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AUTOIMMUNITY (TK TARRANT, SECTION EDITOR)

Stem Cell Therapy as a Treatment for Autoimmune Disease—Updates in Lupus, Scleroderma, and Multiple Sclerosis

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Abstract

Purpose of Review Evidence for hematopoietic stem cell transplantation (HCT) in autoimmune disease has been building since the 1990s; however, many clinicians may not yet be aware of its applications to autoimmune disease. We review the basic tenets of HCT and evidence for autologous HCT in multiple sclerosis (MS), systemic sclerosis (SSc), and lupus with an emphasis on recent advanced phase trials.

Recent Findings In MS, the phase 3 randomized MIST trial and the phase 2 randomized ASTIMS trial demonstrated the efficacy of autologous HCT in refractory MS over disease-modifying therapies and mitoxantrone, respectively. In SSc, the phase 3 randomized ASTIS trial and the phase 2 randomized SCOT trial demonstrated the efficacy of autologous HCT in advanced SSc compared to cyclophosphamide.

Summary The evidence for HCT in autoimmune diseases continues to grow, particularly in MS and SSc. In lupus, large, comparative trials are still needed. Across autoimmune diseases, questions that still remain to be answered include optimizing patient selection to limit TRM, the appropriate use of MAC, and the necessity for graft manipulation. Furthermore, collaboration between disease-specific and transplant physicians is imperative to expand the appropriate use of HCT in routine clinical practice.

Keywords Autoimmune disease · Stem cell transplant · Autologous transplant · Lupus · Multiple sclerosis · Systemic sclerosis

Introduction

A long-term disease-free state is often unachievable in autoimmune disease [1]. While disease-modifying therapies (DMT) are available for certain conditions like rheumatoid arthritis (RA) [2], multiple sclerosis (MS) [3], and inflammatory bowel disease (IBD) [4], responses are not necessarily durable [1]; furthermore, the management for others like systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) continues to be largely supportive rather than targeting the underlying cause. The use of hematopoietic stem cell transplant (HCT) in autoimmune disease was first described in patients with autoimmune conditions who received allogeneic HCT from matched donors for hematologic malignancies in which long-term follow-up suggested a clinically disease-free state for both the malignant and autoimmune conditions [5]. Since initial consensus recommendations for use of stem cell transplant in autoimmune disease were published in 1997 [6], HCT has been used to treat a range of autoimmune conditions including MS, SSc, RA, SLE, juvenile inflammatory arthritis (JIA), autoimmune cytopenias, and IBD [7]. Over this time period while the use of HCT has grown, particularly in MS and SS [8•], many treating physicians may not be familiar with the evidence for HCT in autoimmune disease [9]. Here we review the principles of HCT for autoimmune diseases and describe the evolution of evidence for its use, with a focus on MS, SSc, and lupus.

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Principles of Stem Cell Transplantation

Overview of HCT

Hematopoietic stem cell transplantation refers to the replacement of a patient's hematopoietic system with a graft that

comes either from the patient him/herself (autologous HCT, or colloquially "auto-transplant") or from a donor (allogeneic HCT, or "allo-transplant"). In this procedure, patients receive a conditioning regimen incorporating chemotherapy and/or total body irradiation (TBI) to prepare for the transplant, followed by infusion of the graft. The extent to which the conditioning regimen treats underlying disease, induces bone marrow aplasia, and suppresses the immune system varies by the regimen used (see below). The bone marrow is then rescued with the transplant, either using a patient's own cells (autologous HCT) or a donor's cells (allogeneic HCT).

While allogeneic HCT has the benefit of a new hematopoietic system without the patient's impairment (including hematologic malignancy, hemoglobinopathy, immunodeficiency, and autoimmunity), it comes with an increased risk of infection as well as graft-vs-host disease (GVHD) in which the donor's immune system recognizes the patient's body as foreign [10]. GVHD is often manageable, but it can also lead to debilitating acute and chronic toxicities. It is a main contributor to transplantation-related mortality (TRM) [11] which may be around 20% in allogeneic HCT for autoimmune disease [12]. In allogeneic HCT, neutrophil recovery varies and can occur as early as within 2 weeks. However, it may also take several weeks longer depending on several factors including the type of graft, HLA mismatch, and viral infection. Patients are usually admitted or living close to the transplant center for around 3 months for daily evaluation and management of complications. Patients undergoing allogeneic HCT are usually on immunosuppressive medications to prevent GVHD and their post-transplant care is more complicated.

On the other hand, autologous HCT allows for administration of significant immunosuppression (through the conditioning regimen) with earlier count recovery and without the risk of GVHD or the need for prolonged immunosuppression. The risk of mortality from autologous HCT for autoimmune disease is reported to be under 10% [13]. One concern with autologous HCT is related to repopulation after transplant with the patient's own hematopoietic progenitors which previously developed the autoimmune phenotype. However, it is important to note that while genetic factors including alleles in the major histocompatibility complex [14] are linked to autoimmune disease, only a small percentage of the genetics of autoimmunity can currently be explained [15], and it is not known to what degree genetic alterations as opposed to environmental factors are responsible for inciting autoimmunity [14]. Furthermore, while controversial [16•], the practice of CD34 selection (in which more primitive cells are retained and more differentiated immune cells are removed) prior to transplantation may help address this concern.

In both types of HCT, patients are treated with a conditioning regimen for the purpose of allowing acceptance of the transplanted hematopoietic cells and to varying degrees, treating the underlying disease [17]. Regimens include myeloablative conditioning (MAC), so termed because without rescue from the transplant the hematopoietic system would not be expected to recover, or non-myeloablative (NMA) conditioning, so termed because the hematopoietic system would be expected to recover over varying periods of time. Furthermore, NMA regimens can be of varying strength, with stronger regimens termed "reduced intensity conditioning" (RIC) [17].

Steps in HCT

Upon being referred for HCT, the patient is evaluated by a transplant provider who reviews the risks and benefits of HCT with the patient and family. If the decision is made to move forward with HCT, the next step is to determine the graft that will be used and who it will come from.

