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REVIEW ARTICLE

Hematopoietic Stem Cell Transplantation for Systemic Sclerosis: Review of Current Status

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Abstract
Three prospective controlled clinical trials and numerous small series and case reports have confirmed that durable, drug-free remission in systemic sclerosis is possible via an autologous hematopoietic stem cell transplantation. Similar results have been seen in other autoimmune diseases. The exact mechanism by which this immune "reset" was achieved in some but not all cases remains elusive, but includes major reduction of autoreactive immune competent cells, re-establishment of T- and B cell regulatory networks and normalization of tissue niche function, particularly vascular. Some aspects regarding mobilization, conditioning and graft manipulation still remain open, but clearly a significant toxicity is associated with all effective regimens at present, and therefore patient selection remains a key issue. In the hematology/oncology arena, major efforts are being made to reduce genotoxic and other collateral toxicity induced by current mobilization and conditioning protocols, which may also translate to autoimmune disease. These include developments in rapid mobilization and antibody drug conjugate conditioning technology. If effective, such low-toxicity regimens might be applied to autoimmune disease at an earlier stage before chronicity of autoimmunity has been established, thus changing the therapeutic paradigm.

Key Points

There are now ample data to support the concept of a "once only" autologous hematopoietic stem cell transplantation (aHSCT) to turn off active autoimmune disease (AD) and "reset" self-tolerance.

The toxicity of aHSCT limits the current use of aHSCT to highly selected cases and has been recommended by several international learned societies (e.g., the European League Against Rheumatism [EULAR], American Society for Bone Marrow Transplantation [ASBMT], and the Scleroderma Clinical Trials Consortium).

A general move towards very early or even preclinical pre-emptive therapy for AD is gathering momentum.

If reduced toxicity conditioning regimens, e.g., antibody drug conjugates, currently being employed in hematology/oncology settings translate to AD, a new era of treatment may evolve.

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1 Introduction

In the pre-biologic era of the mid-1990s, a growing frustration with the available therapeutic options for autoimmune diseases (ADs) led to a dialogue between hematopoietic stem cell transplantation (HSCT) experts and specialists treating ADs in several centers [1–4]. This evolved into an international collaboration [4, 5] (4), which continues to this day.

The concept arose from case reports describing patients receiving an HSCT for a conventional hematological/oncological indication and in whom a coincidental AD showed improvement [6, 7] and animal model AD data which indicated positive outcomes after both allogeneic HSCT and autologous HSCT (aHSCT) [8, 9]. Several AD patients were successfully treated [2, 10–12], case reports became small series, and eventually two decades later, over 3000 patients have received an HSCT as treatment of an AD. This includes four prospective controlled trials which have established a positive role of aHSCT in systemic sclerosis (SSc), also called scleroderma, [13–15] and multiple sclerosis (MS) [16]. This has been extensively and recently reviewed [17–20] and as the biologics and other targeted therapies appeared, many indications such as rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) became less urgent (Fig. 1). However, no treatment of AD has induced durable drug-free remission as effectively as

has aHSCT, and despite the toxicity (see Sect. 2), there may still be a place for aHSCT in such cases, given the cost of lifelong treatment with biologics, drug retention rates of 80–50% [21, 22] and relapse after stopping biologics (80% in RA) [23].

Recent data (August 2018) from the European Group for Blood and Marrow Transplantation (EBMT) shows that a total of 2549 patients have received an aHSCT for AD in Europe, including 1259 for MS, 546 for SSc and 192 for CD [24]. Furthermore, over 40% of these transplants occurred in the past 7 years, the majority of which being for MS, SSc and CD.

Thus far, SSc has defied the search for an effective disease-modifying therapeutic agent, and not surprisingly has been, along with MS, the main focus of attention and will be the subject of this review.

