Autoimmune Disease

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Tobias Alexander, Basil Sharrack, Montserrat Rovira, Riccardo Saccardi, Dominique Farge, John A. Snowden, and Raffaella Greco

92.1 Introduction

Autoimmune diseases (ADs) are a heterogeneous group of diseases affecting 8–10% of the Western population, which constitute a heavy burden to society and are often debilitating and disabling for affected individuals. ADs are defined as an impairment of the immune system resulting in the loss of immune tolerance against self-tissues, by the existence of autoreactive T and B cells and by a complex mechanism of multifactorial aetiology, across genetics and environmental factors (Alexander and Greco 2022). Autoimmunity is also linked to autoinflammation, having common features as the activation against self, with subsequent systemic inflammation (Chap. 93).

Current therapeutic strategies for AD are based on systemic immunosuppression (IS) or targeted biologic disease-modifying therapies (DMTs), which ameliorate symptoms and halt progression in the vast majority of patients but usually require continuous administration and

T. Alexander
Department of Rheumatology and Clinical Immunology, Charité-University Medicine Berlin, Berlin, Germany
e-mail: tobias.alexander@charite.de

B. Sharrack
Academic Department of Neuroscience and Sheffield NIHR Translational Neuroscience BRC, Sheffield Teaching Hospitals, NHS Foundation Trust, University of Sheffield, Sheffield, UK
e-mail: Basil.Sharrack@sth.nhs.uk

M. Rovira
Hematopoietic Stem Cell Transplantation Unit, Hematology Department, Institute of Hematology and Oncology, Hospital Clínic, Barcelona, Spain

August Pi i Sunyer Biomedical Research Institute, Barcelona, Spain

Institute Josep Carreras, Hospital Clínic, Barcelona, Spain
e-mail: mrovira@clinic.cat

R. Saccardi
Department of Haematology, Careggi University Hospital, Florence, Italy
e-mail: riccardo.saccardi@unifi.it

D. Farge
Unité de Médecine Interne (UF 04): CRMR MATHEC, Maladies auto-immunes et thérapie cellulaire, Centre de Référence des Maladies auto-immunes systémiques Rares d'Ile-de-France FAI2R, EBMT CIC 0461, Hôpital St-Louis, AP-HP, Paris, France

Université de Paris-Cité, IRSL, URP 3518, Eq 3: MATHEC-EUROCORD, Paris, France
e-mail: dominique.farge-bancel@sls.ap-hop-paris.fr

J. A. Snowden
Department of Haematology, Sheffield Teaching Hospitals NHS Foundation Trust, Royal Hallamshire Hospital, and University of Sheffield, Sheffield, UK
e-mail: john.snowden@sth.nhs.uk

R. Greco (✉)
Unit of Hematology and Bone Marrow Transplantation, IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy
e-mail: greco.raffaella@hsr.it

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may be associated with long-term side effects and substantial costs. Although biologic DMT has improved specificity and efficacy in the treatment landscape, cure remains elusive, and many patients still suffer from progressive disability with shortened life expectancy and comorbidity.

Initially supported by preclinical animal models and 'serendipitous' case reports, auto-HCT has grown as a promising and feasible treatment option for severe treatment-resistant patients, especially in diseases for which effective therapies are lacking. The annual number of patients treated with autologous HCT is constantly increasing (Alexander and Greco 2022), and AD are among the fastest growing disease category reported to the EBMT for autologous HCT (Passweg et al. 2021). Allo-HCT has also been undertaken, although caution related to its intrinsic risks has precluded widespread application.

The EBMT Autoimmune Diseases Working Party (ADWP) was established in 1997 by Alois Gratwohl, Alberto Marmont, Alan Tyndall and Athanasios Fassas, who developed the registry covering AD indications and produced early guidelines based on consensus opinion (Tyndall and Gratwohl 1997).

Subsequently, the ADWP built productively on these initial achievements, generating studies from the growing registry and developing relationships with other specialist societies, culminating with successful publication of three randomised controlled trials (van Laar et al. 2014; Hawkey et al. 2015; Mancardi et al. 2015), along with updated guidelines for clinical practice (Snowden et al. 2012), immune monitoring and biobanking (Alexander et al. 2015; Cencioni et al. 2022).