Grafts, which are basically a collection of cells enriched for hematopoietic stem cells but also contain varying degrees of differentiated cells, can be harvested from the bone marrow or peripheral blood. When a bone marrow graft is chosen, the harvest is done under general anesthesia with multiple (between 70 and 100 or more) bone marrow aspirates from the posterior (or less commonly, anterior) iliac crest to collect a sufficient number of primitive hematopoietic stem cells. In the last 30 years, due to the discovery that primitive stem cells can be mobilized into the peripheral blood, peripheral blood progenitor cell (PBPC) grafts have become more common [18]. To collect PBPC grafts, a Hickman (tunneled central venous) catheter is placed and patients then receive one or a combination of granulocyte colony–stimulating factor (GCSF), cyclophosphamide, or plerixafor (a CXCR4 antagonist), to help mobilize primitive hematopoietic cells from the bone marrow into the peripheral blood [19]. White blood cells are collected by centrifugation through apheresis and cryopreserved until use. Given the peripheral blood source, PBPC grafts do contain a greater number of mature lymphocytes [19] that theoretically could transfer autoimmunity; for this reason, some studies have employed ex vivo graft manipulation using selection for primitive, CD34+ cells to decrease risk of transferring autoimmune T cells [20, 21••]; however, no comparative studies have proven the efficacy of this technique. Once the graft is collected (or simultaneously in allogeneic HCT), the conditioning regimen is administered over several days and then the transplant is done through simple transfusion of the graft through the Hickman catheter. The stem cells in the graft migrate to the bone marrow and begin to form the cellular components of blood. In autologous HCT, neutrophil recovery usually occurs around 10–14 days, with the myelotoxicity (MAC vs NMA) of the conditioning regimen and the source of the graft (peripheral blood vs bone marrow) being some of the determinants. During this vulnerable period, patients usually receive a combination of antibacterial and antifungal prophylaxis per institutional standards. Full immune recovery can

take months longer [22] and patients are recommended to receive anti-viral prophylaxis (with acyclovir or similar agent) against herpes zoster for 1 year after autologous HCT [23]. Similarly, patients require re-vaccination, with consensus recommendations available on necessary vaccinations and appropriate schedule [23].

Stem Cell Transplantation in Autoimmune Disease

Pre-clinical models suggest that autoimmunity may reflect changes very early in lymphocyte differentiation [24–27]). However, autologous HCT has been associated with significant remissions and even cure for autoimmune diseases [28]. The first case report of autologous HCT for systemic sclerosis was published 24 years ago [29]; since then, autologous HCT for autoimmune disease has been associated with much lower rate of TRM [30, 31] than allogeneic HCT. Furthermore, long-term responses are possible: A review of 900 patients with auto-HCT for autoimmune diseases including MS, SSc, SLE, RA, as well as others, over 12 years found a 5-year overall survival and progression-free survival rate of 85 and 43%, respectively, with TRM of 5% ([7]).

The benefit of autologous HCT seems to come partly from the conditioning regimen, which has an immunosuppressive effect and may help to restore balance to the immune system. The significance of the conditioning regimen is evidenced by the utility of the common conditioning backbone cyclophosphamide in autoimmune disease outside of transplant in lower dose intravenous pulses [32, 33] and daily oral [34] forms, and in higher doses equivalent to those used in stem cell transplantation [35], where delayed hematopoietic recovery increases the risk of infection.

The mechanism by which conditioning regimens contribute to treatment is not clear. It may be the case that the repopulation of a more "naïve" immune system once committed, differentiated lymphocytes are eliminated by the conditioning regimen, promotes a less auto-reactive state: this is illustrated by a post-transplant increase in CD4+ T cell receptor diversity associated with a renewal in thymic function, a potential expansion of regulatory T cells (though this may not be a consistent effect), and lysis/apoptosis of autoimmune plasma cells [36, 37, 38•]. As shown in Tables 1, 2, and 3, a variety of conditioning regimens have been used in HCT for autoimmune diseases without head-to-head comparisons on disease-specific efficacy. However, comparisons between pre- and post-transplant immune reconstitution suggest differential effects of total body irradiation (TBI) [36] and anti-thymocyte globulin (ATG) [39] on post-transplant normalization of the CD4/CD8 ratio and timing of naïve CD4+ T cell reconstitution [38•], suggesting the specific conditioning regimen used does matter. Further subtleties to conditioning regimens may include patient-specific dosing of widely used adjuncts like ATG where benefit may be related to dosing by lymphocyte count [40••], a modification that has not yet been done in large-scale trials in autoimmune disease [38•].

Whether the stem cell graft plays a role in the clinical benefit of autologous HCT is less clear: For instance, ex vivo graft manipulation with CD34 graft selection may be a source of benefit but this is controversial. In ex vivo CD34 selection, primitive CD34+ cells are selected for transplantation [41] with the aim of removing differentiated, self-reactive lymphocytes. While there are no prospective direct comparisons between unmanipulated autologous HCT with CD34-selected autologous HCT, CD34 selection was used in multiple prospective randomized studies showing benefit for autologous HCT [21••, 42] including in the Autologous Stem cell Transplantation International Scleroderma (ASTIS) [20] and Scleroderma: Cyclophosphamide or Transplantation (SCOT) [21••] trials in which HCT was compared to cyclophosphamide. However, a retrospective analysis using the European Bone Marrow Transplant (EBMT) database suggested CD34 selection may not be associated with improved outcomes [16•]) with disadvantages including cost and potential increased infection risk. It may be that the benefit of graft manipulation is disease-specific, which will require prospective, comparative studies.

