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Hematopoietic stem cell transplantation in autoimmune diseases: update from the EBMT Autoimmune Diseases Working Party with special reference to Poland

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Abstract

Hematopoietic stem cell transplantation (HSCT) is now evolving into a standard treatment in some autoimmune diseases (AD) alongside other modern therapy. The main indications are multiple sclerosis and systemic sclerosis for which HSCT has become an integral and standard-of-care part of treatment algorithms. From 1994 to the beginning of 2021, data from the (European Society for Blood and Marrow Transplantation) EBMT Registry indicates that 3,442 patients (60% females, 40% males; 91% adults, 9% pediatric) received 3,514 transplant procedures for autoimmune diseases, with over 90% receiving autologous transplant. Autoimmune diseases are currently the fastest growing indication for autologous HSCT in EBMT, whilst allogeneic HSCT for ADs is mainly restricted to pediatrics, especially diseases with a genetic component. Patient selection plays a key role in providing the best risk/benefit ratio of the procedure. Intensity of conditioning regimen and center experience are also important. Ultimately, the future of HSCT for ADs depends on the standard of care therapy, which influences uptake within national/international disease specialist communities. Further studies are necessary in order to establish relative benefit over current/future standard of care therapy, to establish the best HSCT regimen for each disease, to define mechanisms, develop clinical biomarkers to help select and monitor patients, and to define health economic benefits and public health delivery. We present a current perspective summarizing activity across EBMT, including centers in Poland.

Key words: autoimmune diseases, stem cells, transplantation, autologous, allogeneic

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Introduction

Autoimmune diseases (AD) are relatively common, affecting 5–8% of the population. MS occurs in about 1 in 1,000 people, while acute myeloid leukemia (AML) occurs in approximately 1 in 100,000. Not all ADs are severe, but some are very disabling and life-threatening. Cures remain elusive and almost all patients with severe ADs require long-term therapy. The impacts of both the disease and its treatment are severe, since patients require steroids or other immunosuppressive drugs. The consequences of treatment can be as damaging as the disease itself, in terms of the combined short-term and chronic effects of both ADs and treatments. Additionally, the costs of the disease are high in terms of drugs, personal costs (disability) and societal impact. For a long time, there has been a desire for a one-off intensive means of long-term disease control, to achieve disease eradication, rather than chronic suppression.

Autoimmune diseases (ADs) are the fastest growing area of autologous hematopoietic stem cell transplantation (HSCT) worldwide, yet they still comprise only 2% of all transplants. Even with the significant advances made in transplants in patients with multiple sclerosis (MS) and systemic sclerosis (SSc), this is still a very specialized area and will never be considered as a treatment for anything other than the most severely affected poor-prognosis patients with autoimmune diseases where the risk:benefit ratio can be justified comfortably.

The objective of this paper is to present an overview of HSCT as an exciting and evolving therapeutic avenue in severe ADs.

Concept of HSCT in autoimmune diseases

The concept of HSCT in ADs is already four decades old. It started in the 1980s in animal models and in 1995 the first patients were treated with autologous HSCT specifically for AD. In 1996–1997, the Autoimmune Diseases Working Party (ADWP) of the European Society for Blood and Marrow Transplantation (EBMT) was formed, and this was followed by developing the EBMT database and guidelines [1, 2]. Activity in ADs predominantly involves autologous HSCT (auto-HSCT), while allogeneic HSCT (allo-HSCT) procedures are rare in ADs, particularly outside of pediatrics, because children can tolerate this treatment better than adults. On the other hand, allogeneic HSCT can provide complete 'immune replacement'. The outcome of allogeneic HSCT has dramatically improved over the past decade. A recent retrospective EBMT study assessed the use and long-term outcomes of allogeneic HSCT in 128 patients with various hematological and non-hematological severe ADs within the registry between 1997 and 2014 [3]. In multivariate analysis, age <18 years, male gender, and more recent transplant were found to be significantly associated with improved outcomes.