With increasing evidence, the guidelines have become more disease specific. A successful international collaboration involving also non-European experts resulted in the EBMT guidelines for auto-HCT in systemic sclerosis (Farge et al. 2017b). A further collaborative review with the European Crohn's and Colitis Organisation (ECCO) has included recommendations for patient selection, transplant technique and follow-up of HCT in patients with Crohn's disease (Snowden et al. 2018). EBMT guidelines for MS and other neurological diseases were published in 2020 (Sharrack et al. 2020). Guidelines for best practices were also provided during the COVID-19 pandemic (Greco et al. 2021, 2023).

The current state of the EBMT database in relation to various ADs is summarised in Tables 92.1 and 92.2. At the time of writing, over 4000 patients receiving HCT for an AD have been reported to the EBMT, the largest international database, with activity reported to other registries adding substantially to the worldwide numbers.

Based on this reported activity, this chapter will cover the main neurological, rheumatological and gastroenterological indications for auto-HCT, along with reference to the rare AD indications and allogeneic HCT. More detailed literature can be sourced from recently published reviews (Achini-Gutzwiller et al. 2022; Alexander and Greco 2022; Snowden et al. 2017).

Table 92.1 Overview of data reported to the EBMT database (March 2023)

Patients	4055
Transplant procedures	4140
Centres/countries	323/44
Autografts/allografts	3854 (93%)/286 (7%)
Median age at autografts/allografts (years)	38 (3–76), 11 (<1–64)
Male/female	40/60%

Table 92.2 Distribution of diagnosis in the EBMT database (March 2023)

Multiple sclerosis (MS)	*2132*	*Haematological diseases*	*161*
Connective tissue diseases	*1028*	Immune thrombocytopenia purpura (ITP)	42
Systemic sclerosis	835	Haemolytic anaemia	36
Systemic lupus erythemathosus	126	Evans syndrome	24
Polymalgia/dermatomyositis	18	Other	60
Sjögren's syndrome	6	*Vasculitis*	*67*
Antiphospholipid syndrome	6	Granulomatosis with polyangiitis (GPA)	12
Other	37	Behcet's disease	18
Arthritis	*209*	Takayasu's arteritis	3
Rheumatoid arthritis	82	*Polyarteritis nodosa* (PAN)	4
Juvenile chronic arthritis (JIA):		*Eosinophilic granulomatosis with polyangiitis* (EGPA) (EGPA)	2
• Systemic JIA	74	Other	28
• Other JIA	19	*Other neurological diseases*	*146*
• Articular JIA	22	Chronic inflammatory demyelinating polyneuropathy (CIDP)	65
Psoriatic arthritis	3	Neuromyelitis optica	29
Other	9	Myasthenia gravis	11
Inflammatory bowel diseases	*283*	Other	41
Crohn's disease	233	*Insulin dependent diabetes mellitus (IDDM)*	*20*
Coeliac disease	18	*Other*	*94*
Other	32		

92.2 Mechanisms of Action

HCT represented an opportunity to gain insights into the aetiology and pathogenesis of AD, characterised by aberrant activation of the immune system with failure of the immune regulation to maintain adapted tolerance. HCT exerts its therapeutic effect through various mechanisms, including the immunosuppressive conditioning regimen able to eradicate the autoreactive immunologic memory, and the regeneration and renewal of the immune system, leading to the re-induction of immune tolerance to rewire aberrant immune response toward self-antigens (Cencioni et al. 2022; Lima-Junior et al. 2021). The effect of HCT on immunologic renewal has been the focus of many mechanistic studies. They collectively demonstrated that many of the age- or autoimmune-mediated immune disturbances may improve or even resolve. For example, immune reconstitution studies indicated a predominant repopulation of CD27-IgD+ naïve B cells (Alexander et al. 2009; Arruda et al. 2018), a stable output of recent thymic emigrants (RTE) (Farge et al. 2017a; Muraro et al. 2005), leading to a re-diversification of the receptor repertoire, and recurrence of both regulatory B and T cells in various disease settings (Alexander et al. 2013; Lima-Junior et al. 2021). Allo-HCT has been less well explored, although there is an element of immune replacement and evidence for a 'graft-versus-autoimmune effect' (Greco et al. 2019). Further, areas for exploration include the impact of the microbiome on autoimmunity and the impact of HCT (Alexander et al. 2021).