Autologous HCT for Multiple Sclerosis

Initial retrospective reviews and single-arm prospective trials confirmed the utility of autologous HCT in MS, with sustained improvement in both clinical outcomes [43, 44–46] and imaging evidence of disease stability after failing multiple lines of therapy [45, 46] (Table 1). However, with the growing number of DMTs in MS [47], these studies did not clarify the comparative efficacy and appropriate clinical timing of HCT. Recent studies have provided more clarity: The rate of long-term disease control at 4 years with DMT therapy only is about 18% [48•], and two recent randomized trials helped to establish the validity and appropriate use of auto-HCT in the current era [30, 49]:

In the phase 2 autologous hematopoietic stem cell transplantation in multiple sclerosis (ASTIMS) trial [49], 21 patients with relapsed refractory MS (RRMS) or secondary progressive MS (SPMS) refractory to conventional therapy in the last year with Expanded Disability Status Scale (EDSS) score 3.5 to 6.5 (0–10 scale of neurologic/functional impairment, with 0 indicating normal function and 10 indicating death related to MS) were randomized to (1) autologous HCT with cyclophosphamide/granulocyte colony–stimulating factors (GCSF) mobilization and myeloablative BEAM (carmustine, etoposide, cytarabine, and melphalan) + rabbit ATG (rATG) conditioning ($n = 9$) or (2) monthly mitoxantrone (MTX; $n = 11$) for 6 months. The study was initially planned as a phase 3 trial with the primary endpoint of EDSS improvement;

Table 1 Prospective trials of autologous HCT in MS. *EDSS*, Expanded Disability Status Scale; *PBSC*, peripheral blood stem cell; *fxn*, function; *NMSC*, non-melanoma skin cancer; *MS*, multiple sclerosis; *RRMS*, relapsing remitting multiple sclerosis; *SPMS*, secondary progressive multiple sclerosis; *WBC*, white blood cell; *PFS*, progression-free survival; *ORR*, overall response rate; *SD*, stable disease; *MTX*, methotrexate; *Cy*, cyclophosphamide; *GCSF*, granulocyte colony–stimulating factor; *MAC*, myeloablative conditioning; *NMA*, non-myeloablative conditioning; *RIC*, reduced intensity conditioning; *(r)ATG (rabbit)*, anti-thymocyte globulin; *Bu*, busulfan; *BEAM*, carmustine etoposide cytarabine melphalan; *FN*, febrile neutropenia; *APML*, acute promyelocytic leukemia; *ITP*, immune thrombocytopenia; *CMV*, cytomegalovirus

Trial, PMID, design	Phase	Published year	*n*	Patients (selected inclusion/exclusion criteria)	Primary outcome	(1) Mobilization (2) Conditioning	Graft manipulation?	Outcomes	AEs in transplant arm
Shevchenko et al. PMID 18468768; single arm	2	2008	50	(1) Adults age 18–55 (2) EDSS score 1.5–8 (3) No "severe concomitant disease"	Improvement in EDSS at 6 months of 0.5	(1) Cy/GCSF (2) BEAM (MAC)	No	(1) Primary outcome: 63% (2) 6-year PFS 72%	(1) TRM 0 (2) Infectious: FN 51.6% (3) G1–2 hepatotoxicity: 48.1% (4) One patient of APML in 3 years
Burt et al. PMID 19186105; single arm	1–2	2009	21	(1) Adults age 18–55 (2) EDSS 2–5.5 (3) Normal renal, cardiac, pulmonary, hepatic fxn; no prior NMSC	(1) PFS (2) 1 point EDSS improvement	(1) Cy/GCSF (2) Cy+ either alemtuzumab or rATG (NMA)	No	(1) PFS 100% (2) 81% with EDSS improvement (3) 5 of 21 pts relapsed (mean 11 months) and all achieved remission with first-line therapy	(1) TRM 0 (2) Infectious: FN 5/21 patients, zoster 2/21 pts (3) G2 liver 1/21 (4) ITP 2 of 17 patients who received alemtuzumab (5) None 11/21
Schevchenko et al. PMID 22771495; single arm	2	2012	95	(1) Adults age 18–55 (2) EDSS score 1.5–8	Not specified	(1) GCSF (2) Reduced BEAM (RIC)	No	(1) 6-month ORR 41%, SD 58% (2) 5-year PFS 82% higher in early (95%) vs later (73%) transplant	(1) TRM 0 (2) Infectious: FN 31.6% (3) G1–2 hepatotoxicity 42.1%
Mancardi et al. PMID 25672923; randomized, HCT vs mitoxantrone	2	2015	21	(1) RRMS or SPMS (2) EDSS 3.5–6.5	Number of new T2 lesions in 4 years	(1) Cy/GCSF (2) BEAM + ATG (MAC)	No	(1) New T2 lesions: 79% reduction with auto-HCT (rate ratio 0.21) (2) No EDSS differences up to 3 years (3) Annual relapse rate 0.6 (MTX) vs 0.19 (HCT)	(1) TRM 0 (2) Infectious: FN 8/9, zoster 1/9 (3) Pneumothorax 1/9 (4) Grade 3 ATG reaction (1), grade 4 CMV reactivation and engraftment failure
Atkins et al. PMID 27291994; single arm	2	2016	24	(1) Adults age 18–50 (2) EDSS 3–6 (3) Excluded "substantial" cardiac, renal, pulmonary, hepatic dysfunction, as well as active infection and "other medical problems" with increased risk	MS activity-free survival (AFS) at 3 years	(1) Cy/GCSF (2) Bu/Cy/rA-TG (MAC)	Yes	(1) AFS at 3 years: 69.6% (2) No relapses with median 6.7 years f/u (3) Except for 1 scan with prior 5 months ago, no follow-up MRI scans showed new lesions (4) 40% had improvement in EDSS	(1) TRM 1 of 24 patients (2) Infectious: FN 100% (3) 2 patients (1 oral, 1 IV) developed busulfan-related SOS with severe hepatotoxicity
Nash et al. PMID 28148635; single arm	2	2017	25	(1) Adults age 18–60 (2) EDSS 3–5.5	EFS	(1) GCSF (2) BEAM (MAC)	No	(1) EFS 69% (median f/u 62 months) (2) PFS 91%	(1) TRM 0 (2) "Predominantly cytopenias and infections"

Table 1 (continued)

Trial, PMID, design	Phase	Published year	*n*	Patients (selected inclusion/exclusion criteria)	Primary outcome	(1) Mobilization (2) Condition-ing	Graft manipulation?	Outcomes	AEs in transplant arm
Burt et al. PMID 30644983; randomized, HCT vs DMT	3	2019	110	(1) Adults age 18–55 (2) EDSS 2–6 (3) Excluded: pulmonary, cardiac, hepatic, renal dysfunction, active infection, abnormal WBC or platelet	Disease progression (EDSS increase after 1 year of 1 point)	(1) Cy/GCSF (2) CY + rATG (NMA)	No	(1) Progression in 3 (HCT) vs 34 (DMT), HR 0.07 (2) Disease progression at 5 years 75% DMT and 9.7% HCT (3) During first year, EDSS improved in HCT and worsened DMT	(3) No grade 4 AEs (1) TRM 0 (2) Infectious: FN 13/55 in HCT group (3) G3 elevated transaminases: 5 in HCT group (4) No non-hematologic grade 4 AEs (5) 2 pts in HCT developed ITP

however, low accrual resulted in revision of the primary endpoint to the cumulative number of new central nervous system (CNS) lesions on T2-weighted imaging at 4 years. In this study, autologous HCT was associated with a 79% improvement in the primary endpoint (median 8 new lesions with mitoxantrone vs 2.5 with auto-HCT) and transplant itself was well tolerated with no TRM. Secondary outcomes included annual relapse rate (0.6 for MTX vs 0.19 for auto-HCT, $p = 0.026$) and progression at the end of follow-up (48% MTX vs 57% auto-HCT, $p > 0.50$). While there were no differences in EDSS between the two groups, the enrolled sample only allowed for 26% power to detect a significant difference at the expected level.

