (13events)	0 (0 events)	0 (0 to 1), p=0.01	34.8 (13.0 to 55.1), p=0.002
viral	5 (9 events)	0 (0 events)		
sepsis	8 (9 events)	4 (4 events)		
localized	5 (8 events)	3 (8 events)		
Gastrointestinal SAEs	7 (18 events)	8 (12 events)	0 (-1 to 1), p=0.53	-5.9 (-31.4 to 20.4), p=0.66
Disease flares	5 (7 events)	7 (10 events)		
Nonflare symptoms	4 (11 events)	1 (2 events)		
Hematologic	3 (8 events)	0 (0 events)	0 (0 to 0), p=0.27	13.0 (-4.1 to 32.1), p>0.99
Anemia	1 (5 events)	0 (0 events)		
Neutropenia	2 (2 events)	0 (0 events)		
Pancytopenia	1 (1 events)	0 (0 events)		
Fever SAEs	4 (4 events)	1 (1 events)		
Renal SAEs	2 (2 events)	2 (2 events)		
Repsiratory SAEs	4 (4 events)	0 (0 events)		
Other	8 (14 events)	8 (11 events)		
CYC = Cyclophosphamide; aHCT = autologous hematopoietic cell transplantation; SAE = severe adverse Events				

* note: Burt et al., 2011 and Burt 2018 did not report on adverse events

Appendix 8. aHCT Regimen

Study	Mobilization	Conditioning
Multiple Sclerosis		
Burt, 2019 (non-myeloablative)	Cyclophosphamide 2.0 g/m^2 and G-CSF 5-10 mcg /kg/day.	Cyclophosphamide 200 mg/kg and ATG (Rabbit)
Manardi, 2015 (non-myeloablative)	CYC (4 g/m^2) in 1 day. G-CSF (5 µg/kg/d) starting 5 days, after chemotherapy daily until collection Unmanipulated stem cell graft	BEAM, which includes BCNU (carmustine, 300 mg/m^2 on day -6); cytosine-arabinoside (200 mg/m^2) and etoposide (200 mg/m^2) from day -5 to day -2); and melphalan (140 mg/m^2) on day -1). rATG 3.75 gm/m^2/d day +1 and +2
Systemic sclerosis		
Van Laar, 2004 (non-myeloablative)	CYC IV 2g/m^2/d × 2 days G-CSF 10 µg/kg daily until collection CD34 selected stem cell graft	CYC IV 200 mg/kg day -5 to -2 rATG 7.5 mg/kg over 3 days day -3 to -1.
Burt, 2011 (non-myeloablative)	CYC IV 2g/m^2 × 1 G-CSF 10 µg/kg daily until collection Unmanipulated stem cell graft	CYC IV 200mg/kg day -5 to -2 rATG IV 0.5 mg/kg day -5, then 0.5 mg on d-5, 1.0 mg/kg on d-4 and then 1.5 mg/kg/d from d-3 to -1 Methylprednisolone IV 100 mg (pre rATG doses)
Sullivan, 2017 (myeloablative)	G-CSF 16 µ/kg/d × 4 days); Concurrent steroids. CD34 selected stem cell graft	Fractionated total-body irradiation (200 cGy bid day -5 and -4), Pulmonary and renal shields limited organ exposure to a target of 200 cGy CYC (60 mg/kg/d day -3 and -2), equine anti-thymocyte globulin (15 mg/kg/d q2days starting d-5 × 6 doses
Inflammatory Bowel Disease		
Hawkey, 2015(type: NR)	CYC 2 g/m^2/day × 2 days; G-CSF10µg/kg/d Unmanipulated stem cell graft	CYC 50 mg/kg/d for 4 d; rabbit ATG 2.5mg/kg/d x 3 days; methylprednisolone 1mg/kg/d for 3 d
aHCT = autologous hematopoietic cell transplantation; cyc = cyclophosphamide; G-CSF = granulocyte-colony stimulating factor		