92.3 HCT for Multiple Sclerosis (MS)

Since the first case report of using auto-HCT as a treatment for MS was published in 1995 (Fassas et al. 1997), the EBMT registry has now accumulated over 2000 patients (Table 92.2). This treatment was initially used in patients with advanced and progressive disease as a rescue therapy with limited efficacy. More recently, its use in patients with active relapsing MS has been associated with prolonged clinical and MRI responses and, in some cases, significant improvement in disability to a degree rarely seen with disease-modifying therapies (DMT) (Muraro et al. 2017b;

Tolf et al. 2019). The bulk of the data has been provided by observational cohort studies in which patients failing to respond to standard DMT were treated with an auto-HCT. Burman et al. identified the four most rigorously conducted cohort studies in which a total of 188 relapsing MS patients received auto-HCT (Burman et al. 2018). In these studies, PFS was observed in 70–91% of patients at 5 years (where progression is defined as a deterioration of at least 0.5–1 points from baseline in the Expanded Disability Status Scale (EDSS). Furthermore, no evidence of disease activity (NEDA), defined as the absence of clinical relapses, disability progression and MRI disease activity, was observed in 70–92% of patients at 2 years post-transplantation (Boffa et al. 2021; Muraro et al. 2017a). Such results were compared with DMT efficacy data reported in registration studies (Muraro et al. 2017a). Higher rates of NEDA were achieved with auto-HCT than with any other DMT, including those that are considered to have high efficacy, although these studies included different patient populations. Only two randomised trials of auto-HCT have been reported in the literature. The first was a phase II trial which showed auto-HCT to be more effective than mitoxantrone on MRI disease activity (Mancardi et al. 2015). The second was a phase III randomised controlled trial which showed that auto-HCT resulted in prolonged time to disability progression compared to DMTs. Improvement in the EDSS score (3.4–2.4 vs 3.31–3.98), reduction in relapse rate (1 vs 39) and reduced disability progression (6% vs 60%) were seen in the aHCT group vs controls, respectively. There were no significant side effects and no treatment related mortality in the aHCT arm (Burt et al. 2019). Three phase III randomised controlled trials, aimed to compare auto-HCT to DMTs are currently recruiting (BEAT-MS: Identifier: NCT04047628, RAM-MS Identifier: NCT03477500, STAR-MS: EudraCT Identifier: 2019-001549-42) and others are expected to be started (Sharrack et al. 2022). The conditioning regimens used in MS vary between treatment centres. The balance of efficacy and acceptable safety profile of 'intermediate intensity' regimens, i.e. either the specific 'BEAM + ATG' regimen or the more generic regimen of CY 200 mg/kg combined with ATG, led to their recommended use in the current EBMT ADWP guidelines (Sharrack et al. 2020). Single-centre data suggest that 'high-intensity' regimens, incorporating Busulfan and ex-vivo T-cell depletion, have higher rates of PFS but potentially greater toxicity, including TRM (Atkins et al. 2016). Retrospective registry data suggest that graft purging has no added benefit to the transplant outcome (Sharrack et al. 2020).

Currently, auto-HCT is recommended as a standard of care for patients with active relapsing MS failing DMTs and as a treatment option for patients with progressive MS with evidence of disease activity or patients with aggressive MS as a first-line treatment. The best results are seen in patients who are not older than 45 years, have had the illness for less than 10 years, are not very disabled (EDSS $\leq$6) and have active disease with evidence of enhancement on their MRI. The ADWP has recently provided guidelines for the management of HCT in MS and other immune-mediated neurological ADs (Sharrack et al. 2020), and current clinical trials are summarised in a recent review (Sharrack et al. 2022). Updated interspecialty guidelines have been finalised following a joint EBMT-ECTRIMS workshop (Muraro et al. unpublished).

92.4 HCT for Systemic Sclerosis (SSc)

Over the past 25 years, results from large European prospective observational studies and analysis of the European Scleroderma Trials and Research Group (EUSTAR) registry data base (Elhai et al. 2017) confirmed that SSc patients benefit only marginally from standard immunosuppressive drugs, including CY, with a progressive increase in SSc-specific mortality, predominantly related to cardiac (31%) and pulmonary causes (18%). Since three successive randomised trials, namely, ASSIST [American Scleroderma Stem cell versus Immune Suppression Trial, (Burt et al. 2011)], ASTIS

[Autologous Stem cell Transplantation International Scleroderma trial, (van Laar et al. 2014)] and SCOT [Scleroderma: Cyclophosphamide Or Transplantation, (Sullivan et al. 2018)], have now demonstrated that auto-HCT is superior to CY for early rapidly progressive SSc in terms of long-term survival as well as improvement of lung function and skin fibrosis, AHCT for early severe dcSSc patients is now recommended with a grade I level of evidence by the EBMT (Snowden et al. 2022), and by the American Rheumatism Association (ACR) and The European League Against Rheumatism (Kowal-Bielecka et al. 2017) and the American Society for Transplantation and Cellular Therapy (Majhail et al. 2015), with increased transplant activity reported to the EBMT registry and worldwide over the last decade.