In the phase 3 multiple sclerosis international stem cell transplant (MIST) trial, 110 patients with refractory RRMS and EDSS score of 2–6 were randomized to (1) autologous HCT with cyclophosphamide/GCSF mobilization and non-myeloablative cyclophosphamide (200 mg/kg) + rATG conditioning ($n = 55$) or (2) further alternative DMT ($n = 55$). Notably patients with SPMS and primary progressive MS (PPMS) were excluded. Patients in the DMT group could cross over after 1 year of progression. The primary endpoint was time to progression (defined as EDSS score increase of 1). After a median follow-up of 2 years, mean time to progression was 24 months with DMT and not reached with autologous HCT. Notably within the first year, 69% of patients in the DMT group relapsed vs 2% in the auto-HCT group with HR for time to first relapse 0.097. Disease progression at 5 years occurred in 75% of patients in the DMT group and only 9.7% in the autologous HCT group. Differences in EDSS were seen as early as the first year, with improved EDSS in the first year with autologous HCT (− 1.02) and worsened with DMT (+ 0.67). Transplant resulted in comparative improvement over DMT in new MRI lesions, quality of life, and 25-ft walk time. TRM was 0 and there were no non-hematologic grade 4 toxicities.

The ASTIMS and MIST trials confirm that auto-transplant has a significant role to play in the era of DMT in MS, with no TRM in either trial. Patient selection, however, appears to be a key factor. One difference between these studies was improved clinical/functional outcomes in MIST but not in ASTIMS. Prior studies suggested that transplant early in the disease course (EDSS 1.5–3) was associated with greater benefit in PFS [50, 51]. It is also possible that transplantation during RRMS may result in better outcomes than once the disease has entered the progressive state [52, 53]. In ASTIMS, 67% of patients had SPMS while these patients were excluded from MIST [49]. Thus, RRMS may be a more optimal disease state for HCT candidacy. Secondly, included patients in these studies were otherwise relatively healthy—while exclusion criteria for end organ function is not reported for ASTIMS, patients with pulmonary, cardiac, renal, and liver dysfunction, as well as patients with abnormal platelet

Table 2 Prospective trials of autologous HCT in SSc. *mRSS*, modified Rodnan skin score; *GI*, gastrointestinal; *PAH*, pulmonary arterial hypertension; *Hgb*, hemoglobin; *ESR*, erythrocyte sedimentation rate; *ILD*, interstitial lung disease; *G3–4*, grades 3–4; *TRM*, transplant-related mortality; *FVC*, forced vital capacity; *EFS*, event-free survival; *PRO*, patient-reported outcomes; *RR*, relative risk; *QOL*, quality of life; *GRCS*, global rank composite score; *DMT*, disease-modifying therapy; *PTLD*, post-transplant lymphoproliferative disorder; *CMV*, cytomegalovirus; *EBV*, Epstein-Barr virus; *HSV*, herpes simplex virus; *FN*, febrile neutropenia; *BCC*, basal cell carcinoma; *PNA*, pneumonia; *MI*, myocardial infarction; *FUO*, fever of unknown origin; *AEs*, adverse events

Trial, PMID, design	Phase	Published year	*n*	Patients (selected inclusion/exclusion criteria)	Primary outcome	(1) Mobilization (2) Conditioning	Graft manipulation?	Outcomes	AEs in transplant arm
McSweeney et al. PMID 1217687-8; single arm	1–2	2002	19	(1) Adults age ≤ 65 (2) high-risk SSc (mRSS ≥ 16 with duration 3 years or less plus pulmonary, cardiac, or renal disease, or diffuse SSc and progressive pulmonary disease over 6 months) (2) Exclusion criteria: Significant cytopenias, pulmonary/cardiac/hepatic/renal impairment	G3–4 toxicity and engraftment	(1) GCSF (2) TBI 800 cGy, Cy, and horse ATG (MAC)	Yes	(1) 1 G4 toxicity and total of 3 TR deaths; neutrophil engraftment median 9 days (2) 3-month disease response: 13/15 (87%); 12-month disease response 12/12 (100%) (3) 2-year OS (estimated) 79% (4) mRSS and mHAQ-DI improved overtime (no pts with progression); pulmonary disease did not	(1) TRM 16% (*n* = 3), 2 pts from pneumonitis, 1 from PTLD; further pneumonitis did not occur after protocol modification to use lung shielding (2) Infxn: Bacteremia *n* = 3, catheter infection *n* = 2, CMV reactivation *n* = 3, EBV PTLD *n* = 1, HSV *n* = 1
Oyama et al. PMID 1764684-4; single arm	1	2007	10	(1) mRSS ≥ 14 and internal organ involvement (GI, pulmonary, renal, cardiac) (2) Exclusion criteria: Significant pulmonary/cardiac dysfunction, or PAH	TRM engraftment, mobilization	(1) Cy/GCSF (2) Cy/rATG (NMA)	No	(1) Median neutrophil engraftment 9 days (2) Improved mRSS in 9/9 long-term f/u at 12 months but stable cardiac/pulmonary/renal function; 2 pts had skin progression at 1 and 2 years, responded to MMF (3) Median f/u 25.5 months, PFS 70%, OS 90%	(1) TRM 0; engraftment syndrome in 1 patient (2) Infxn: FN in 5 of 9 (56%) but no sepsis; cdiff in 1, no CMV (3) Volume overload in 4 pts (4) Acute renal failure at 3 weeks in 1 pt (requiring dialysis), stabilized/Cr normalized after 8 months
Vonk et al. PMID 1752655-4; single arm	1–2	2007	26	(1) Adults age < 66 (2) Rapidly progressive disease, duration less than 2 years and mRSS > 20 with high ESR or low Hgb, or disease > 2 years plus mRSS progression plus major organ involvement (4) Exclusion (selected): Arrhythmia, LVEF < 50%, significant pulmonary/renal dysfunction on TCP	Not specified	(1) Cy/GCSF (2) Cy (NMA)	Yes	(1) 81% clinical benefit at median 5.3 years follow-up (2) mRSS decreases 11.6 in first year, then 2.6 per year afterward (2) EFS 64% at 5 years, estimated OS 96% at 5 years (3) Improved WHO performance status at 5 years (median 2 at baseline, 0.6 at 5 years) (4) Stable cardiac, renal, and pulmonary function	(1) TRM *n* = 1, total mortality at 6 months *n* = 2 (2) Infxn: Zoster (*n* = 3), atypical mycobacterium (*n* = 2) (3) One persistent pancytopenia with recovery after stopping co-trimoxazole (4) One BCC at 4 years
Burt et al. PMID 2177797-2; randomized, HCT vs Cy	2	2011	19	(1) Age < 60 (2) A-Diffuse SSc, mRSS > 14, and internal involvement (3) Exclusion: Significant pulmonary/cardiac dysfunction, significant PAH	Improved mRSS or increased FVC at 12 months	(1) Cy/GCSF (2) Cy/rATG (NMA)	No	(1) mRSS improvement at 12 months: 10/10 HCT arm vs 0/9 controls (2) 8/10 sustained mRSS/FVC improvement with HCT	(1) TRM 0 (2) Infxn: During hospitalization, 1 cdiff, 1 bacteremia; late: 1 CMV reactivation (3) During hospitalization, 2 atrial arrhythmias