Table I. Hematopoietic stem cell transplantations (HSCTs) for autoimmune diseases (ADs) in European Society for Blood and Marrow Transplantation (EBMT) registry (1994–2021*)

	Autologous HSCT (n =3,277)	Allogeneic HSCT (n =237)
First	3,245	197
Second	39	34
Third	2	6
Median age at first HSCT	38 years (range 3–76)	11 years (range <1–65)

*As at February 2021

For auto-HSCT, the procedure is relatively straightforward in well-selected patients. The standard pathway of transplant procedure includes granulocyte-macrophage colony-stimulating factor (G-CSF)-mobilization of peripheral blood stem cells, which are then frozen until the patient receives conditioning, followed by thawing and re-infusion of cells into the patient, who is then supported through the period of pancytopenia until hematopoietic recovery. Immune reconstitution is associated with an 'immune reboot', which, in some diseases leads to long-term drug-free remission, and in others re-sets disease activity to controllable levels [4].

Transplant activity in autoimmune diseases

Data from the EBMT Registry of ADs indicates that 3,442 patients (60% females, 40% males; 91% adults, 9% pediatric) have received 3,514 transplants for autoimmune disease, with over 90% getting autologous transplant (Table I). There are a smaller number of allogeneic transplants, mainly in pediatric patients. Some patients have received a second transplant. Overall, transplants for ADs have been performed in 310 EBMT centers in 44 countries.

Indications for transplant in autoimmune diseases

ADs have been the fastest growing indication for autologous HSCT in the EBMT Registry in recent years. The main indications since 1994 have been MS and SSc. The evolution of HSCT has coincided with a period when many biological therapies for autoimmune diseases have competed. However, not all patients respond to biologics, so in recent years the number of transplantations has grown in diseases where biological therapies have a limited effect. The growth has been highest for MS, followed by SSc.

Many countries are active in this field. Ranked according to the number of auto-HSCTs in AD, the 10 most active countries are Italy (n =520), United Kingdom (n =494), Germany (n =352), Sweden (n =321), the Netherlands

Table II. Indications for transplant in autoimmune diseases according to European Society for Blood and Marrow Transplantation (EBMT) Registry (1994–2021)

Indications	Number	Indications	Number
Multiple sclerosis	1738	**Hematological**	139
		ITP	37
Connective tissue	886	AIHA	33
SSc	702	Evans syndrome	26
SLE	121	Other	43
PM-DM	18		
Sjögren syndrome	6	**Vasculitis**	64
Antiphospholipid syndrome	6	Wegener's	14
Other/unknown	33	Behçet's	14
		Takayasu	3
Arthritis	196	Polyarteritis	4
Rheumatoid arthritis	83	Churg-Strauss	2
Juvenile chronic arthritis:		Other/Unknown	27
• systemic JIA	66		
• other JIA	19	**Other neurological**	134
• polyarticular JIA	17	NMO	26
Psoriatic arthritis	3	CIDP	62
Other	8	Myasthenia gravis	9
		Other/unknown	37
Inflammatory bowel	258		
Crohn's disease	212	Insulin-dependent diabetes	20
Ulcerative colitis	4	Other	79
Other	42		

SS — systemic sclerosis; SLE — systemic lupus erythematosus; PM-DM — polymyositis and dermatomyositis; JIA — juvenile idiopathic arthritis; ITP — immune thrombocytopenic purpura; AIHA — autoimmune hemolytic anemia; NMO — neuromyelitis optica; CIDP — chronic inflammatory demyelinating polyradiculoneuropathy

(n =229), Spain (n =226), France (n =195), Poland (n =189), Australia (n =162), Russia (n =99) and Belgium (n =93). Some countries are more active in neurological, some in rheumatological, and some in gastroenterological and other diseases.

In EBMT indications guidelines, MS and SSc are recommended as a standard care indication for transplant, and supported by randomized control trials [5]. Most patients have been treated for MS (Table II). The other indications include connective tissue diseases such as SSc and systemic lupus erythematosus. Arthritis is no longer a frequent indication, as conservative treatment of arthritis has been established since the early 2000s.

Among inflammatory bowel diseases, Crohn's disease has been a long-time indication for auto-HSCT. There have been a number of rare conditions, such as insulin-dependent diabetes in its 'honeymoon' phase, which have proceeded to auto-HSCT to produce remission in some patients.

