Hematopoietic stem cell transplantation in autoimmune disorders: from immune-regulatory processes to clinical implications

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Abstract

Autoimmune diseases are characterized by the development of autoreactive T- and B-cells targeting self-antigens, which eventually can result in chronic and persistent organ damage. The autologous hematopoietic stem cell transplantation (AHSCT) opened new avenues in the treatment of patients with severe, treatment-resistant autoimmune diseases. This paper reviews the immune-regulatory mechanisms behind AHSCT, and also summarizes the experiences of clinical practice related to the therapy in organ-specific and systemic autoimmune diseases.

It seems that the intricate interplay of various immune competent cells with regulatory capacity control in a synergistic manner the repopulated immune system after AHSCT, which potentially leads to a significant clinical improvement in certain autoimmune diseases. However, the widespread use of AHSCT was intrinsically limited, due to the serious side-effects of conditioning treatment and relatively high treatment-related mortality; moreover, the development of new effective and safe therapeutic approaches and the dawn of biological agents further limited its indications in the last decade. Nevertheless, with an appropriate patient selection and increased experience of transplant centres, the risks can be minimized, and AHSCT remained still a reasonable choice in multiple sclerosis and systemic sclerosis when the conventional therapy failed and further progression of disease is inevitable.

Keywords: autoimmune diseases; autologous hematopoietic stem cell transplantation; clinical response; immunological background

1. Introduction

Autoimmune diseases are common clinical conditions arising from an abnormal immune response against self-structures of the body. The breakdown of peripheral and central immune tolerance results in the generation and activation of autoreactive T- and B-cells, which leads to tissue damage and functional loss under appropriate conditions [1]. In order to normalize the derailed immune responses, a wide set of immune-modulating agents, anti-inflammatory and immunosuppressive drugs including biological therapies were developed in the last decades. Although disease progression can be decelerated, even temporarily stopped with the aforementioned treatments, the autoimmune diseases cannot be cured. Expectation for a complete healing have turned the attention to novel therapeutic approaches, such as autologous hematopoietic stem cell transplantation (AHSCT), which opened new avenues for the treatment of autoimmune diseases [2].

The rationale involves non-specific abrogation of autoreactive T- and B-cell responses by the use of high dose immunosuppression during conditioning and the successful reconstitution of a new and tolerant immune system by the re-infusion of hematopoietic stem cells [3]. However, the application of non-myeloablative AHSCT, with a more tolerable conditioning regimen, carries less risk in autoimmune diseases and associates with lower treatment-related mortality (TRM) compared to myeloablative procedure. Generally, AHSCT is beneficial in those conditions, where the loss of immune tolerance is pivotal in the pathogenesis, and tolerance induction is important in the deceleration of ongoing immune-processes.

2. AHSCT in autoimmune diseases: the underlying immunological mechanisms

Autoimmune diseases are characterized by faulty immune tolerance mechanisms, leading to the escape of autoreactive T- and B-cell clones, self-perpetuating proinflammatory cascades and eventually tissue damage. A crucial aspect of hematopoietic stem cell transplantation therefore is to achieve tolerance induction in autoimmune diseases, opposed to hematological malignancies where the major goal is to repopulate the myeloid and lymphoid lineages post conditioning regimens. Interestingly stem cells have been shown to mediate cell death of host-derived T-cells, which presumably can be executed by antigen-presenting cells. This T-cell deletion takes place both in the peripheral, as well as in the central T-cell pool in thymus [4]. Animal models aid in understanding the molecular mechanisms behind transplantation. A special sort of animal models of autoimmunity, denoted as antigen-induced disease models are characterized by autoreactive T- and B-cell clones, where stable remission could be achieved. Other models of autoimmunity, the spontaneously developing animal models where defective immune tolerance plays a minor role, stem cell transplantation seemed ineffective. These animal models are characterized by stem cell disorders. During AHSCT the previously existing lymphocyte subsets are eliminated and the adaptive immune system is rebuilt from the T- and B-cell repertoires by newly formed cells. It has been shown previously that following stem cell transplantation cells of the immune system are repopulated in a particular order. Cyctotoxic T-cells, B-cells and natural killer(NK) cells reconstitute rapidly and completely, however CD4+ T-cells appear later in time, and this repopulation can also be incomplete. Following conditioning and AHSCT, T-cell receptor (TCR) rearrangement analyses indicate that the previous autoreactive T-cell repertoire is deleted giving raise of novel, non-autoreactive T-cells to repopulate. TCR rearrangement analyses, as well as the assessment of the cellular repopulation clearly shows a robust post-transplant modifications of

the adaptive immune system. Naturally, these AHSCT-related molecular transformations also lead to the elimination of autoreactive B-cells besides T-lymphocytes, in addition to that transplantation promotes the development of novel lymphocyte subset distribution. In other words, these processes altogether can re-establish self-tolerance and quench previously existing autoimmune processes. Presumably following AHSCT regulatory T-cells also contribute to the development of immune tolerance in these patients [5,6]. On the other hand, the complete elimination of these autoreactive T-cells is impossible, and autoreactive clones still persist in the host after even myeloablative conditioning therefore autoreactive T-cell clones can be repopulated in some extent. An important physiological mechanism of the immune system, denoted as homeostatic proliferation also contribute to the repopulation of non-autoreactive T- and B-cell clones post transplantation. Graft T- and B-cells therefore can expand rapidly after being transferred into immunodeficient hosts by homeostatic proliferation. Severe lymphopenia following conditioning regimens leads to homeostatic proliferation. T-helper (Th)17 cells have been described to be associated with autoimmune processes. Following transplantation, CD4+ T-cells can be activated and subsequently progress to become Th17 cells [7]. However, only few percent of patients with autoimmune diseases relapse following transplantation. Based on reports from animal models, as well as humans the most plausible explanation could be that in parallel regulatory T-cells (Tregs) arise and silence pro-inflammatory/autoimmune processes driven by Th17 cells, and decelerate the development of autoreactive T-cell clones [8-11]. A selective and preferential Treg expansion controls autoreactive T- and B-cell clones in the repopulated lymphocyte repertoire [11]. On the other hand, although after conditioning treatment and subsequent AHSCT various regulatory cell-based controlling/protection mechanisms are activated, it cannot completely prevent disease recurrence because these autoimmune diseases have a specific genetic makeup still driving autoreactive processes, giving raise of autoreactive

lymphocyte clones. A certain hierarchy in cell repopulation has been described following transplantation. The first line of repopulated cells are members of the innate immune system, giving a quick, however less sophisticated immunological protection to the patients. Monocytes are the first cells to engraft, with a subsequent repopulation by granulocytes, and NK cells. The repopulation process shows very special dynamics. Cells of the innate immune system, such as myeloid cells or NK cells have been described to appear just within weeks after AHSCT, while the recovery of the sophisticated adaptive immune system needs more time [12,13]. Approximately a month after transplantation, lymphocyte counts normalize. However, it has been shown that, the functional readiness and efficacy of lymphocytes can be impaired for years following AHSCT [12,13]. Interestingly the number of Tregs of SLE patients who achieved complete remission after AHSCT seems to be steadily increasing. Regarding T-cells with regulatory capacity, in patients following AHSCT, both the conventional Tregs (CD4+CD25+ Foxp3+), as well as an unusual phenotype, CD8+ Foxp3+ Treg cell subsets have been shown to normalize, accompanied by the functional silencing of pathogenic T-cell responses to anti-nuclear antigens [14]. We have previously described that the frequency of Tregs did not change significantly after AHSCT, which raises the possibility that qualitative, rather than quantitative changes in the Treg repertoire are responsible for autoreactivity-control in patients with autoimmune diseases [15]. Besides the aforementioned immune cell subsets with regulatory capacity, the role of other cell types (e.g. tolerogenic dendritic cells, suppressor macrophages, or other myeloid-derived suppressor cells) cannot be excluded to play a beneficial role following stem cell transplantation in patients with autoimmune diseases [16-18].