2 Clinical Results

Table 1 shows the results of the only five published clinical trials of aHSCT in AD, three of which are in SSc. The Autologous Stem cell Transplantation International Scleroderma (ASTIS) [13] and the Scleroderma: Cyclophosphamide Or Transplantation (SCOT) [14] trials employed very similar selection criteria and control arms, but differed in that ASTIS used cyclophosphamide (CYC) in the mobilization phase and a non-myeloablative conditioning regimen, i.e., CYC 200 mg/kg + anti-thymocyte globulin (ATG) versus CYC 120 mg/kg + ATG + total body irradiation (TBI) in SCOT. Both employed a CD-34 selected graft. The outcomes were positive in both trials regarding the primary outcomes, i.e., event-free survival (EFS) in ASTIS (events being death or permanent end organ failure) and, in SCOT, a Global Rank Composite Score at week 54.

The treatment-related mortality (TRM) differed: 10% at 12 months in ASTIS, and in the SCOT trial, 3% at 54 months and 6% at 72 months. There was no TRM in the SCOT trial in the first 12 months after transplant, in contrast to ASTIS and other studies employing CYC (2–4 g/m^2 mobilization and 200 mg/kg conditioning). The reasons for this difference remain obscure given that early registry data have indicated that the increased toxicity of myeloablative regimens overall was not justified by a significant increased efficacy [25]. In the same study, low-intensity regimens such as thiotepa had a significantly lower efficacy. It could be that the higher doses of CYC are especially toxic to SSc-associated overt or covert cardiac disease, and indeed more intensive cardiac screening is now recommended (see Sect. 3). It could also be that the higher numbers of patients transplanted in ASTIS (twice those of SCOT) account for the difference, or that with time the increased incidence of secondary malignancy in SCOT may surpass that of ASTIS.

In addition, the same early registry data study from 2005 indicated that regimens which included CYC in the mobilization protocol had higher efficacy than those which did not [25]. SCOT used only granulocyte colony-stimulating factor (G-CSF) for mobilization, but perhaps this potentially negative factor was overshadowed by the more intensive myeloablative conditioning regimen.

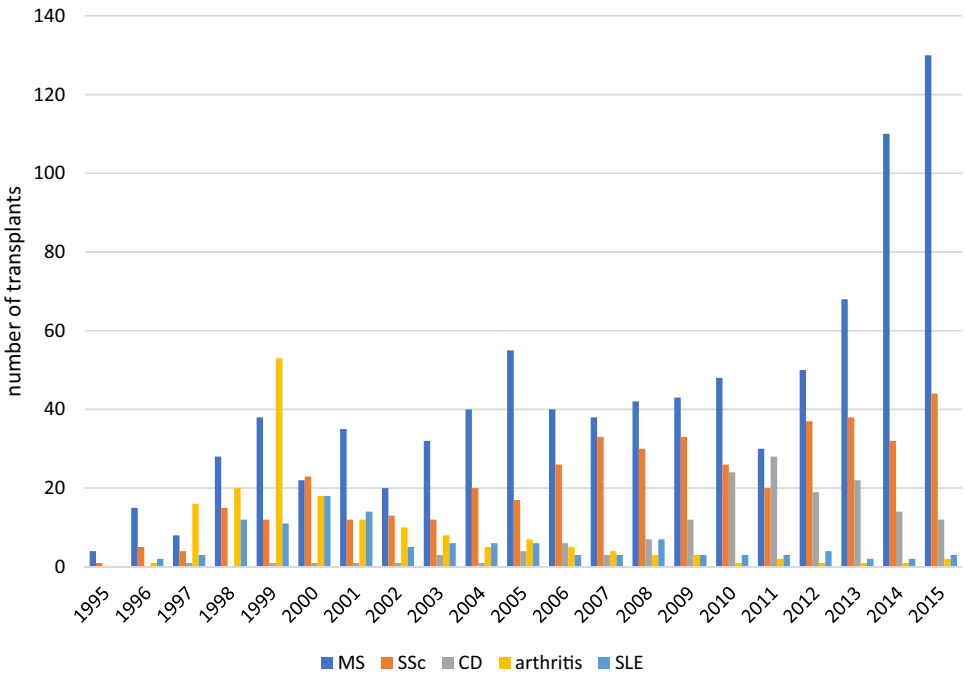

Fig. 1 Transplants per year by disease. *CD* Crohn's disease, *MS* multiple sclerosis, *SLE* systemic lupus erythematosus, *SSc* systemic sclerosis. Adapted from Snowden et al. [18]