Multiple sclerosis (MS)

MS is the most frequent autoimmune disease for which HSCT has been used, accounting for 1,738 patients reported in the EBMT registry. The countries most active in auto-HSCTs for MS are Italy (n =306), United Kingdom (n =293), Sweden (n =245), Poland (n =139), and Spain (n=98). These figures support the strong evidence in treatment algorithms.

In most patients, MS is a two-phase disease: an inflammation (relapsing-remitting) phase and a progressive (destructive) phase [6]. First line treatments include: steroids, plasmapheresis, glatiramer-acetate, interferon-beta, fingolimod, fumaric acid, and teriflunomide. Second-line treatments include: natalizumab, alemtuzumab, ocrelizumab and cladribine. Auxiliary treatments include regular physical activity, sun exposure, and vitamin D. MS may be assessed by Expanded Disability Status Scale (EDSS) Disability Score, ranging from 0 to 10, as well as a "no evidence

of disease activity" (NEDA3) assessment, which requires neurologists to assess patients clinically (relapse and disability progression) and radiologically with magnetic resonance imaging (MRI).

In most patients, there is an inflammatory phase, relapsing/remitting MS, which is followed by a secondary, progressive phase. It is during this inflammatory relapsing/remitting phase when a significant therapeutic effect with either drugs or autologous transplant is possible. In the inflammatory phase, 'enhancing' lesions with reactive areas of inflammation damage the brain and the spinal cord. Periods of disability often partly recover, but inflammatory lesions that continually reoccur cause permanent damage and lead to progressive disease.

If auto-HSCT is performed in the inflammatory phase, the inflammatory lesions disappear for long periods, potentially permanently. In the progressive phase, there is ultimately no inflammation and a different disease process for which there is a limited or no response to transplant, even with the most intensive forms of transplant conditioning. Therefore, it is important to be in the right phase of disease, and patient selection plays a key role in providing the best risk/benefit ratio of the procedure [7].

Accumulating evidence and follow up in the literature indicate the potential of auto-HSCT to induce a disability improvement in patients transplanted in the relapsing-remitting phase. Improvement is usually sustained and free of immunosuppression for several years, and potentially permanently. Patients considered for transplant should be clinically severe enough and have resisted at least first line treatment. Guidelines prepared by ADWP support this process and also summarize transplant technology [8]. Early transplantation, which demonstrates the potential to stop disease progression and to prevent disability formation in up to 92% of patients, appears to be the most promising treatment strategy in MS. The favorable factors for HSCT in MS are: early transplantation (EDSS <4.0), age <30 years, disease duration <5 years, and relapsing-remitting type.

In contrast, secondary progressive MS patients with rapid disability accrual, low inflammatory activity, and severe spinal cord involvement are at high risk of treatment failure and should be extremely carefully selected because some inflammatory activity may be suppressed [9].

Since the drawing up of the EBMT ADWP guidelines, which summarize the evidence base [8], there have been a few remarkable publications. In a recent retrospective analysis of the Italian database on long-term clinical outcomes of HSCT in MS, 210 patients were included (58% in RR). With median baseline EDSS score 6 (range, 1–9), in RR-MS patients, the use of the BEAM+ATG (74%) conditioning protocol was independently associated with a reduced risk of NEDA3 failure [hazard ratio (HR) =0.27; 95% confidency interval (CI): 0.14–0.50, p <0.001] [10]. There has been a non-significant trend of a correlation between treatment intensity and quality of outcome in the results of recent studies [11–13].

In addition, 20 patients with 'aggressive' MS received auto-HSCT as a first-line DMT in five European and North American centers. Median interval between diagnosis and auto-HSCT was 5 months (range 1–20). Conditioning regimens used Bu–Cy–ATG, BEAM–ATG or Cy–ATG. After a median follow-up of 30 months (range 12–118), the median EDSS score improved to 2.0 (range 0–6.5), p <0.0001. Following auto-HSCT, no patient had clinical relapse or confirmed disability progression. When MRIs were re-baselined at 6 months, the cumulative NEDA rate was 100%. There was no TRM [14].