Altogether it seems that the intricate interplay of various immune competent cells with regulatory capacity control in a synergistic manner the repopulated immune system, giving

hope that this therapeutic possibility will be a beneficial alternative in patients with autoimmune diseases.

3. Clinical efficacy of AHSCT in autoimmune diseases

In a number of onco-hematological diseases, such as Hodgkin's, non-Hodgkin's lymphoma and multiple myeloma, AHSCT may lead to remission or complete cure. In the last two decades, AHSCT appeared in the therapeutic repertoire of therapy-resistant autoimmune diseases. Numerous phase I and II trials were launched in certain autoimmune conditions and several thousand patients have been registered in various databases. In Europe, based on the database of the European Society for Blood and Marrow Transplantation (EBMT), more than 2000 patients with autoimmune disease received AHSCT so far (Table 1) [19]. Based on the promising outcomes of studies, AHSCT can be a reasonable choice when the conventional therapy failed in certain autoimmune diseases, such as systemic sclerosis and multiple sclerosis.

3.1 Systemic sclerosis

Systemic sclerosis (SSc) is a progressive systemic autoimmune disease. The characteristics of SSc include autoreactive immune activation, vascular abnormalities and increased fibroblast activity leading to excessive extracellular matrix deposition. The fibrotic and inflammatory processes are prominent in the skin and certain internal organs, such as heart, lungs or kidneys [20,21]. SSc can be classified into two clinical subsets: the diffuse cutaneous form is characterized by rapidly progressive fibrosis of skin and visceral organs, while in limited cutaneous form, the extension of fibrosis is limited and the disease progression is slow [22].

Since the therapeutic options are limited to the treatment of the complications, thus decelerating disease progression by stopping fibrosis is still an unsolved issue primarily in the diffuse cutaneous form.

The majority of patients treated with AHSCT had diffuse cutaneous form with a rapid disease progression and early kidney and/or lung involvement. In recent years, the treatment-related mortality has been improved to 5-6% due to the careful patient selection [23]. The relatively good general health status is fundamental in reducing transplant-related mortality; moreover, in order to achieve the best clinical results, AHSCT should be applied before the development of any irreversible organ damage. As the consequence of improving safety and efficacy of treatment, the number of SSc patients received AHSCT procedures increased rapidly in the past few years, and present days, there are more than 430 registered SSc patients, who undergone AHSCT in Europe. In the past 15 years, numerous phase I/II trials were reported. One of the earliest multicenter open phase I/II study on AHSCT evaluated the results of 41 SSc patients [24]. The results were promising, 69% of patients showed an improvement in skin score of >25% after transplantation; however, 17% of patients died related to the procedure. A few years later, the EBMT/EULAR report analysed the durability of the responses after AHSCT for severe SSc [25]. Fifty-seven patients with SSc, treated by HSCT in European phase I-II studies from 1996 up to 2002, with more than 6 months of follow-up were included. After 22.9 months, partial or complete response was seen in 92%; however, 35% of them relapsed within 10 months after AHSCT. Of note, TRM was only 8.7%; furthermore, and at 5 years, the probability of progression was 48% and the estimated survival was 72%. Based on smaller trials, the clinical amelioration induced by AHSCT includes improvement in the extent of skin fibrosis, as well as in capillary microcirculation, besides the expected anti-inflammatory effects. In the majority of the treated SSc patients, the modified Rodnan skin score (mRSS) was decreased by more than 20% after the treatment; however, the

effect of AHSCT on the status of affected visceral organs is limited to stabilization or moderate improvement only [26-28]. Until now, three randomized control trials assessed the safety and long-term clinical effects of AHSCT in SSc. The American Scleroderma Stem cell versus Immune Suppression Trial (ASSIST) compared the results of autologous non-myeloablative HSCT with the effects of monthly administered pulse intravenous cyclophosphamide therapy [29]. After randomization, 10 patients underwent AHSCT, while 9 control patients received 6 monthly pulses of cyclophosphamide. All patients received AHSCT showed significant improvements, while 8 control individuals had disease progression. The results of two-year follow-up after AHSCT suggested that improvements in skin score and forced vital capacity were persistent. The Autologous Stem cell Transplantation International Scleroderma Trial (ASTIS) was the first phase III trial in SSc [30]. A total of 156 patients were randomly assigned to receive AHSCT (n=79) or 12-monthly pulses of intravenous cyclophosphamide (n=77). The ASTIS trial demonstrated an improvement in both event-free and overall survival rates in AHSCT group. During a median follow-up of 5.8 years, 19 deaths and 3 irreversible organ failures occurred in AHSCT group, while in the control group 23 deaths and 8 irreversible organ failures were recorded. Among patients with early diffuse cutaneous form, AHSCT was associated with increased treatment-related mortality in the first year after treatment. Overall, there were 8 AHSCT-related deaths (10%) in the study, but on the other hand, AHCST had a significant long-term event-free survival benefit. The Scleroderma: Cyclophosphamide Or Transplantation (SCOT) trial is the most recent, randomized, controlled phase III trial which compared high-dose immunosuppressive therapy and myeloablative HSCT to monthly pulse cyclophosphamide treatment [31]. Seventy-five patients suffering from diffuse cutaneous SSc with a high risk of lung and/or renal involvement were randomized to AHSCT after myeloablation and cyclophosphamide treatment. The 54 months post-treatment event-free survival was 79% in

AHSCT group and 50% in control group. The overall survival of AHSCT-treated patients was 91%, while it was 77% of control patients. Treatment related mortality was 3% in AHSCT versus 0% in controls. Based on these results, the SCOT trial reported improved survival and supported myeloablative AHSCT as a potential treatment option in diffuse cutaneous SSc. Taking all these observations together, AHSCT should be reserved for those diffuse cutaneous SSc patients, whose disease is refractory to conventional treatments. Additionally, patients with high risk of mortality but without significant irreversible organ damage should be also considered [32].

3.2 Multiple sclerosis

Multiple sclerosis (MS) is an incurable inflammatory neurological disease, characterized by progressive disease course resulting in chronic neurological disability. Regarding the cellular background, autoreactive CD4+ T-cells play a crucial role in the development of inflammatory plaques, demyelization and consequently contribute to axonal loss [33]. The disease course is highly variable between individuals, various form of MS can be distinguished based on clinical symptoms, including rapidly evolving severe (RESMS), relapsing-remitting (RRMS), secondary progressive (SPMS) and primary progressive (PPMS) forms. In about 85% of cases, the disease starts with relapsing-remitting course, and after certain number of relapses the disease enters in secondary progressive phase with accumulating disability in 90% of RRMS patients [34]. The current disease-modifying treatments include several immune-modulating therapies, such as interferon-beta, glatiramer acetate, teriflunomide, fingolimod, natalizumab, and alemtuzumab. These drugs are effective in reducing the frequency of relapses in certain subsets of patients; however, they have only limited effect on secondary progression leading to increasing degree of disability.