Table 1 Randomized prospective aHSCT clinical trials in autoimmune disease

	ASTIS systemic sclerosis [13]	SCOT systemic sclerosis [14]	ASSIST systemic sclerosis [15]	ASTIC crohns disease [68]	Randomised prospective trial in multiple sclerosis [16]
PI	Van Laar, UK	Sullivan, USA	Burt, USA	Hawkey, UK	Burt, USA
Patients	156	75	19	46	110
Mobilisation	CYC 4 g/m^2 + G-CSF	G-CSF	CYC 2 g/m^2 + G-CSF	CYC 4 g/m^2 + G-CSF	CYC 2 g/m^2 + G-CSF
Graft selection	CD 34 selection	CD34 selection	None	CD34 selection	None
Conditioning	CYC 200 mg/kg ATG rabbit 7.5 mg/kg	CYC 120 mg/kg + TBI ATG equine 90 mg/kg	CYC 200 mg/kg ATG rabbit 6.5 mg/kg	CYC 200 mg/kg ATG rabbit 7.5 mg/kg	CYC 200 mg/kg ATG rabbit 6 mg
Control	Monthly CYC 750 mg/m^2 IVI × 12	Monthly CYC 750 mg/m^2 IVI × 12	Monthly CYC 1 g/m^2 x 6	Mobilised: Transplant delayed 12 months	Disease modifying therapy
Primary end point	Event free survival (EFS) organ failure and death	Composite end point at 54 months	Skin score and/or LFTs at 12 months	Sustained remission at 12 months	Disease progression
Outcome	Significantly better EFS 10% TRM	Significantly better EFS. 3% TRM	Significant difference 0% TRM	No sustained difference 4.5% TRM	Less progression. 0% TRM

aHSCT autologous hematopoietic stem cell transplantation, *ATG* anti-thymocyte globulin, *CYC* cyclophosphamide, *G-CSF* granulocyte colony-stimulating factor, *IVI* intravenous infusion, *LFTs* liver function tests, *PI* principle investigator, *TBI* total body irradiation, *TRM* treatment-related mortality

It should be noted that registry data is often incomplete. In the EBMT registry of MS transplants, details of the conditioning regimens were absent in 9.5% of cases [26].

The ASSIST trial was smaller (19 patients) than both ASTIS and SCOT and used lower CYC doses for mobilization (2 g/m^2 vs 4 g/m^2), a non-myeloablative regimen (CYC/ATG) and no graft manipulation [15]. The primary outcome was improvement of the modified Rodnan skin score (mRSS) of > 25% and/or increased forced vital capacity of > 10% at 12 months and was positive, with benefit sustained out to at least 2 years. There was no TRM. A retrospective American and Brazilian study of 90 SSc patients treated with the intermediate intensity CYC/ATG regimen and an unselected graft showed a 6% TRM and 70% relapse-free survival up to 5 years. Eight of the 22 relapses were fatal [27].

3 Patient Selection

A major issue which emerged with time was patient selection. From the outset, it was advised that severely affected patients with irreversible end organ damage and precarious clinical state should not be transplanted, based on decades of experience in the hematology/oncology setting [28]. However, as the experience in AD grew, further refinements were added to patient selection in the various ADs, especially SSc. Patients with severely impaired cardio/pulmonary function were particularly at risk of TRM, especially during the phases of hyperhydration during CYC infusion and the cytokine storm induced by ATG and alemtuzumab. Protocols were adjusted accordingly with consensus selection criteria and organ screening recommendations have since been published (Table 2) [29, 30]. In essence, these recommendations are aimed at suggesting upper and lower limits to various functional parameters measuring pulmonary artery hypertension, left ventricular function, arrhythmias and pulmonary function.