Of note, ASSIST and ASTIS utilised a non-myeloablative regimen of cyclophosphamide (200 mg/kg total dose) and rabbit antithymocyte globulin (rATG), and the main difference between the two studies was that ASSIST mobilised stem cells with 2 g/m^2 CY and infused unmanipulated peripheral blood stem cells (PBSC), while ASTIS mobilised stem cells with 4 g/m^2 CY and infused CD34+ selected PBSC. The SCOT trial used no CY with only G-CSF for mobilisation and a lower dose of CY (120 mg/kg total dose) for conditioning plus TBI (800 cGy/4 fractions over 2 days/200 cGy to lungs and kidneys with shielding), which induces myeloablation.

In addition, patient selection was shown to directly affect transplant outcomes (Henes et al. 2021) with specific concern for cardiac involvement, undetected by echocardiography alone, becoming clinically overt during the transplant procedure, under the stress of fluid overload, CY and ATG administration and sepsis. Current guidelines recommend auto-HCT for SSc patients, according to the 2013 ACR/EULAR classification criteria (van den Hoogen et al. 2013), aged 18–65 years (certain paediatric indications may be considered on a case-by-case basis), with disease duration less than 2 years and a clinical phenotype of diffuse SSc, a modified Rodnan score (mRSS) greater than 20, a sedimentation rate >25 mm or an elevated C-reactive protein >5 mg/L or a haemoglobin level less than 11 g/dL not explained by causes other than the evolvability of SSc; or less than 5 years SSc with a) a modified Rodnan skin score ≥15 *plus* severe organ involvement in respiratory, cardiovascular or renal systems or b) a mRSS <14 (limited skin involvement), in case of coexisting severe progressive lung involvement (alteration of FVC and/or TLC ≥10% and/or DLCO ≥15% compared to an initial value obtained 12 ± 6 months previously). Treatment should be performed in JACIE-accredited centres where combined expertise from SSc disease specialists and dedicated transplant teams can assess and follow patients before, during and after the procedure according to Good Clinical Practices (Snowden et al. 2017). Since toxicity and efficacy arise from individual patient selection and the conditioning regimen, different chemotherapies may account for subtle differences in results, and further studies are warranted to analyse the use of attenuated conditioning regimens according to cardiac function and risk for renal crises (Burt et al. 2021).

92.5 HCT for Systemic Lupus Erythematosus (SLE)

Despite the era of DMTs, a considerable number of patients with SLE do not achieve clinical remission, with an accumulating risk of organ failure and increased mortality. For these patients, autologous HCT has been applied since 1996 with more than 300 cases reported worldwide (Alexander and Greco 2022). The two largest experiences on auto-HCT for SLE come from the EBMT data registry (n = 53; mean follow-up, 25 months) and from a single-centre trial performed at the Northwestern University (n = 50; mean follow-up, 29 months), both demonstrating a probability of 5-year DFS of 50% despite discontinuation of chronic immunosuppression. Subsequently, a follow-up study from the EBMT registry reported the outcome of auto-HCT in SLE with various regimens between 2001 and 2008 (n = 28; median follow-up, 38 months; range, 1–110 months) (Alchi et al. 2013).

Although PFS in this study was only 29% at 5 years, TRM had gradually improved. In addition, this study indicated that CD34-selection was associated with a significantly reduced risk for relapse. More recently, Richard Burt reported a remission rate of 92% at 1 year, 81% at 2 years, 71% at 3 years, and 62% at 4 and 5 years post-HCT, respectively, for 26 patients receiving a CYC/ATG/RTX conditioning (Burt et al. 2018). Long-term outcomes (Burt et al. 2021) are available from two independent Chinese reports, both with 10-year follow-up, demonstrating remarkable clinical responses with PFS of 86% and 68%, respectively, while TRM across both studies was only 2%.