After the promising results in experimental models, human phase I/II AHSCT studies began in the middle of the 1990s, and so far more than 800 MS patients have received transplantation only in Europe. In the last decade, a number of studies reported the effectiveness of AHSCT in MS based on the improvements in disease severity measured on a 10-point ordinal expanded disability status scale (EDSS) and based on magnetic resonance imaging (MRI) scans after the therapy. Former MRI studies revealed that inflamed, gadolinium-enhancing lesions improve and their gadolinium enhancement abolish in the central nervous system after AHSCT [35]. In 2006, a retrospective survey on 178 MS patients recruited from the database of EBMT demonstrated a progression free survival of 63% at 42 months. The overall transplant related mortality was 5.3% [36]. More recently, an Italian multi-center study enrolled 74 MS patients in the period from 1996 to 2008 and demonstrated a 66% progression-free survival at 5 years after AHSCT, with a 2.7% of TRM [37]. A number of studies suggest that AHSCT is most likely to be beneficial in earlier phase of disease course [38,39]. Burt et al. reported that the responses in RRMS patients were excellent, 81% of them showed improvement in EDSS point after treatment [38]. On the contrary, AHSCT was not effective for patients suffering from progressive disease with a more advanced disease course and high pre-transplantation disability scores [40]. Recently, Burt et al. reported data on 145 MS patients received AHSCT [41]. The authors demonstrated a significant improvement in disability in 50% of patients at 2 years with no treatment-related mortality. Four-year relapse-free survival was 80% and progression-free survival was 87% at 4 years. Another novel investigation demonstrated similar results with 78.4% of overall event-free survival at 3 years with no TRM. The progression-free survival and clinical relapse-free survival were 90.9% and 86.3%, respectively, at 3 years [42]. Interestingly, no treatment-related death was reported in MS following AHSCT in recent studies. This presumably reflects a better patient selection and increased experience of transplant centres.

Since in the majority of patients, the previously developed neurological damages are often irreversible, only limited improvement could be achieved with AHSCT in patients with advanced, progressive MS. Nevertheless, transplantation has also been reported to be beneficial in RESMS, without effective response to conventional treatments. In numerous cases, the disease responds well to AHSCT, its progression stops, often with an unexpected recovery from the previous disability [43-45].

Moreover, a phase II trial on aggressive form of MS published a few months ago, demonstrated that AHSCT can fully halt all detectable CNS inflammatory activity in patients with MS for a prolonged period in the absence of any ongoing disease-modifying drugs [46].

The joint EBMT-CIBMTR study is the largest and most up-to-date retrospective study including 281 MS patients who received AHSCT in 1995-2006 at 25 transplant centres of 13 countries [47]. Based on the results, five-year probabilities of progression free and overall survival were 49% and 93%, respectively. Younger age, relapsing MS and fewer lines of prior immune-modifying therapy were associated with better outcomes. Neurological improvements during the 12 months following transplant were reported in 52% of relapsing patients and in 31% of progressive patients.

The only available randomized trial in MS is the recently published Autologous Stem cell Transplantation International Multiple Sclerosis (ASTIMS) trial [48]. Although patients were a mixture of RRMS and SPMS, and only 21 patients were randomized between AHSCT and mitoxantrone, a significant reduction was observed in both relapses and new T2 lesions on MRI in patients received AHSCT compared to mitoxantrone arm. There is on other ongoing international multicentre randomized clinical trial (MIST trial - Stem Cell Therapy for Patients With Multiple Sclerosis Failing Alternate Approved Therapy - A Randomized Study) comparing AHSCT against FDA approved disease-modifying treatments. This trial is due to be completed in 2017 [49].

3.3 Crohn's disease

Crohn's disease (CD) is an autoimmune inflammatory bowel disease affecting all segments of the gastrointestinal tract. A combination of immunosuppression and biological therapies is the standard therapy, although in severe cases, surgical interventions are also often required [50]. Both prospective and case report data are available for AHSCT in CD, demonstrating its potential to induce remission of symptoms [51]. A phase I/II study evaluated the safety and clinical outcome of AHSCT in 24 patients with severe, refractory CD [52]. Clinical symptoms and Crohn's disease activity index (CDAI) improved before hospital discharge, whereas radiographic and colonoscopy findings improved gradually over months to years following the transplantation. The percentage of patients in medication-free remission (CDAI<150) more than 5 years after transplantation was above 60%. Another small clinical trial with only 4 patients with refractory CD observed clinical remission in all patients, and in case of three patients, both the clinical and endoscopic remissions remained for a longer term despite the withdrawal of all medicaments [53]. Based on a subsequent single-arm trial, AHSCT resulted in a clinical and endoscopic improvement in five from nine CD patients. However, relapses occurred in seven patients during follow-up period, but the disease activity was effectively controlled by low-dose corticosteroids and conventional immunosuppressive therapy [54]. In the first randomized controlled trial in DC, namely, the Autologous Stem Cell Transplantation for Crohn Disease (ASTIC) study, 45 patients with refractory CD were randomized to AHSCT (n=23) or standard treatment (n=22) after stem cell mobilization [55]. Only 2 patients in AHSCT arm achieved sustained remission, while one in controls. One patient died of treatment-related complications, which led to early discontinuation of the trial. Therefore, the trial analysis became limited; nevertheless, based on the results, AHSCT improved clinical and endoscopic disease activity.

3.4 Systemic lupus erythematosus

Systemic lupus erythematosus, referred to as SLE or lupus, is a clinically heterogeneous, chronic systemic autoimmune disease characterized by the presence of autoantibodies directed against nuclear antigens and damage of multiple organ systems, including renal, cardiovascular, musculoskeletal neural and cutaneous systems. SLE is a relapsing and remitting disease, encompassing mild to moderate forms, and also severe, progressive variants with a potentially debilitating, even fatal outcome [56].

Until a few years ago, SLE was one of the most common indications for AHSCT and in the last 20 years, more than 110 SLE patients have undergone this treatment in Europe, and more than 200 patients worldwide. However, the development of cell-based therapies for SLE has undergone a dramatic expansion in this decade [57], and the improving outcomes of biological therapies and other standard treatments such as cyclophosphamide or mycophenolate mofetil have resulted in decreasing AHSCT in lupus in the last years. Based on clinical experience, the rate of disease relapse is high, and the average treatment-related mortality rate is about 7-15%, which are still major concerns [23]. In 2006, Burt et al. published the largest single-centre report on autologous non-myeloablative HSCT, enrolling 50 patients with SLE refractory to conventional immune-modulating therapies and either organ- or life-threatening visceral involvement [58]. According to their promising results, the treatment-related mortality was 4% and with a mean follow-up of 29 months, the overall 5-year survival was 84%, and probability of disease-free survival at 5 years following HSCT was 50%. However, other studies revealed much higher TRM in lupus. A retrospective registry survey was carried out by the EBMT/EULAR registry by collecting data from 53 patients with SLE treated by autologous HSCT in 23 centres [59]. Remission of disease activity was achieved by 66% of patients by six months, but 32% of them relapsed during the

subsequent six months of follow-up. TRM was 12%, and mortality was associated with a longer disease course before AHSCT. Similarly high TRM was reported by Alchi et al., who carried out the retrospective survey of 28 SLE patients treated with AHSCT from eight centres reported to the EBMT [60]. The five-year overall survival was 81%, but disease-free survival was only 29% with a high relapse incidence (56%) and TRM (15%). Regarding the combination of AHSCT with other immunemodulatory treatments, a previous study showed that administration of fludarabine and anti-CD20/B-cell specific biologics with AHSCT turned out to be advantageous in lupus [61]. These studies revealed the relatively high procedural risks and mortality, and despite the initial interest, clinicians and researchers looked towards other effective and promising treatments [62] and the number of AHSCT declined in lupus. Nevertheless, AHSCT is still one of the accepted therapies and may be considered in severe refractory SLE as a salvage strategy [63].