Importantly, cardiac magnetic resonance imaging (MRI) has been recommended, since it has become clear that potentially fatal cardiac involvement in SSc may be more extensive than initially suspected [31].

In a study of causes of death in SSc from the EUSTAR database, 55% were directly attributable to the SSc, 35% pulmonary fibrosis, 26% pulmonary artery hypertension and 26% all cardiac [32].

It is hoped, but not guaranteed, that more careful cardiopulmonary screening will reduce the TRM, but clearly the experience of the treating center, including accreditation by the Joint Accreditation Committee of the International Society for Cellular Therapy (ISCT)-Europe and EBMT, known as JACIE, is of paramount importance [30]. Some cases of SSc have undergone successful aHSCT despite significant cardiac disease in such centers, including the use of defibrillating pacemakers (Matucci-Cerinic M., personal communication).

Clearly early rather than late cases are preferred since the most rapid deterioration of lung function occurs in the first 3–5 years of disease [33] and, although slowing or arrest of lung function deterioration due to fibrosis is to be expected, significant improvement after any treatment is unlikely [34]. Some case reports of markedly improved lung function and

Table 2 Cardio/pulmonary exclusion criteria for aHSCT for systemic sclerosis Adapted from Farge et al. [29]

Cardiac
Baseline (resting) PASP > 40 mmHg or mPAP > 25 mmHg
PASP > 45 mmHg or mPAP > 30 mmHg after fluid challenge
Decrease or lack of augmentation of cardiac output after fluid challenge
Pulmonary vascular resistance > 3 Wood units
D-sign of septal bounce on cardiac MRI
LVEF < 45%
Unrevascularized severe coronary artery disease
Untreated severe arrhythmia
Cardiac tamponade
Constrictive pericarditis
Pulmonary
FVC < 65%
DLCO-SB < 40%

If pre-HSCT echocardiogram, CMR, and cardiac catheterization with and without fluid challenge demonstrate no contraindication, patients with lower DLCO and FVC may be considered candidates. Patients should be strongly encouraged to stop smoking

aHSCT autologous hematopoietic stem cell transplantation, *CMR* cardiac magnetic resonance, *DLCO-SB* single-breath carbon monoxide diffusion capacity, *FVC* forced vital capacity, *LVEF* left ventricular ejection fraction, *mPAP* mean pulmonary artery pressure, *MRI* magnetic resonance imaging, *PASP* pulmonary artery systolic pressure

reduced High Resolution Computer Tomography (HRCT) opacification most likely reflect reduced inflammatory alveolitis rather than removal of fibrosis and re-establishment of alveolar/capillary architecture [35].

For reasons which are incompletely understood, significant improvement in symptoms related to hypomobility of the gastrointestinal tract, e.g., esophageal reflux, blind loop syndrome and megacolon rarely respond to any immune-modulating treatment, including aHSCT [36]. This may be due to established atrophy and fibrosis resulting from loss of myenteric plexus function early in disease [37].

In general, patients with the diffuse cutaneous form of SSc (dcSSc) have been the main target for aHSCT, but given the degree of overlap between dcSSc and the limited cutaneous form (lcSSc), a final decision to offer aHSCT to a patient with SSc should be a consensus between SSc experts and transplantation colleagues.

Currently, efforts are underway to determine which patients may be poor responders to conventional CYC or other immunomodulatory therapy at an early stage of the treatment. Based on clinical and laboratory data from the ASTIS and other studies, this may facilitate the optimal timing for an aHSCT (van Laar J., personal communication).

4 Relapse

Relapse after an apparently successful aHSCT has been observed in all AD, and the prediction of such an event is not currently possible. It has been observed that some patients respond well to immunodulatory agents which pre-transplant were ineffective. Others have undergone a successful second transplant.