Summarising the results from the most relevant 15 studies in the field covering 339 patients with a median follow-up of 5 years, the median remission rate achieved was 65% with a median mortality of 8%, with a gradual decline of TRM from 12% in the first EBMT registry survey in 2004 to <5% in most recent reports between 2017 and 2019 (Burt et al. 2021). Overall, responding patients are usually free of clinical symptoms and may regain seronegativity for antinuclear antibodies, which is rarely seen under conventional therapies. Early use of HCT also has the potential to protect against organ failure and toxicity-related morbidity and improve quality of life (Burt et al. 2018). The relapse rate is higher in patients receiving unmanipulated stem cell grafts and conditioning regimens without serotherapy (Alchi et al. 2013). Current evidence and expert consensus suggest HCT in SLE as 'clinical option' in patients with active disease (BILAG category A), state despite chronic immunosuppression with or without B-cell-targeted therapies (Illei et al. 2011; Snowden et al. 2012, 2022).

92.6 HCT for Crohn's Disease (CD)

Despite the major recent progress in the treatment of CD, based around corticosteroids, IS (thiopurines, MTX) and DMTs (Ab targeting TNFα, α4β7 integrin or IL-12/IL-23), some patients fail all available therapies. In many cases, surgery may be an option but may lead to short bowel syndrome or to a permanent stoma, which may be unacceptable to patients. With this background, in the past few years, auto-HCT has emerged as a promising therapy in a subset of patients in whom the disease is refractory to all available therapies, with progressive tissue damage and potentially reduced life expectancy.

Auto-HCT has been investigated in several studies with encouraging responses, some prolonged, although a progressive incidence of relapse with long-term follow-up is recognised (Burt et al. 2010; Lopez-Garcia et al. 2017). Furthermore, patients regain response to anti-TNF therapy, although they had been refractory to this drug class prior to HCT.

In Europe, the EBMT-sponsored ASTIC trial in patients with refractory CD produced apparently negative results as few patients after auto-HCT met the stringent primary composite endpoint of clinical remission for 3 months (Hawkey et al. 2015). However, it should not be assumed that this single trial provides the definitive answer to the benefit of auto-HCT in CD, as the number of patients included was limited and encouraging long-term follow-up of ASTIC trial patients has since been reported (Lindsay et al. 2017). Encouraging results have also been reported by an EBMT retrospective analysis of 82 treatment-resistant patients who were not in the ASTIC trial. In this difficult-to-treat group of patients, around a quarter maintained remission without further medical therapy, and long-term disease control was maintained with the reintroduction of salvage therapies in the majority of patients who relapsed. TRM occurred in one patient (Brierley et al. 2018).

The EBMT ADWP and ECCO (European Crohn's and Colitis Organisation) have published a joint position paper of auto-HCT in CD, which recommends auto-HCT ideally in the context of a multicentre clinical trial but on an individual basis may currently be considered for patients with active CD refractory to IS and biological treatments or unacceptable risks of surgical management (Snowden et al. 2018). These recommendations include conditioning regimens using

CY/ATG, which has been used in the majority of HCT for CD with an acceptable and predictable balance between safety and efficacy in these challenging CD cases. A cautionary note should be taken from a recent randomised controlled trial using FLU, CY and ATG-based conditioning regimens, which was stopped early due to unexpected severe toxicity, including thrombotic microangiopathy (Lindsay 2021).

The next steps in this field focus on minimising the risk of infectious complications in this setting. In this sense, CY-free mobilisation seems to be safe and effective (Giordano et al. 2022) and other modifications will be key to further development and deliverability of autologous HCT in patients with severe CD refractory to modern DMTs.

92.7 Allogeneic HCT for Autoimmune Diseases

Autoimmune diseases have also been treated with allo-HCT from MRD, URD and CB sources. In the last 25 years, the EBMT registry has collated 286 cases. Because of the higher procedural risks and potential long-term impact on quality of life from late effects, allo-HCT has been largely restricted to life-threatening AD in paediatric practice with the most common indications in immune cytopenia followed by arthritis. In a recent summary of cases from the registry (Greco et al. 2019), 128 patients undergoing allo-HCT were treated between 1997 and 2014. The median age was 12.7 years (range 0.2–62.2). The incidence of grades II–IV aGvHD was 20.8% at 100 days. The cumulative incidence of cGvHD was 27.8% at 5 years. Non-relapse mortality (NRM) was 12.7% at 100 days. OS and PFS were 70.2 and 59.4% at 5 years, respectively. By multivariate analysis, age <18 years, males and more recent year of transplant were found to be significantly associated with improved PFS. Reduced conditioning intensity was associated with a lower NRM. In a subgroup of 64 patients with detailed information, a complete clinical response was obtained in 67% of patients at 1 year.