At least eight prospective phase II and III studies are ongoing across the world in MS patients in order to establish the treatment as a standard of care [8, 15]. Further studies are needed to assess the optimal intensity and transplant technique, including mobilization and conditioning regimens, as well as graft manipulation.

As with all transplantation decisions, the benefits need to be justified alongside the risks. A number of published clinical trials and other studies have reported no or very low level TRM, which, when pitched against high rates of success in preventing relapse and/or progressive disability, justify a role for auto-HSCT in carefully selected patients. Overall, recent retrospective EBMT data [2] reported 100-day TRM of 1.1%, 3-year TRM of 1.5%, relapse incidence of 34.4%, progression-free survival of 64%, and an overall survival of 95.5%. A tailored approach, with close working between transplant hematologists and neurologists, should optimize the risk/benefit ratio.

Systemic sclerosis (SSc)

SSc is a rare disease, associated with inflammation of the skin (scleroderma), lungs (fibrosis), and heart (pulmonary hypertension). It affects the kidneys and is associated with fibrosis and scarring. In severe cases, it carries a poor life expectancy, even in the biologics era. The European League Against Rheumatism (EULAR) now recommends transplant to treat skin and lung disease in systemic sclerosis.

SSc is a standard indication in EBMT guidelines, with increases over the last decade. Up to 2021, the number of reported auto-HSCTs for SSc was 702. The countries with the highest number of transplants were Germany (n =149), the Netherlands (n =123), France (n =92), Italy (n =78), Australia (n =58), United Kingdom (n =26), Spain (n =24), Poland (n =20), Norway (n =18) and Switzerland (n =17).

Durable responses to auto-HSCT in the skin have been observed, so transplant is effective in reducing skin inflammation and fibrosis. It is also successful in inflammation and fibrosis in the lungs, which is a feature associated with a poor prognosis. Three randomized controlled trials have

been performed for SSc [16–19], resulting in a grade 1 recommendation for auto-HSCT in patients with SSc. These trials support improved overall and progression-free survival with HSCT.

Systemic sclerosis, apart from skin, can cause pulmonary, cardiac (valvular disease of endocardium, microvascular disease of myocardium with myocarditis and fibrosis, and pericardial effusion), gastrointestinal, renal, musculoskeletal and exocrine complications, as well as digital ulceration and macrovascular disease [20, 21]. In a prospective non-interventional study of ADWP-EBMT on auto-HSCT with progressive systemic sclerosis, OS was 90%, PFS 81.8%, and TRM was 6.25% [22].

Inclusion and exclusion criteria, as well as principles of the necessary multidisciplinary approach were updated recently [23]. Toxicity of HSCT has been predominantly attributed to SSc-related cardiac dysfunction, especially related to pulmonary arterial hypertension, and drug-induced cardiotoxicity, which should be part of routine pre-transplant screening [24]. For patients with poor cardiac function, a cardiac 'safe' HSCT regimen was reported in a pilot study that showed safety using fludarabine-based conditioning [25].

Crohn's disease

Crohn's disease is the most frequent indication for transplantation in the gastroenterology field. Between 1995 and 2021, 212 patients were auto-transplanted due to Crohn's disease, with three countries performing more than 20 auto-HSCTs for Crohn's disease overall (Spain, United Kingdom, and Italy).

Consideration of auto-HSCT in Crohn's Disease include: established diagnosis of CD, objective evidence of inflammatory activity, severe course of the disease over time, inadequate response to available medical therapies, and surgery considered an unsuitable option [26, 27].

In an EBMT retrospective study [28], 82 patients were transplanted between 1996 and 2015 due to previous failure of a median six medical therapies, including surgery in 74% of cases. Transplants have been performed in 19 centers from eight countries. Overall, 68% remission or significant improvement was observed, and no re-treatment was required in 27% of cases. In 24 out of 42 patients (57%), remission or significant improvement was observed after re-treatment.

Auto-HSCT provides a therapeutic alternative to Crohn's disease patients with severe and refractory disease, although it is not curative or permanently effective in most patients, at least not without re-introduction of salvage or maintenance treatment, where there appears to be some evidence for re-setting and better disease control. In addition to implementation of extraordinary supportive measures before, during, and after transplant to improve safety, a number of studies are ongoing to evaluate different mobilization and conditioning regimens. Allo-HSCT might be an option in highly selected patients [29, 30], but further studies are warranted.