Table 2 (continued)

Trial, PMID, design	Phase	Published year	*n*	Patients (selected inclusion/exclusion criteria)	Primary outcome	(1) Mobilization (2) Conditioning	Graft manipulation?	Outcomes	AEs in transplant arm
								(3) 7/9 patients in control group later received HCT with subsequent improvement (4) General health PRO (SF36) improved at 1 year after HCT but worsened after Cy only	
Van Laar et al. PMID 25058083;, randomized, HCT vs Cy	3	2014	156	(1) Age 18–65 (2) Disease duration < 4 years and mRSS ≥ 15 and heart/lung/kidney involvement; later amended to < 2 years and no major organ involvement if mRSS ≥ 20 and ESR elevation/anemia (3) Exclusion: Severe organ involvement including PAH or serious comorbidities	EFS	(1) Cy/GCSF (2) Cy/rATG (NMA)	Yes	(1) Long-term EFS (4 years): Events 19% HCT vs 26% Cy, RR 0.7, favored HCT (2) Short-term EFS (1 year): Events 16.5% HCT 10.4% Cy, RR 1.6, favored Cy (3) Long-term mortality (4 years) 16.5% with HCT vs 26% Cy (4) Short-term mortality (1 year) 13.9% HCT vs 9.1% Cy (5) Long-term mRSS, pulmonary, and QOL favored HCT; renal function worsened with HCT	(1) TRM 10% ($n = 8$; vs 0 with Cy) (2) Infxn: G3/4 10% with HCT, 5% with controls (3) Overall G3/4 AEs 63% HCT, 37% controls (4) Cancers 0 with HCT, 3 (3.9%) with controls
Helbig et al. PMID 29526111; single arm	1–2	2018	18	(1) Adults age 70 or less (2) Duration < 10 years (3) Refractory SSC, mRSS ≥ 15 or coexistent skin/pulmonary involvement (4) Exclusion: PAH, renal/cardiac insufficiency, adjusted DLCO < 40%	Not specified	(1) Cy/GCSF (2) Several: Cy/alemtuzumab, Mel/alemtuzumab, Cy/rATG, Cy alone (all NMA)	Yes	(1) Reduced mRSS at 12 months: 61% (2) OS: 11/18 (61%) alive at 42 months	(1) TRM 22% (4/18), 3 from bilateral PNA, 1 from MI (2) Infectious: FUO (8/18), no bacteremia; *Candida* throat culture+ (2/18) and sputum+ (1/18) (3) 3 more deaths overall in follow-up including another MI (4) Both cardiac deaths received alemtuzumab
Sullivan et al. PMID 29298160; randomized, HCT vs Cy	2	2018	75	(1) Adults age < 70 (2) Disease duration < 5 years with pulmonary/renal involvement (3) Exclusion (selected): Significant pulmonary/renal dysfunction, PAH	GRCS at 54 months	(1) GCSF (2) TBI/Cy/rATG (MAC)	Yes	(1) 67% pairwise GRCS comparisons favoring HCT arm at 54 months (2) Per-protocol EFS 79% vs 50% favoring HCT at 54 months (3) 6-year OS 86% vs 51% favoring HCT (4) DMT initiation at 54 months 9% vs 44% favoring HCT	(1) TRM $n = 1$ (3%) at 54 months, $n = 2$ (6%) at 72 months, no deaths within 1 year after HCT (2) Infxn: Rate of G3+ infxn higher with transplant 0.21 vs 0.13; zoster in 12 HCT patients, mostly after 1 year; CMV reactivation in 5 cases overall (2) Cancers: 3 pts in HCT arm (2MDS, 1 thyroid) and 1 in Cy arm (breast cancer)

Table 2 (continued)

Trial, PMID, design	Phase	Published year	*n*	Patients (selected inclusion/exclusion criteria)	Primary outcome	(1) Mobilization (2) Conditioning	Graft manipulation?	Outcomes	AEs in transplant arm
									(3) Serious AEs 74% in transplant arm vs 51% in Cy arm; 96% of sAEs in HCT arm within 26 months

and white blood cell counts, were excluded from MIST. Age may also be significant here: HCT at a younger age is associated with better outcomes [43], and median age in ASTIMS was 35.5 years and in MIST 36 years. Whether HCT is a viable option for older patients and those with mild end organ dysfunction needs to be determined on a case-by-case basis and with caution from the treating physician. Lastly, while ASTIMS used MAC, MIST used NMA conditioning and neither employed ex vivo graft manipulation (i.e., CD34 selection). The positive results of MIST suggest that the low intensity NMA regimen without expensive graft manipulation may be sufficient in MS; however, further comparative studies are needed to address this point.