3.5 Rheumatoid arthritis

Rheumatoid arthritis (RA) is characterized by the inflammation of the synovial tissue and progressive joint destruction. Although RA usually does not lead to life-threatening complications, it often results in significant deterioration in the quality of life. Biologics and early aggressive disease-modifying antirheumatic drugs (DMARDs) are very effective in RA, especially in early phase of disease. Although numerous new pharmacological therapies emerged for RA in the last decade, there are still about 15% of patients who do not response to any modern DMARDs, or biologics. AHSCT seems to be a possible treatment option when the disease is refractory to other treatments and the patient's clinical condition is good enough for the procedure [64]. Until now, more than 80 RA patients received AHSCT in Europe. Based on a former study on 14 patients with active, destructive, refractory RA, AHSCT treatment led to significant clinical amelioration, and 67% of patients reached ACR50. Clear

improvement was observed in the activity index and in joint function, moreover the radiological analysis found reduction in the cartilage destruction [65]. Nevertheless, the ability of AHSCT to maintain a sustained ACR 70 response was low with only 28% achieving a progression free survival at the end of three-year follow-up [66]. An EBMT/ABMTR database study on 73 patients reported that the transplantation was generally well tolerated without TRM. On the other hand, the initial good responses were frequently followed by early relapses, although, the disease activity did not reach the pre-treatment level, and the patient becomes responsive to conventional treatment modalities including DMARDs and biologics again [67]. The early relapses in RA after AHSCT might be due to the surviving autoreactive T-cells in inflamed synovia and pannus, where the lymphoablative treatment do not have sufficient effects; which raises the possibility that eradication of these intraarticular T-cell clones with special myeloablative conditioning treatment might prolong the remission and symptom-free period in RA after transplantation [68]. Of note, a multicenter randomized controlled trial in RA was established (Autologous Stem cell Transplantation In Rheumatoid Arthritis - ASTIRA); however, it was closed due to the failure to recruit sufficient patients. In conclusion, with the advent of rituximab and other biologics, the number of AHSCT performed for RA patients decreased worldwide and RA remained no longer an indication for AHSCT.

3.6 Juvenile idiopathic arthritis

Based on the last Annual Report of EBMT, until now 89 children with juvenile idiopathic arthritis (JIA), mostly the systemic form, have been treated with AHSCT in Europe. The high transplant-related mortality (9-11%) is still a major concern [23]. After a median follow-up of 3 years, 53% of the patients were still in complete drug-free remission, while 18% showed only partial response, and in 21% of patients there was no improvement [69,70]. In a long-

term follow-up study, the prolonged drug-free remissions were confirmed, although the transplant-related mortality was still high [71]. Similar to RA, the treatment of JIA has also changed with the emerge of biological agents, nevertheless, a few sporadic RA and JIA patients are still reported to EBMT database.

3.7 Systemic vasculitides

Systemic vasculitides are a complex group of disorders characterized by the inflammation of blood vessels leading to tissue and organ injury. So far, less than 50 patients were treated with AHSCT in Europe. A recent retrospective registry-based analysis summarized 15 patients with various forms of vasculitis [72]. Fourteen patients received AHSCT, while one patient underwent allogeneic stem cell transplantation. In three patients, further transplantation was necessary due to relapse. The overall response to treatment was 93%, with 46% complete response and 46% partial response rates. Three patients died during the follow-up, due to different reasons (advanced disease course, cancer and graft-versus-host disease). Similar results were observed in other studies investigating only four and two AHSCT-treated patients [73,74].

3.8 Chronic inflammatory demyelinating polyneuropathy

Chronic inflammatory demyelinating polyneuropathy (CIDP), which is an acquired immune-mediated disorder, is the most common chronic autoimmune sensorimotor neuropathy. Around 70-80% of CIDP patients respond to moderate doses of immunomodulating therapy including corticosteroids, intravenous immunoglobulin and plasma exchange. However, some patients need high doses of immunosuppression continuously. If these increased doses are poorly tolerated, AHSCT may be considered. Until now, more than 30 CIDP patients received AHSCT in Europe. Although, only a limited number of studies were conducted on the effect

of AHSCT on CIDP, the results are promising. In a case report, the neurological status of a CIDP patient improved after AHSCT [75]. Additionally, in the last years, other clinical studies also reported a relatively small number of CIDP patients, who showed clinical improvement after AHSCT [76,77]. Moreover, a phase II trial Hematopoietic Stem Cell Transplantation in Chronic Inflammatory Demyelinating Polyneuropathy is currently ongoing [78].

3.9 Autoimmune cytopenia

Autoimmune cytopenias are characterized by the production of antibodies against blood cells and include immune thrombocytopenic purpura (ITP), autoimmune hemolytic anemia (AIHA), autoimmune neutropenia (AIN), and various combinations of these conditions. These disorders may develop idiopathically, or can be associated with other malignant or non-malignant diseases, such as lymphoid malignancies, autoimmune disorders or infections. The treatment of the malignant, autoimmune or infectious diseases may induce the remission of secondary autoimmune cytopenia, as well. In primary cytopenia, specific immunosuppressive therapy is needed; however, resistance to immunomodulating agents or relapse after therapy is not rare. For steroid-refractory patients with ITP and AIHA, splenectomy is usually recommended, while in AIN, granulocyte colony-stimulating factor (G-CSF) could be administered. In the last decade, biologics became a promising treatment modality in autoimmune cytopenias, as well [79]. However, severe, refractory autoimmune cytopenia is still a challenge. According to a study on AHSCT in the treatment of severe refractory autoimmune cytopenia, the transplantation may induce a prolonged good clinical response, albeit transplant-related mortality is remarkably high, circa 8% [23]. Based on the EBMT registry, more than 75 patients were treated with AHSCT so far.

3.10 Type 1 diabetes mellitus

Type 1 diabetes mellitus (T1DM) is a common organ-specific autoimmune disease characterized by the destruction of insulin-producing β-cells in islets of Langerhans within the pancreas [80]. For the appropriate administration, immune-suppression required to be launched within the first 12 weeks of the disease onset. Albeit glucocorticosteroids have strong immune-suppressive properties, in T1DM they can induce islet-cell apoptosis and further deterioration of the disease [81].