Moreover, allo-HCT may represent a potential treatment option for the novel entity called VEXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) (Bruno et al. 2023).

In summary, experience in allo-HCT is limited, but long-term data are supportive of basic biological differences in the responses of AD to allo- and auto-HCT in terms of curability. However, due to related NRM risks, the application of allo-HCT remained limited and developmental in AD. With time, allo-HCT in AD has become safer and activity continues, particularly in the paediatric field. Moreover, improved patient selection, reduced toxicity conditioning regimens and new strategies for GvHD prophylaxis (i.e. PT-CY) are currently under investigation, generating interest in extending the application to non-malignant disorders. In addition, there has been increasing recognition that the nature of the genetic component of some AD means that allo-HCT is the only realistic approach for long-term disease control. Thus, there is renewed interest in this area, particularly where there is overlap with autoinflammatory and immunodeficiency diseases, particularly in the paediatric setting as summarised in a recent EBMT review (Achini-Gutzwiller et al. 2022).

92.8 Other Indications

A variety of other ADs have been treated (Table 92.2). Haematological immune cytopenias have been treated with a mixture of auto-HCT and allo-HCT. Type 1 diabetes in early 'honeymoon' phase has been the subject of clinical trials, with some ability to prevent or reduce insulin requirements. Otherwise, there is a mixture of rarer neurological, rheumatological and gastroenterological indications for which the registry is essential for developing an evidence base. Cautious recommendations for these rare indications are provided in the EBMT ADWP guidelines (Snowden et al. 2012; Greco et al. 2021) and recently updated EBMT recommendations on haematopoietic cellular therapy indications (Snowden et al. 2022).

92.9 Conclusions and Future Directions

With accumulating evidence and improved outcomes, along with the recognition that modern biological and other therapies are not universally effective, ADs have become the fastest-growing indication for HCT (Alexander and Greco 2022; Passweg et al. 2021). Initially applied as salvage therapy in patients with poor prognosis, HCT has emerged as a promising treatment option for AD patients earlier in the treatment algorithm. This is the result of successful large phase II and randomised controlled phase III trials and updated guidelines for patient selection and transplant techniques in SSc, MS and CD, respectively (Farge et al. 2017b; Sharrack et al. 2020; Snowden et al. 2012).

In 2023, the major indications for HCT in AD are MS, SSc and CD (Alexander and Greco 2022) for which significant subsets of patients still show an unsatisfactory response to both conventional and targeted biologic therapies.

Moving forward, further efforts are needed to drive HCT into routine clinical care. It is recommended that patients should be treated in experienced and JACIE-accredited transplant centres in a multidisciplinary setting. A future goal is to optimise the conditioning regimens according to disease-specific requirements and to outbalance the intensity to maintain outcomes while minimising toxicity and TRM risk. Moreover, positive preliminary experiences have been recently reported with chimeric antigen receptors (CAR) T cells, paving the way for the use of innovative cell therapy approaches in AD field (Chap. 93).

In addition, comprehensive data reporting, harmonisation and exploitation of existing biobanking infrastructure (Alexander et al. 2015), education at individual centre and network level, including ADWP educational activities (Burt et al. 2021) and health economic evaluations along with evidence-based recommendations will establish the future place of HCT in the treatment algorithms for various autoimmune and inflammatory diseases.

Key Points

- With accumulating evidence, including randomised controlled trials, AD has become one of the fastest-growing indication for autologous HCT.
- Major indications for HCT in AD include multiple sclerosis (MS) and systemic sclerosis (SSc), where auto-HCT is now featuring in treatment algorithms.
- Although HCT for ADs is predominantly autologous, there is renewed interest in allo-HCT, particularly in ADs with autoinflammatory and immunodeficiency components.
- It is recommended that all patients should be treated in experienced and JACIE-accredited transplant centres with close multidisciplinary collaboration and reporting of data to the EBMT registry.
- Immune reconstitution studies are providing insights into the mechanisms of immune reset following HCT and disease processes underlying various AD.

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