5 Mechanisms

Most patients experience a marked improvement in the mRSS and other inflammatory features of SSc immediately after an aHSCT, most likely due to the known potent anti-inflammatory components of the mobilizing and conditioning regimens. In addition, the period of profound immunosuppression during the initial aplasia and later slow immune reconstitution adds to this effect.

However, in those patients who experience durable remissions years after the "once only" immunosuppressive impact of aHSCT has worn off, there must have been a re-setting of autoimmunity to account for the sustained improvement. In addition, improved tissue structure and function has been observed, so called "de-remodeling" or "reverse remodeling," involving cells which are not directly targeted by the agents (CYC, ATG, alemtuzumab, etc.) employed in aHSCT. Examples include normalization of microcapillary structure in nail folds [38, 39] and skin [40], improved macrovascular changes in gastric antral vascular ectasia (GAVE) [41], and reversed collagen deposition in skin [42]. In other cases, secondary skin organs such as hair follicles and sweat glands have begun to function again after years of inactivity (Fig. 2).

This implies some form of niche management must have taken place, presumably due to removal of autoaggressive putative cells, allowing normal homeostasis and repair to operate. Exactly which cells these are remains enigmatic, but presumably they must be susceptible to the agents used in aHSCT and therefore are most likely of hematopoietic origin. One candidate is the plasmacytoid dendritic cell which forms a bridge between the innate and adaptive immune system and mediates immune reactivity or tolerance [40, 43].

Attempts to target specific components of the immune system such as B cells, T cells and pan-lymphocyte monoclonal antibodies have not induced long-term drug-free remission.

Perhaps it requires the broad based, major reduction of a whole network of dysfunctional immune competent cells to allow re-establishment of a normal self-tolerant system. Some clues as to how this may take place are emerging.

6 Immune "Reset"

Early on it was appreciated that despite full reconstitution of the immune system post-aHSCT, some responding patients with systemic lupus erythematosus (SLE) and MS remained in remission. In seven SLE patients, both autoreactive and protective memory were lost post-aHSCT and replaced by normal B cell numbers and an expanded T-cell repertoire as evidenced by T-cell receptor Vβ gene usage at 3 years post-aHSCT. In addition, increased regulatory T cells (T_{reg}) and recent thymic emigrants were evidence of increased thymic function post-aHSCT [44].

In MS, in CD4+ T cells, dominant T cell receptor (TCR) clones present before treatment were undetectable following reconstitution, and patients largely developed a new repertoire. However, dominant CD8+ clones were not effectively removed, and the reconstituted CD8+ T-cell repertoire was created by clonal expansion of cells present before treatment. Patients who failed to respond to treatment had less diversity in their T-cell repertoire early during the reconstitution process [45].

From the Utrecht group it was found that aHSCT induced functional renewal of regulatory T cells as well as a strong T_{reg} TCR diversification in JIA and juvenile dermatomyositis. However, adding T_{reg} to the graft did not lead to additional clinical improvement, but resulted in delayed donor T-cell reconstitution in a murine proteoglycan arthritis model [46]. This emphasizes the complexity of immune homeostasis following aHSCT including the normalisation of regulatory B cell networks (reviewed in [47]).