In a clinical study, AHSCT was carried out on patients with newly onset T1DM. From the 15 patients received AHSCT, 14 patients became insulin-free and only one resumed insulin use 1 year after AHST. Serum levels of hemoglobinA1c were maintained at less than 7% in 13 of 14 patients, and there was no mortality [82]. For the first time, this study indicated that patients with T1DM can become insulin free with normal HgbA1c for extended periods of time. Two years later, Couri at al. reported on 23 patients with T1DM undergoing AHSCT and showed that C-peptide levels increased after the procedure [83]. The level of C-peptide refers to the islet cell mass and its increase after transplantation clearly indicates the restoration of islet cells. Twenty from 23 patients became insulin-free, and the mortality was zero. A multicenter study on 65 patients reported that 59% of patients achieved remission at 6 months after AHSCT and 32% remained insulin-free even after 48 months [84]. A recent meta-analysis demonstrated that 58,9% of 149 T1DM patients became insulin independent after AHSCT during a mean follow-up period of 16 months [85]. Nevertheless, the question is still open whether a three year disease-free survival expectation is worth confronting with transplant-related complications and an AHSCT related reduction in the bone marrow functional reserve.

4. Discussion

Over the last two decades, there has been an extensive development of AHSCT for autoimmune diseases and the procedure has gradually translated into clinical practice. Although the transplant-related complications and mortality are still a major issue, the increasing knowledge on AHSCT resulted in a significant improvement in both the efficacy and safety of its administration in various autoimmune diseases. In the beginning, the rate of treatment-related mortality was over 10%; however, this high rate has decreased with an improved patient selection and increased experience of transplant centres. Previously, based on the safety and toxicity considerations, AHSCT was reserved for unique, and often end-stage cases of severe autoimmune diseases not responding to a wide range of immunosuppressive treatments. Consequently, the procedure further debilitated the patients' poor general health status and frequently led to serious treatment-related complications, even death. However, subsequent studies demonstrated that AHSCT is hardly beneficial in end-stage patients with irreversible organ damage, and getting AHSCT in a very early stage of autoimmune diseases, before any permanent organ damage or disability occur, results in less complications and better clinical outcome.

In addition to the type and stage of autoimmune disease, the conditioning regimen also determines the sustained clinical remissions or even cure. In the beginning, myeloablative protocols were administered mostly, however this aggressive conditioning protocol accompanied with a significantly high rate of mortality. On the contrary, non-myeloablative conditioning modality was better tolerated and accompanied with lower risk of treatment-related mortality. Today, the aim of conditioning regimen is lymphoablation only, and myeloablation has become an unwanted side effect.

Even though over 100 studies on AHSCT in autoimmunity have been published, there are still a number of unanswered questions regarding the cellular background of the immune-modulating effect during treatment. The restoration of regulatory immune mechanisms may play a role in the clinical amelioration; however, further functional assessments of the repopulated immune system from stem cells have to be carried out to understand mechanisms behind inhibition of autoreactivity.

It is also important to underline the relative high chance of disease relapse after AHSCT. Unlike autologous HSCT, allogeneic HSCT seems to offer a more curative potential since the auto-reactive immune system is replaced by a new one. Although autologous HSCT can restore the self-tolerance, cannot eliminate genetic risk factors for the development of autoimmune diseases and therefore relapses are not unexpected in the treated patients. On the contrary, allogeneic HSCT offers a completely new immune system for the recipient with a higher chance for a definitive cure. Nevertheless, the high risk of graft-versus-host disease limits its wide clinical use, and the complications of its ablative treatment are also associated with significant treatment related mortality [86].

For the appropriate evaluation of the risks of AHSCT, it is important to consider the most common complications of ablative therapy, including infections with aplasia, bleeding, and organ failures (such as cardio-respiratory system). The period of pancytopenia is unfortunately long and patients are exposed to high risk of infection and haemorrhage until the re-infused autologous stem cells repopulate the peripheral blood with mature progeny [15]. In order to shed light on the real efficacy and the suitable therapeutic role of AHSCT in autoimmune diseases, successful completion of further large scale trials, including randomized controlled studies is mandatory, which are actually available for a few autoimmune diseases in a limited number only (Table 2).

5. Conclusions and future perspectives

The development of autoimmune diseases is driven by an intricate interplay between genetic and environmental factors. However, AHSCT in the therapeutic arsenal can only target just one element of the pathogenesis; consequently, the final healing or long-lasting cure cannot always be achieved and the good initial responses are commonly followed by early relapses. Nevertheless, the intensity of disease activity does not reach the pre-treatment level, and the patients often become responsive to conventional treatment options, such as DMARDs, or biologics again. Currently, it is not clear if the immune resetting after AHSCT is temporary, neither which mechanisms are responsible for the clinical remission. However, the considerable rate of post-transplantation relapse suggests that further immunological interventions are still required after AHSCT. Understanding the mechanisms of disease remission and relapse are essential for personalizing AHSCT regimen and post-transplantation treatment.

In the last five years, the best results with AHSCT have been reported for patients with multiple sclerosis and systemic sclerosis. In Crohn's disease and type 1 diabetes mellitus, a few promising reports were also published. In contrast, high procedural risks and mortality were revealed in other conditions such as SLE, RA and JIA; and due to the development of novel, effective and low-risk biological agents, the number of AHSCT has declined strongly in these diseases.

It is important to underline, that besides its beneficial effects in some selected diseases, AHSCT remained still a controversial procedure. After the treatment, besides the possibility of treatment-related complications and relapse of the original autoimmune disorder, various other autoimmune diseases can also develop both organ specific and systemic ones [87].

Development of autoimmune thrombocytopenia, acquired hemophilia, autoimmune hemolytic anemia, Evans' syndrome, autoimmune thyroiditis and ulcerative colitis have been reported following AHSCT. Rheumatoid arthritis and spondylarthropathy can also develop, additionally, myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) could be a major complication, as well. The previous chemotherapy and irradiation during conditioning play presumably an important role in the development of these complications.

The effects of AHSCT on fertility are another important issue. Since there is a high prevalence of young females suffering from autoimmune disease, fertility preservation is one of the major factor in quality of life. Although there are only a limited data available on fertility after AHSCT in autoimmune diseases, recently, a retrospective EBMT study demonstrated a relative promising fertility finding with 22 pregnancies from 324 adult female, and 68% of them achieved a healthy live birth [88].

In summary, based on the lessons we learned in SLE and RA, it should be conceded that the current efficacy of AHSCT in MS and SSc are fundamentally based on the lack of effective, disease-specific treatment options in these diseases. However, in the near future, the accelerated technological improvement will hopefully lead to the better understanding of disease pathogenesis, which will results in further development of target specific therapeutic modalities even in MS and SSc, as well. Therefore, the range of indications for AHSCT in autoimmune diseases will presumably become substantially narrower in the next decade. Alternatively AHSCT combined with individually-tailored biologics may give better results. The other possibility is that in the future allogeneic stem cell transplantation may have a more substantial role in the therapeutic arsenal of the management of autoimmune disease however conditioning-related mortality needs to be reduced. Better conditioning regimens, which are better tolerable, need to be implemented for this alternative.

On the other hand, patients who have undergone stem cell therapy and relapse afterwards may show better response to conventional therapy/biological therapy compared to responses before ASCT. We assume that the combination therapy of AHSCT and modern targeted biologics can open novel avenues in the better managements of patients with systemic autoimmune diseases giving better perspectives to these patients.