Despite the long duration of response after autologous HCT, relapses may still occur. It is possible however that the process of transplant resets the propensity of the disease to respond to conventional therapies: In one study, 5 of 21 patients with refractory disease prior to auto-HCT relapsed (mean 11 months) and all achieved remission with first-line therapy [52]. Furthermore, larger trials are needed, but if confirmed, this effect would suggest more reason to pursue autologous HCT.

Two trials of autologous HCT for MS are currently recruiting in the USA: (1) NCT04047628, best available therapy vs autologous hematopoietic stem cell transplant for multiple sclerosis (BEAT-MS), is a multicenter randomized trial of 156 patients with treatment-resistant relapsing MS. This study will assess the use of BEAM MAC and rATG in the autologous HCT arm (as in ASTIMS) but address the unanswered question of efficacy compared to DMTs in the comparator arm (as in MIST). PPMS is excluded in this study. (2) NCT00716066, autologous peripheral blood stem cell transplant for neurologic autoimmune disease, is a phase 2 single-arm study (40 patients) of BEAM MAC with ATG but addresses the appropriate use of autologous HCT in 13 other neurologic autoimmune diseases as well as MS.

Autologous HCT for Systemic Sclerosis

Systemic sclerosis (SSc) is a progressive autoimmune disease characterized by inflammation and fibrosis of skin and internal organs [54]. Current therapies used in routine care include cyclophosphamide and mycophenolate mofetil [55], as well as azathioprine and methotrexate [54]. However, the durability of response and impact of these therapies on clinical progression of SSc is not understood [54]. Three randomized trials (Table 2) have helped to establish autologous HCT as a tolerable therapy with durable response, but as discussed below, differences between the approaches in each of these trials raise many questions, and patient selection/TRM remains serious considerations [20, 21••, 56].

Table 3 Prospective trials of autologous HCT in lupus. *WHO*, World Health Organization; *GN*, glomerulonephritis; *Cy*, cyclophosphamide; *APS*, antiphospholipid syndrome; *CNS*, central nervous system; *OS*, overall survival; *DFS*, disease-free survival; *Cy*, cyclophosphamide; *GCSF*, granulocyte colony–stimulating factor; *(r)ATG (rabbit)*, anti-thymocyte globulin; *NMA*, non-myeloablative; *PFS*, progression-free survival; *SLEDAI*, Systemic Lupus Erythematosus Disease Activity Index; *TCR*, T cell receptor; *PE*, pulmonary embolism; *TRM*, transplant-related mortality; *VZV*, varicella zoster virus; *HSV*, herpes simplex virus; *PCP*, pneumocystis pneumonia; *AED*, anti-epileptic drug; *GPC*, Gram-positive cocci; *MRSA*, methicillin resistance *Staphylococcus aureus*; *ITP*, immune thrombocytopenia; *CNS*, central nervous system; *CMV*, cytomegalovirus

Trial, PMID, design	Phase	Published year	*n*	Patients (selected inclusion/exclusion criteria)	Primary outcome	(1) Mobilization (2) Conditioning	Graft manipulation?	Outcomes	AEs in transplant arm
Traynor et al. PMID 110856-88; single arm	1	2000	9	(1) WHO 3–4 GN, lupus cerebritis, transverse myelitis, vasculitis involving heart/-lung, severe cytopenias unresponsive to Cy, or catastrophic APS (2) Exclusion not specified	Efficacy/safety	(1) Cy/GCSF (2) Cy/horse ATG (NMA)	Yes	(1) 100% (7/7 who underwent HCT) PFS at median 25 months (2) Improved pulmonary and renal function	(1) TRM 0 (2) Infectious: VZV (2/7), HSV of V2 (1/7), PCP (1/7), bacteremia (1/7) (3) 2/7 pts required ventilation for pulmonary edema (4) After HCT, 1/7 pts seizure during subtherapeutic AED
Burt et al. PMID 164496-18; single arm	2	2006	50	(1) At least 20 mg/day prednisone or equivalent Cy (2) WHO 3–4 GN, involvement of lungs, CNS, vasculitis, myositis, transfusion-dependent cytopenias, serositis, mucocutaneous disease, APS (2) Exclusion not specified	OS and DFS	(1) Cy/GCSF (2) Cy/horse ATG (NMA)	Yes	(1) 5-year OS for 48 pts undergoing HCT: 84%, 4 deaths from active lupus (2) 5-year DFS 50% (3) Improved SLEDAI for up to 5 years (4) Stable renal function (no new nephritis/renal failure after HCT) (5) Improved DLCO for up to 5 years	(1) TRM: 2/50 (both before HCT), 0/48 who underwent HCT (2) Infectious: Prior to HCT, 1 death from disseminated mucormycosis; overall, PCP (2) Esophageal candidiasis (1), GPC bacteremia (18; no sepsis), *Candida* peritonitis (1), *Candida* fungemia (1), c. diff (3), *Salmonella* enteritis (1), CMV reactivation (2), VZV (5), recurrent MRSA endocarditis (1-prior history before HCT) (3) 2/50 pulmonary edema requiring ventilation (4) Factor VIII deficiency (2) and ITP (1) both reversible
Alexander et al. PMID 188245-94; single arm	1–2	2009	7	(1) Failure of 2 standard immunosuppressants including Cy	Lymphocyte reconstitution	(1) Cy/GCSF (2) Cy/rATG (NMA)	Yes	(1) Normalization of autoantibodies, evidence of thymic reactivation and increased naive CD4+ T cells, increased TCR repertoire diversity, increased regulatory T cells (2) Clinical endpoint of SLEDAI < 3 in 7/7 patients (3) Continued remission at f/u 5/7 (median f/u 60 months), 2 deaths (infxn at 3 months, PE at 38 months)	(1) TRM: 1/7 (invasive CNS aspergillosis 3 months after HCT) (2) Infectious: "frequent" infectious during post-HCT neutropenia, details unspecified; viral infections-VZV (1), HHV6 (1), CMV reactivation (1), HSV (1)

To inform inclusion criteria and gauge response, clinical trials in SSc use several parameters to measure the burden of disease; however, as discussed below, a key limitation of trials of HCT in SSc is the lack of a comprehensive and organ-specific tool that is used across all trials. The modified Rodnan score (mRSS) is a standardized assessment of skin thickening at 20 sites (10 on each side of the body) and commonly used to follow the course of disease in SSc. Its measurements correlate with histologic changes in SSc and it is shown to maintain inter-observer consistency [57]; high mRSS scores are also associated with systemic complications, particularly renal crisis [58]. Pulmonary disease is the leading cause of mortality in SSc [59]: pulmonary function tests (PFTs) to measure forced vital capacity (FVC) as well as diffusion capacity for carbon monoxide (DLCO) and total lung capacity (TLC) are frequently used to measure and follow pulmonary involvement [59].