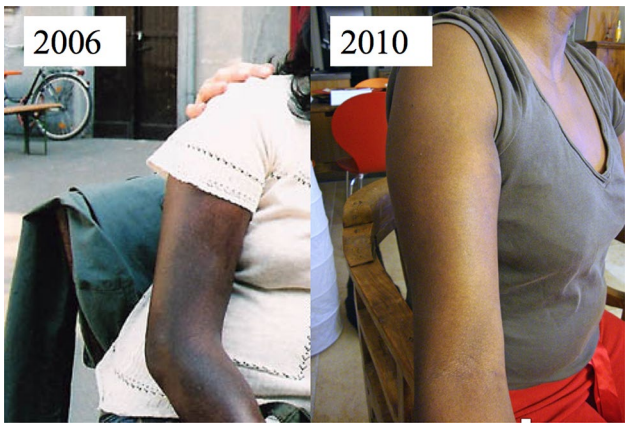

Fig. 2 Normalization of skin after aHSCT for SSc in a patient of Indian origin. *2006* Pre-transplant; thickened, shiny and hyperpigmented dry itchy skin; flexion contracture of the elbows. HSCT performed in 2007. *2010* Normal skin texture and pigmentation; no joint contractures; return of sweat gland and hair follicle function. ANA and Scl70 (Topo1) became and remained negative. Patient status in April 2019: Full drug-free remission with normal skin. *aHSCT* autologous HSCT, *ANA* antinuclear antibodies, *HSCT* hematopoietic stem cell transplantation, *SSc* systemic sclerosis

Fewer data are available for SSc after transplant. Comparing five "responders" to five "non-responders" at 6 years follow-up, "non-responders" had a more rapid T-cell immune reconstitution [48]. More extensive mechanistic data are expected soon from the SCOT study (Sullivan, personal communication).

Several groups have shown that a dysregulated dominant T helper 2 (T_h2) cytokine profile exists in active SSc and that the T_h1/T_h2 ratio may normalize after aHSCT [49] [50].

The hope is that eventually a combination of clinical features and in vitro tests will provide a "responder" profile both for selecting cases suitable for an aHSCT and to determine which cases may require maintenance immunomodulation post-transplant. Some gene expression data in SSc suggests that predominant patterns such as "inflammatory" or "pro-fibrotic" patterns may be used to direct therapy [49–52].

7 The Future

7.1 Pre-Emptive AD Therapy

The past several years have seen an increasing interest and literature regarding the concept of pre-emptive treatment of AD, also referred to as preventative treatment [53]. The concept arose from immune regulatory data, especially autoantibody and cytokine levels, obtained from sera collected years before the first symptoms of AD became manifest [54]. One of the most extensive of such databases is the American Department of Defense Serum Repository (DODSR) in which 60 million sera from 10 million individuals are stored [55]. Fifty-five patients who later fulfilled the criteria for SLE manifested enhanced type II interferon (IFN) activity, followed by elevated INF-α and B-cell stimulator levels. Cases were distinguished by multivariate random forest models incorporating IFN-γ, macrophage chemoattractant protein (MCP)-3, anti-chromatin and anti-spliceosome antibodies (accuracy 93% > 4 years pre-classification; 97% within 2 years of SLE classification) [56].

Similar data were demonstrated in a study of 790 individuals randomly selected at health fairs and screened for double-stranded DNA (dsDNA), chromatin, SSA/Ro, SSB/La, Sm, Sm/RNP, RNP, ribosomal P, Scl-70, centromere B, and Jo-1. Fifty-seven (7%) were antinuclear antibody (ANA) positive, and elevated proinflammatory cytokines (IFN-γ, tumor necrosis factor [TNF], interleukin-17 [IL-17] and G-CSF) showed a stepwise increase from ANA-negative healthy, ANA-positive healthy and SLE patients. In contrast, only SLE patients showed elevated IFN-α, IFN-β, IL-12p40 and stem cell factor/c-kit. In addition, BlyS was elevated in SLE patients, but decreased in ANA-positive

healthy individuals, and only in SLE patients was the protective factor IL-1 RA reduced [57].

Similar data have been observed in other ADs such as "pre-rheumatoid arthritis" [58].

In SSc, there are limited data so far, though this may change with increasing awareness of the Very Early Diagnosis Of Systemic Sclerosis (VEDOSS) project [59]. Patients with ANA positivity, Raynaud's phenomenon and puffy fingers are so classified, and combined with gene expression "big data" mentioned above [52] may enable a pre-emptive therapeutic strategy for SSc.