Funding: This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Article highlights

- Intricate interplay of various immune cells contributes to the development of tolerance after AHSCT
- AHSCT carried out before any irreversible organ damage leads to the best clinical outcome
- Less treatment-related complications would make the application of AHSCT more widespread
- Impact of AHSCT decreased in some diseases due to the development of other novel treatments
- In certain autoimmune diseases AHSCT can be good choice when conventional therapy failed

References

[1] Papp G, Boros P, Nakken B, Szodoray P, Zeher M. Regulatory immune cells and functions in autoimmunity and transplantation immunology. Autoimmun Rev 2017 Mar 7. pii: S1568-9972(17)30066-6. doi: 10.1016/j.autrev.2017.03.011.

[2] Sykes M, Nikolic B. Treatment of severe autoimmune disease by stem-cell transplantation. Nature 2005;435:620-27.

[3] Coleman MA, Steptoe RJ. Induction of antigen-specific tolerance through hematopoietic stem cell-mediated gene therapy: the future for therapy of autoimmune disease? Autoimmun Rev 2012;12:195-203.

[4] Beilhack GF, Scheffold YC, Weissman IL, Taylor C, Jerabek L, Burge MJ et al. Purified allogeneic hematopoietic stem cell transplantation blocks diabetes pathogenesis in NOD mice. Diabetes 2003;52:59-68.

[5] Salomon BL, Sudres M, Cohen JL. Regulatory T cells in graft-versus-host disease. Springer Semin Immunopathol 2006;28:25-9.

[6] Muraro PA, Douek DC, Packer A, Chung K, Guenaga FJ, Cassiani-Ingoni R et al. Thymic output generates a new and diverse TCR repertoire after autologous stem cell transplantation in multiple sclerosis patients. J Exp Med 2005;201:805-16.

[7] Hirota K, Hashimoto M, Yoshitomi H, Tanaka S, Nomura T, Yamaguchi T et al. T cell self-reactivity forms a cytokine milieu for spontaneous development of IL-17+ Th cells that cause autoimmune arthritis. J Exp Med 2007;204:41-7.

[8] Annacker O, Pimenta-Araujo R, Burlen-Defranoux O, Barbosa TC, Cumano A, Bandeira A et al. CD25+ CD4+ T cells regulate the expansion of peripheral CD4 T cells through the production of IL-10. J Immunol 2001;166:3008-18.

[9] Hagen KA, Moses CT, Drasler EF, Podetz-Pedersen KM, Jameson SC, Khoruts A. A role of CD28 in lymphopenia-induced proliferation of CD4 T cells. J Immunol 2004;173:3909-15.

[10] Herrmann MM, Gaertner S, Stadelmann C, van den Brandt J, Böscke R, Budach W et al. Tolerance induction by bone marrow transplantation in a multiple sclerosis model. Blood 2005;106:1875-83.

[11] de Kleer I, Vastert B, Klein M, Teklenburg G, Arkesteijn G, Yung GP et al. Autologous stem cell transplantation for autoimmunity induces immunologic self-tolerance by reprogramming autoreactive T cells and restoring the CD4+CD25+ immune regulatory network. Blood 2006;107:1696-702.

[12] Storek J, Geddes M, Khan F, Huard B, Helg C, Chalandon Y et al. Reconstitution of the immune system after hematopoietic stem cell transplantation in humans. Semin Immunopathol 2008;30:425-37.

[13] Rutella S, Rumi C, Laurenti L, Pierelli L, Sora' F, Sica S et al. Immune reconstitution after transplantation of autologous peripheral CD34+ cells: analysis of predictive factors and comparison with unselected progenitor transplants. Br J Haematol 2000;108:105-15.

[14] Zhang L, Bertucci AM, Ramsey-Goldman R, Burt RK, Datta SK. Regulatory T cell (Treg) subsets return in patients with refractory lupus following stem cell transplantation, and TGF-beta-producing CD8+ Treg cells are associated with immunological remission of lupus. J Immunol 2009;183:6346-58

[15] Szodoray P, Varoczy L, Papp G, Barath S, Nakken B, Szegedi G et al. Immunological reconstitution after autologous stem cell transplantation in patients with refractory systemic autoimmune diseases. Scand J Rheumatol 2012;41:110-5.

[16] Raker VK, Domogalla MP, Steinbrink K. Tolerogenic Dendritic Cells for Regulatory T Cell Induction in Man. Front Immunol 2015;6:569.

[17] Li H, Shi B. Tolerogenic dendritic cells and their applications in transplantation. Cell Mol Immunol 2015;12:24-30.

[18] Carretero-Iglesia L, Bouchet-Delbos L, Louvet C, Drujont L, Segovia M, Merieau E et al. Comparative Study of the Immunoregulatory Capacity of In Vitro Generated Tolerogenic Dendritic Cells, Suppressor Macrophages, and Myeloid-Derived Suppressor Cells. Transplantation 2016;100:2079-89.

[19] European Society for Blood and Marrow Transplantation. EBMT Annual Report 2015. Available from: https://www.ebmt.org/Contents/Resources/Library/Annualreport/Documents/EBMT_AnnualRep_2015.pdf

[20] Abraham DJ, Varga J. Scleroderma: from cell and molecular mechanisms to disease models. Trends Immunol 2005;26:587-95.

[21] Papp G, Horvath I, Barath S, Gyimesi E, Sipka S, Szodoray P et al. Altered T-cell and regulatory cell repertoire in patients with diffuse cutaneous systemic sclerosis. Scand J Rheumatol 2011;40:205-10.

[22] LeRoy EC, Medsger TA Jr. Criteria for the classification of early systemic sclerosis. J Rheumatol 2001;28:1573-6.

[23] Farge D, Labopin M, Tyndall A, Fassas A, Mancardi GL, Van Laar J et al. Autologous hematopoietic stem cell transplantation for autoimmune diseases: an observational study on 12 years' experience from the European Group for Blood and Marrow Transplantation Working Party on Autoimmune Diseases. Haematologica 2010;95:284-92.

[24] Binks M, Passweg JR, Furst D, McSweeney P, Sullivan K, Besenthal C et al. Phase I/II trial of autologous stem cell transplantation in systemic sclerosis: procedure related mortality and impact on skin disease. Ann Rheum Dis 2001;60:577-84.

[25] Farge D, Passweg J, van Laar JM, Marjanovic Z, Besenthal C, Finke J et al; EBMT/EULAR Registry. Autologous stem cell transplantation in the treatment of systemic sclerosis: report from the EBMT/EULAR Registry. Ann Rheum Dis 2004;63:974-81.

[26] Nash RA, McSweeney PA, Nelson JL, Wener M, Georges GE, Langston AA et al. Allogeneic marrow transplantation in patients with severe systemic sclerosis: resolution of dermal fibrosis. Arthritis Rheum 2006;54:1982-6.

[27] Nash RA, McSweeney PA, Crofford LJ, Abidi M, Chen CS, Godwin JD et al. High-dose immunosuppressive therapy and autologous hematopoietic cell transplantation for severe systemic sclerosis: long-term follow-up of the US multicenter pilot study. Blood 2007;110:1388-96.

[28] Miniati I, Guiducci S, Conforti ML, Rogai V, Fiori G, Cinelli M et al. Autologous stem cell transplantation improves microcirculation in systemic sclerosis. Ann Rheum Dis 2009;68:94-8.

[29] Burt RK, Shah SJ, Dill K, Grant T, Gheorghiade M, Schroeder J et al. Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial. Lancet 2011;378:498-506.