Communication with patients

Communication with patients is essential, particularly as HSCT procedures are very different to most other immunosuppressive treatments. Each patient should be managed individually, with appropriate specialist and nursing support. Written information should be provided to patients and carers. Education is crucial, not only for specialist AD clinicians, but also for non-specialists (GPs and other clinical staff), and also for broader HSCT team members who look after patients during their inpatient stay. The EBMT ADWP works closely with the EBMT Patient Advocacy Committee and EBMT Nurses Group to produce guidelines for patients, and also non-specialists [31]. Rehabilitation after transplantation e.g. in MS, is an essential component of recovery [32].

Perspectives: the Polish experience

Overall, 189 transplant procedures have been performed for AD in Poland since 1994. Nine Polish centers are active in HSCT for ADs (Table III): Katowice, Warsaw (Central Clinical Hospital), Poznan, Lodz, Gliwice, Krakow, Warsaw (Military Medical Academy), Lublin (Children's University Hospital) and Lublin. The main indication was MS (n =141), mainly treated in the Department of Hematology and Bone Marrow Transplantation in Katowice, followed by SSc (n =20) and type 1 diabetes (n =20). Increasing interest in transplanting patients with ADs is expected in Poland. We encourage local centers to register all treated patients, and to report on follow-up at designated intervals in order to improve the quality of the EBMT registry.

Conclusions

HSCT for severe ADs reflects the gradual transition from basic science to evidence-based therapy. Autologous HSCT is evolving into a standard treatment in some autoimmune diseases, to be considered alongside modern therapy. HSCT for AD will continue to increase at variable rates between the different types of ADs. As more centers undertake this work, it is important to recognize that HSCT for AD presents significant challenges that may be unfamiliar even to experienced HSCT teams. Allogeneic HSCT is potentially curative through 'immune replacement', but rarely used in the treatment of ADs. Improved outcomes have been reported in recent years. Further clinical studies are warranted to evaluate this therapeutic option, especially in pediatric ADs with a strong genetic component.

Table III. Hematopoietic stem cell transplantation (HSCT) activity according to European Society for Blood and Marrow Transplantation (EBMT) Center and autoimmune diseases (AD) indication in Poland

Centre	Multiple sclerosis	Systemic sclerosis	Type I diabetes	Systemic lupus	Juvenile idiopathic arthritis (Stills)	Autoimmune neutropenia	Other AD	Total
Katowice	134	19		2				155
Warsaw (WUM)	1		20					21
Poznan	3							3
Lodz	2							2
Gliwice		1				1		2
Kraków					2			2
Warsaw (WIM)				2				2
Lublin (peds)							1	1
Lublin	1							1
Total	141	20	20	4	2	1	1	189

WUM (*Warszawski Uniwersytet Medyczny*) – Warsaw Medical University; WIM (*Wojskowy Instytut Medyczny*) – Military Medical Institute

The future of HSCT for ADs depends on the dynamic with modern and future 'standard of care' therapy, and acceptance within national/international specialist communities, which is the goal of specialty society guidelines. Multi-professional and inter-disciplinary team working is vital. Further studies are necessary in order to establish relative benefit over current/future 'standard of care' therapy, to establish the best HSCT regimen for each disease, to define mechanisms and develop clinical biomarkers to select and monitor patients, and to define health economic benefits and public health delivery.

Finally, the impact of coronavirus disease 2019 (COVID-19) has yet to be fully understood. Recently, the ADWP reviewed the impact of the pandemic on specific groups of patients with neurological, rheumatological and gastroenterological indications, along with the challenges of delivering HSCT as a specific treatment in these patient populations during the pandemic. The EBMT has provided consensus-based guidelines and recommendations to support multidisciplinary teams delivering HSCT in ADs [33].

Author's contributions

JAS had primary responsibility for this review. JAS and RG provided data from the EBMT registry. All authors contributed to manuscript writing and critical revision.

Conflict of interest

All authors declare no conflict of interest related to this review.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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