7.2 Low-Toxicity Pre-emptive Treatment Regimens

A randomized placebo-controlled study in 83 "pre-RA" patients (anti-citrullinated peptide antibody (ACPA) or IgM rheumatoid factor positive arthralgia, but no objective arthritis) using dexamethasone 100 mg intramuscular injection at baseline showed no prevention of arthritis development after 6 weeks [60].

For SSc, a similar pre-emptive "Hit Hard and Early" study is being planned using a 12-week, randomized, double-blind, placebo-controlled trial analyzing the effects of high-dose intravenous methylprednisolone in very early SSc [61]. Thirty patients who fulfill the criteria for very early SSc will be randomly assigned in a 2:1 ratio to receive either a 1-g intravenous infusion of methylprednisolone or a placebo on 3 consecutive days over 3 consecutive months. In this study, the primary endpoint will be the change in capillary density between baseline and after 12 weeks of treatment.

It would be enticing to think that a relatively non-toxic, targeted, immunomodulatory regimen might turn off the autoaggressive immune response before an established and recalcitrant dysregulation is established. The recently published PRAIRI study has dampened some of these hopes [62]. Patients with arthralgia and positive ACPA, but no objective synovitis were randomized to receive one course of rituximab or placebo. Both groups developed clinically manifest RA with the same incidence, but with a 12-month delay in the treated group.

A superficial interpretation could be that the progress to RA was already inevitably programmed, and that B-cell reduction was insufficiently profound to prevent this. An alternate explanation could be that the process leading to RA is more complex than just B-cell dysregulation and that a more eclectic immune modulation such as aHSCT is still required to "reset" autoimmunity.

Unfortunately, currently there are no conditioning regimens available with such a potential and of a sufficiently low toxicity as to be acceptable to patients with minimal or even asymptomatic pre-clinical disease. This may change.

8 New Regimens

In the fields of hematology and oncology, efforts are underway to develop such mobilizing and conditioning strategies for, among other indications, non-malignant hematopoietic stem cell-based disorders such as sickle cell disease, thalassemia, metachromic leukodystrophy and various storage diseases. Currently, only an allogeneic HSCT or gene therapy is curative, but carries all the toxicity of conventional conditioning regimens and, in the case of allo HSCT, graft versus host disease (GvHD).

To circumvent this, antibody drug conjugate (ADC) technology is being refined to avoid the genotoxic and off-target toxicity of conventional regimens [63, 64]. Also referred to as a "Trojan horse" approach, ADC is based on a monoclonal antibody targeting a specific cell surface receptor and linked with a cytocidal toxin. The antibody transports the toxin into the cell, where it is then released to block a vital cell function, resulting in cell death. Various toxins targeting various pathways such as protein synthesis or microtubule formation have been used in oncology for some years and are being continually refined. Their application to AD is now being considered.

Autologous HSCT has now been recommended as treatment for selected cases of SSc by the European League Against Rheumatism (EULAR) [65], the American Society for Bone Marrow Transplantation (ASBMT) [66] and the Scleroderma Clinical Trials Consortium and Canadian Scleroderma Research group [67], and is reimbursed in several countries, including the UK, the Netherlands and Switzerland, but is limited by the inevitable toxicity of current regimens. If such toxicity could be reduced and combined with pre-emptive or very early treatment, a once only "reset" of an autoaggressive immune system could usher in a new era of therapy for AD, including SSc.

9 Conclusion

The use of aHSCT in treating severe therapy-resistant AD is being increasingly employed, and a combination of uncontrolled case series and controlled randomized trials has established that in many cases, a durable, drug-free "reset" of autoimmune processes is possible. In addition, clinically relevant reverse remodeling of tissues has been documented. Mostly MS and SSc are being so treated, with around 66% of cases showing an initial positive outcome.

The toxicity of all current regimens limits aHSCT to highly selected AD cases. Efforts are underway to develop less toxic but equally effective mobilizing and conditioning regimens in the hematology/oncology setting, and if

successful, their translation to early onset/poor prognosis AD could usher in a paradigm shift.

Compliance with Ethical Standards

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