[30] van Laar JM, Farge D, Sont JK, Naraghi K, Marjanovic Z, Larghero J et al.; EBMT/EULAR Scleroderma Study Group. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. JAMA 2014;311:2490-8.

[31] Sullivan K, Keyes-Elstein L, McSweeney P, Pinckney A, Welch B, Mayes MD, et al. Myeloablative Autologous Transplantation of CD34+ -Selected Hematopoietic Stem Cells (HSCT) Vs Monthly Intravenous Cyclophosphamide (CYC) for Severe Scleroderma with Internal Organ Involvement: Outcomes of a Randomized North American Clinical Trial [abstract]. Arthritis Rheumatol 2016;68(suppl 10).

[32] Cipriani P, Ruscitti P, Giacomelli R. Stem cell therapies for systemic sclerosis. Br J Haematol 2015;168:328-37.

[33] Frohman EM, Racke MK, Raine CS. Multiple sclerosis-the plaque and its pathogenesis. N Engl J Med 2006;354:942-55.

[34] Confavreux C, Vukusic S. Natural history of multiple sclerosis: a unifying concept. Brain 2006;129(Pt3):606-16.

[35] Saiz A, Blanco Y, Carreras E, Berenguer J, Rovira M, Pujol T et al. Clinical and MRI outcome after autologous hematopoietic stem cell transplantation in MS. Neurology 2004;62:282-4.

[36] Saccardi R, Kozak T, Bocelli-Tyndall C, Fassas A, Kazis A, Havrdova E et al; Autoimmune Diseases Working Party of EBMT. Autologous stem cell transplantation for progressive multiple sclerosis: update of the European Group for Blood and Marrow Transplantation autoimmune diseases working party database. Mult Scler 2006;12:814-23.

[37] Mancardi GL, Sormani MP, Di Gioia M, Vuolo L, Gualandi F, Amato MP et al.; Italian BMT Study Group. Autologous haematopoietic stem cell transplantation with an intermediate intensity conditioning regimen in multiple sclerosis: the Italian multi-centre experience. Mult Scler 2012;18:835-42.

[38] Burt RK, Loh Y, Cohen B, Stefoski D, Balabanov R, Katsamakis G et al. Autologous non-myeloablative haemopoietic stem cell transplantation in relapsing-remitting multiple sclerosis: a phase I/II study. Lancet Neurol 2009;8:244-53.

[39] Fagius J, Lundgren J, Oberg G. Early highly aggressive MS successfully treated by hematopoietic stem cell transplantation. Mult Scler 2009;15:229-37.

[40] Burt RK, Cohen BA, Russell E, Spero K, Joshi A, Oyama Y et al. Hematopoietic stem cell transplantation for progressive multiple sclerosis: failure of a total body irradiation-based conditioning regimen to prevent disease progression in patients with high disability scores. Blood 2003;102:2373-8.

[41] Burt RK, Balabanov R, Han X, Sharrack B, Morgan A, Quigley K et al. Association of nonmyeloablative hematopoietic stem cell transplantation with neurological disability in patients with relapsing-remitting multiple sclerosis. JAMA 2015;313:275-84.

[42] Nash RA, Hutton GJ, Racke MK, Popat U, Devine SM, Griffith LM et al. High-dose immunosuppressive therapy and autologous hematopoietic cell transplantation for relapsing-remitting multiple sclerosis (HALT-MS): a 3-year interim report. JAMA Neurol 2015;72:159-69.

[43] Mancardi GL, Murialdo A, Rossi P, Gualandi F, Martino G, Marmont A et al. Autologous stem cell transplantation as rescue therapy in malignant forms of multiple sclerosis. Mult Scler 2005;11:367-71.

[44] Kimiskidis V, Sakellari I, Tsimourtou V, Papagiannopoulos S, Kazis D, Vlaikidis N et al. Autologous stem-cell transplantation in malignant multiple sclerosis: a case with a favorable long-term outcome. Mult Scler 2008;14:278-83.

[45] Burman J, Iacobaeus E, Svenningsson A, Lycke J, Gunnarsson M, Nilsson P et al. Autologous haematopoietic stem cell transplantation for aggressive multiple sclerosis: the Swedish experience. J Neurol Neurosurg Psychiatry 2014;85:1116-21.

[46] Atkins HL, Bowman M, Allan D, Anstee G, Arnold DL, Bar-Or A et al. Immunoablation and autologous haemopoietic stem-cell transplantation for aggressive multiple sclerosis: a multicentre single-group phase 2 trial. Lancet 2016;388:576-85.

[47] Muraro PA, Pasquini M, Atkins H, Bowen JD, Farge D, Fassas A et al.; the MS-AHSCT Long-Term Outcomes Study Group. Long term outcomes after autologous hematopoietic stem cell transplantation for treatment of MS. ECTRIMS Online Library 2015;116682.

[48] Mancardi GL, Sormani MP, Gualandi F, Saiz A, Carreras E, Merelli E et al; ASTIMS Haemato-Neurological Collaborative Group, On behalf of the Autoimmune Disease Working Party (ADWP) of the European Group for Blood and Marrow Transplantation (EBMT); ASTIMS Haemato-Neurological Collaborative Group On behalf of the Autoimmune Disease Working Party ADWP of the European Group for Blood and Marrow Transplantation EBMT. Autologous hematopoietic stem cell transplantation in multiple sclerosis: a phase II trial. Neurology 2015;84:981-8.

[49] Northwestern University. Stem Cell Therapy for Patients With Multiple Sclerosis Failing Alternate Approved Therapy-A Randomized Study. ClinicalTrials.gov NCT00273364. Available from: https://clinicaltrials.gov/ct2/show/NCT00273364

[50] Shanahan F. Crohn's disease. Lancet 2002;359:62-9.

[51] Dryden GW. Overview of stem cell therapy for Crohn's disease. Expert Opin Biol Ther 2009;9:841-7.

[52] Burt RK, Craig RM, Milanetti F, Quigley K, Gozdziak P, Bucha J et al. Autologous nonmyeloablative hematopoietic stem cell transplantation in patients with severe anti-TNF refractory Crohn disease: long-term follow-up. Blood 2010;116:6123-32.

[53] Cassinotti A, Annaloro C, Ardizzone S, Onida F, Della Volpe A, Clerici M et al. Autologous haematopoietic stem cell transplantation without CD34+ cell selection in refractory Crohn's disease. Gut 2008;57:211-7.

[54] Hasselblatt P, Drognitz K, Potthoff K, Bertz H, Kruis W, Schmidt C et al. Remission of refractory Crohn's disease by high-dose cyclophosphamide and autologous peripheral blood stem cell transplantation. Aliment Pharmacol Ther 2012;36:725-35.

[55] Hawkey CJ, Allez M, Clark MM, Labopin M, Lindsay JO, Ricart E. Autologous Hematopoetic Stem Cell Transplantation for Refractory Crohn Disease: A Randomized Clinical Trial. JAMA 2015;314:2524-34.

[56] Tarr T, Papp G, Nagy N, Cserép E, Zeher M. Chronic high-dose glucocorticoid therapy triggers the development of chronic organ damage and worsens disease outcome in systemic lupus erythematosus. Clin Rheumatol 2017;36:327-33.