The autologous non-myeloablative hematopoietic stem cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST) [56] and ASTIS [20] trials used NMA conditioning. In the phase 2 ASSIST trial, 19 patients with pulmonary and/or cardiac involvement with time from diagnosis less than 4 years were randomized between (1) autologous HCT ($n = 10$) with GCSF/cyclophosphamide mobilization and cyclophosphamide/rATG conditioning or (2) monthly cyclophosphamide for 6 months ($n = 9$). Patients without pulmonary or renal involvement were included if they demonstrated early, rapidly progressive skin disease. The primary outcome was improvement in mRSS at 12 months or increased FVC by more than 10%. At 1 year, no patient in the autologous HCT arm had progression of disease vs 8 patients in the cyclophosphamide arm. Quality of life, as measured by the SF-36 (36-item short form survey), improved at 1 year after autologous HCT but declined with monthly cyclophosphamide. Furthermore, clinical benefits in mRSS and FVC persisted at 2 years, and 7 patients initially randomized to the non-transplant arm experienced improvements in mRSS and lung function after undergoing autologous HCT.

In the phase 3 ASTIS study, 156 patients were randomized to either (1) autologous HCT ($n = 79$) with GCSF/cyclophosphamide mobilization and cyclophosphamide conditioning and CD34+ graft selection, or (2) monthly cyclophosphamide pulses ($n = 77$). Patients had SSc for up to 4 years with involvement of the heart, lungs, or kidney. Patients with significant cyclophosphamide exposure (5 g intravenously for more than 2 mg/kg body weight orally for 3 months), severe PAH, and serious comorbidities were excluded. The primary end point of the study was EFS, defined as the time in days from randomization until the occurrence of death, or the development of persistent major organ failure of the heart, lung, or kidney. The results demonstrated a hazard ratio (HR) for EFS of 0.35 at 2 years and 0.34 at 4 years favoring HCT. Notably, while pulmonary disease and skin manifestations improved with HCT, renal function declined. Unfortunately, the first year mortality was 16.5% in the HCT arm (including 8 treatment-related deaths, 7 of which occurred in patient with current or prior tobacco exposure) and 10.4% in the control arm (no treatment-related deaths); however, despite the initial higher mortality, the HR for OS was 0.29 at 2 and 4 years, favoring HCT over time.

The SCOT trial [21••] took a different approach by using MAC. In this phase 2 study, patients were randomized between (1) monthly cyclophosphamide (CYC) for 12 treatments ($n = 39$) or (2) myeloablative autologous HCT ($n = 36$) with GCSF mobilization, TBI/CYC/rATG conditioning, and CD34+ graft selection. Patients with SSc for less than 5 years who had pulmonary and renal involvement were included; however, severe lung disease, pulmonary arterial hypertension, cardiac EF < 50% (high-dose cyclophosphamide is associated with cardiotoxicity), and significant prior cyclophosphamide exposure were excluded. The primary outcome was the global rank composite score (GRCS) assessed at 54 months, which was changed from the initial primary outcome of EFS due to low accrual. The GRCS is a composite score based on an ordered hierarchy of mortality and longitudinal outcomes in the following order: death, failure of event-free survival, FVC, the disability index of the health assessment questionnaire (HAQ-DI), and mRSS. The GRCS is computed by comparing each subject in the study to each other subject starting with the highest measure of the hierarchy and if there is a tie at that level moving on to the next level. For each subject, the pairwise comparison with each other subject is thus assigned a score of 1 (better off), 0 (no different), and −1 (worse off), and the GRCS is the sum across all such comparisons. At both 48 months and 54 months, transplantation was associated with significant improvement in pairwise comparisons of GRCS (68% vs 32% of comparisons at 48 months, and 67% vs 33% at 54 months). The efficacy of HCT was also seen in terms of further therapy, with only 9% requiring initiation of disease-modifying therapies in the HCT group vs 44% in the CYC group. Treatment-related mortality was higher in the transplant group (6% vs 0% at 72 months); however, the rate of OS was 86% at 72 months with HCT and only 51% with cyclophosphamide alone. Rates of infection were similar between both groups but rates of zoster were higher in the transplant group, occurring in 36% of those patients. One patient in the transplant group died from acute myeloid leukemia at 70 months; however, given the known risk of malignancy in scleroderma, further follow-up will be needed to determine if risk of malignancy truly deferred in the two arms.

Review of these trials suggests multiple cautionary lessons. As in MS, patient selection appears to be very important. While internal organ involvement was largely necessary for inclusion, significant cardiac disease (EF < 50% in SCOT, EF < 40% in ASSIST), significant pulmonary disease (DLC < 40% predicted and FVC < 45% predicted in SCOT; TLC <

45% predicted in ASSIST), and PAH were excluded. Furthermore, previous disease duration was limited to 5 years in SCOT, 4 years in ASSIST, and initially 4 years in ASTIS but later amended to 2 years. Patients who smoke may be at risk for early TRM, and pre-existing renal disease may worsen with auto-HCT. While these factors may limit the population of patients considered for auto-HCT, for patients who meet the common inclusion criteria of age under 60–65 (median age across the 3 trials in the 40s), moderate pulmonary/renal involvement, but without significant pulmonary/renal/cardiac compromise, we now have 3 randomized trials proving that autologous HCT for SSc is a valid, reasonable, and disease-modifying treatment.

Many questions remain: how necessary is CD34 selection [16•, 60], how best to avoid early mortality, and what is the risk of secondary malignancies. We still do not know the risk/benefit in patients that did not fit the inclusion criteria such as those with mild cardiac disease, patients without pulmonary involvement, or patients with a disease duration of greater than 4–5 years. There are currently 2 trials of HCT for SSc recruiting in the USA: (1) TBI using IMRT and cyclophosphamide prior to stem cell transplant for the treatment of severe systemic sclerosis (NCT NCT04380831), which is a single-arm study (15 patients) examining the use of intensity-modulated radiation therapy (IMRT)-based conditioning to prevent radiation exposure to sensitive organs. (2) Autologous stem cell transplantation in patients with systemic sclerosis (NCT NCT03630211), which is a single-arm study (8 patients) MAC using TBI, thiotepa, cyclophosphamide, and biologics (rituximab/alemtuzumab), along with CD34 selection; importantly, this study uses a threshold EF of 40% rather than 50% (as in SCOT) for inclusion. Both studies will help determine if conditioning regimens can be better optimized for efficacy and toxicity.

Autologous HCT for Lupus

Lupus is a multi-system autoimmune disease with variable manifestations including mucocutaneous, cardiac, pulmonary, renal, gastrointestinal, hematologic, dermatologic, and ophthalmologic involvement. Like other autoimmune diseases, lupus is treated with immunosuppressants, ranging from corticosteroids to steroid-sparing agents like calcineurin inhibitors, cyclosporine, and azathioprine. In 2011, the anti-BLyS (B lymphocyte stimulator) monoclonal antibody belimumab was approved for the treatment of lupus and was associated with a response rate of about 51% [61]. However, the use of biologics in lupus has been limited when compared to MS, RA, or IBD: While belimumab has some clinical benefit over placebo [62], meta-analysis [63] and randomized prospective studies have found no benefit of rituximab over placebo in lupus nephritis [64] and multi-system disease [65].

Like in SSc, the use of auto-transplantation in lupus may be limited by baseline end organ dysfunction; however, the evidence of autologous HCT in lupus is also more limited. While some limited mostly retrospective studies have suggested auto-HCT may be able to achieve disease control with long-term PFS [66, 67•, 68], improved proteinuria [67•], improved serologic markers of disease [66], and improved cardiac function [69], others have suggested TRM up to 12% [70] and inferior outcomes compared to autologous HCT in other autoimmune conditions. A registry-based study of 85 patients from the European group for Blood and Marrow Transplantation (EBMT) found a 6-month remission rate of 66%, though many of these patients later relapsed [71]. Prospective studies in lupus have been limited: few studies have been published of autologous HCT for lupus alone (Table 3) and limited enrollment of 1–3 patients with lupus has occurred in other prospective studies enrolling multiple autoimmune diseases [72–74].

However, the largest prospective trial of autologous HCT in lupus did find significant benefit: In 2006, Burt et al. published results of a single-arm study of autologous HCT in refractory lupus [31]. Fifty patients with refractory disease (including 20 mg or more of prednisone daily despite use of cyclophosphamide) were included in the study. Patients had significant disease, with inclusion criteria including WHO class III or IV glomerulonephritis, lung involvement, CNS involvement, vasculitis, myositis, transfusion-dependent autoimmune cytopenias, severe serositis, and refractory antiphospholipid syndrome; furthermore, out of those enrolled, cerebritis/myelitis and nephritis made up a significant number (18 and 10, respectively) of the transplant indications. The treatment consisted of GCSF/cyclophosphamide mobilization, conditioning with 200 mg/kg cyclophosphamide/rabbit ATG, and CD34 graft selection. HCT was found to be effective: transplant was associated with disease control and improved serologic markers of disease, and the primary outcomes, disease-free survival and overall survival at 5 years, were 50% and 84%, respectively. Toxicities included 2% TRM, 2 patients requiring intubation, and infectious complications including bacteremia/endocarditis, fungemia, peritonitis, zoster, and PCP pneumonia. Importantly, autologous HCT in this study permitted higher dose of cyclophosphamide (about 250 mg/m^2 in total including mobilization) and grafts underwent CD34 selection, offering two potential variations over a previous negative study of high-dose cyclophosphamide only in lupus [75]. While recognizing that measurements of autoantibodies are an imperfect biomarker, titers of both antinuclear antibodies (ANA) and anti-double-stranded DNA antibodies decreased after transplant.

In sum, studies of autologous HCT in lupus have had variable results ranging from very promising to prohibitively toxic. This may be related to variations in patient selection, conditioning regimen, graft manipulation (i.e., CD34+ selection),

and supportive treatments. As illustrated by Burt et al., potential benefits of autologous HCT over traditional high-dose cyclophosphamide without stem cell rescue include the use of very high doses of cyclophosphamide (250 mg/kg including mobilization dosing) and removal of differentiated alloreactive T cells with CD34+ selection; however, to better understand how and when auto-HCT should be applied in lupus, larger, comparative studies are needed to clarify patient selection, the optimal conditioning regimen including dose of cyclophosphamide, infectious risks (which have included CMV reactivation [66], and bacterial/fungal infections [31]), and necessity for CD34+ selection. Currently, there are no actively recruiting trials of stem cell transplantation for lupus listed on clinicaltrials.gov.

Next Directions

Across MS, SSc, and lupus, prospective and even randomized studies have demonstrated benefit. However, as we look to employ auto-HCT into clinical care and to minimize TRM, further studies are needed. Areas of particular interest include patient selection as it pertains to end organ function, conditioning regimen intensity, graft manipulation, disease-specific activity measurements for tracking the effects of therapy, and biomarkers for disease activity and relapse risk. This work will require collaboration between neurologists/rheumatologists and transplant physicians. Lastly, as we employ HCT for these autoimmune diseases, to truly expand availability to patients, we need greater awareness of its efficacy in the broader medical community as well as among payers.

Conclusion

Randomized studies in MS and SSc have found significant benefit to autologous HCT in the appropriate clinical situation. These patients tend to have refractory disease including moderate end organ involvement, but largely preserved end organ function. Further studies are needed to better define this population. In lupus, autologous HCT may be limited by greater toxicity and should be reserved for refractory disease though with preserved cardiac function.

Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest The authors declare no conflicts of interest.

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- • Of importance
- •• Of major importance

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