[57] Liao J, Chang C, Wu H, Lu Q. Cell-based therapies for systemic lupus erythematosus. Autoimmun Rev 2015;14:43-8.

[58] Burt RK, Traynor A, Statkute L, Barr WG, Rosa R, Schroeder J et al. Nonmyeloablative hematopoietic stem cell transplantation for systemic lupus erythematosus. JAMA 2006;295:527-35.

[59] Jayne D, Passweg J, Marmont A, Farge D, Zhao X, Arnold R et al.; European Group for Blood and Marrow Transplantation; European League Against Rheumatism Registry. Autologous stem cell transplantation for systemic lupus erythematosus. Lupus 2004;13:168-76.

[60] Alchi B, Jayne D, Labopin M, Demin A, Sergeevicheva V, Alexander T et al.; EBMT Autoimmune Disease Working Party members. Autologous haematopoietic stem cell transplantation for systemic lupus erythematosus: data from the European Group for Blood and Marrow Transplantation registry. Lupus 2013;22:245-53.

[61] Pavletic SZ, Illei GG. The role of immune ablation and stem cell transplantation in severe SLE. Best Pract Res Clin Rheumatol 2005;19:839-58.

[62] Relle M, Weinmann-Menke J, Scorletti E, Cavagna L, Schwarting A. Genetics and novel aspects of therapies in systemic lupus erythematosus. Autoimmun Rev 2015;14:1005-18.

[63] Leone A, Radin M, Almarzooqi AM, Al-Saleh J, Roccatello D, Sciascia S, et al. Autologous hematopoietic stem cell transplantation in Systemic Lupus Erythematosus and antiphospholipid syndrome: A systematic review. Autoimmun Rev. 2017 Mar 7. pii: S1568-9972(17)30061-7. doi: 10.1016/j.autrev.2017.03.008.

[64] Tyndall A, Saccardi R. Haematopoietic stem cell transplantation in the treatment of severe autoimmune disease: results from phase I/II studies, prospective randomized trials and future directions. Clin Exp Immunol 2005;141:1-9.

[65] Verburg RJ, Kruize AA, van den Hoogen FH, Fibbe WE, Petersen EJ, Preijers F et al. High dose chemotherapy and autologous stem cell transplantation in patients with rheumatoid arthritis: results of an open study to assess feasibility, safety and efficacy. Arthritis Rheum 2001;44:754-60.

[66] Ramaswamy S, Jain S, Ravindran V. Hematopoietic stem cell transplantation for auto immune rheumatic diseases. World J Transplant 2016;6:199-205.

[67] Snowden JA, Passweg J, Moore JJ, Milliken S, Cannell P, Van Laar J et al. Autologous hematopoietic stem cell transplantation in severe rheumatoid arthritis. J Rheumatol 2004;31:482-8.

[68] Zeher M, Papp G, Szodoray P. Autologous haemopoietic stem cell transplantation for autoimmune diseases. Expert Opin Biol Ther 2011;11:1193-201.

[69] Barron KS, Wallace C, Woolfrey CEA, Laxer RM, Hirsch R, Horwitz M et al. Autologous stem cell transplantation for pediatric rheumatic diseases. J Rheumatol 2001;28:2337-58.

[70] Wulffraat NM, de Kleer IM, Prakken BJ, Kuis W. Stem cell transplantation for autoimmune disorders. Refractory juvenile idiopathic arthritis. Best Pract Res Clin Haematol 2004;17:277-89.

[71] Brinkman DM, de Kleer IM, ten Cate R, van Rossum MA, Bekkering WP, Fasth A et al. Autologous stem cell transplantation in children with severe progressive systemic or polyarticular juvenile idiopathic arthritis: long-term follow-up of a prospective clinical trial. Arthritis Rheum 2007;56:2410-21.

[72] Daikeler T, Kötter I, Bocelli Tyndall C, Apperley J, Attarbaschi A, Guardiola P et al; EBMT Autoimmune Diseases Working Party. Haematopoietic stem cell transplantation for vasculitis including Behcet's disease and polychondritis: a retrospective analysis of patients recorded in the European Bone Marrow Transplantation and European League Against Rheumatism databases and a review of the literature. Ann Rheum Dis 2007;66:202-7.

[73] Statkute L, Oyama Y, Barr WG, Sufit R, Ho S, Verda L et al. Autologous non-myeloablative haematopoietic stem cell transplantation for refractory systemic vasculitis. Ann Rheum Dis 2008;67:991-7.

[74] Maurer B, Hensel M, Max R, Fiehn C, Ho AD, Lorenz HM. Autologous haematopoietic stem cell transplantation for Behcet's disease with pulmonary involvement: analysis after 5 years of follow up. Ann Rheum Dis 2006;65:127-9.

[75] Vermeulen M, Van Oers MH. Successful autologous stem cell transplantation in a patient with chronic inflammatory demyelinating polyneuropathy. J Neurol Neurosurg Psychiatry 2002;72:127-8.

[76] Mahdi-Rogers M, Kazmi M, Ferner R, Hughes RA, Renaud S, Steck AJ et al. Autologous peripheral blood stem cell transplantation for chronic acquired demyelinating neuropathy. J Peripher Nerv Syst 2009;14:118-24.

[77] Press R, Askmark H, Svenningsson A, Andersen O, Axelson HW, Strömberg U. Autologous haematopoietic stem cell transplantation: a viable treatment option for CIDP. J Neurol Neurosurg Psychiatry 2014;85:618-24.

[78] Northwestern University. Hematopoietic Stem Cell Transplantation in Chronic Inflammatory Demyelinating Polyneuropathy. ClinicalTrials.gov NCT00278629. Available from: https://clinicaltrials.gov/ct2/show/NCT00278629

[79] Rao VK, Price S, Perkins K, Aldridge P, Tretler J, Davis J et al. Use of rituximab for refractory cytopenias associated with autoimmune lymphoproliferative syndrome (ALPS). Pediatr Blood Cancer 2009;52:847-52.

[80] Bluestone JA, Herold K, Eisenbarth G. Genetics, pathogenesis and clinical interventions in type 1 diabetes. Nature 2010;464:1293-300.

[81] Milanetti F, Abinun M, Voltarelli JC, Burt RK. Autologous hematopoietic stem cell transplantation for childhood autoimmune disease. Pediatr Clin North Am 2010;57:239-71.

[82] Voltarelli JC, Couri CE, Stracieri AB, Oliveira MC, Moraes DA, Pieroni F et al. Autologous nonmyeloablative hematopoietic stem cell transplantation in newly diagnosed type 1 diabetes mellitus. JAMA 2007;297:1568-76.

[83] Couri CE, Oliveira MC, Stracieri AB, Moraes DA, Pieroni F, Barros GM et al. C-peptide levels and insulin independence following autologous nonmyeloablative

hematopoietic stem cell transplantation in newly diagnosed type 1 diabetes mellitus. JAMA 2009;301:1573-79.

[84] D'Addio F, Valderrama Vasquez A, Ben Nasr M, Franek E, Zhu D, Li L et al. Autologous nonmyeloablative hematopoietic stem cell transplantation in new-onset type 1 diabetes: a multicenter analysis. Diabetes 2014;63:3041-6.

[85] El-Badawy A, El-Badri N. Clinical Efficacy of Stem Cell Therapy for Diabetes Mellitus: A Meta-Analysis. PLoS One 2016;11:e0151938.

[86] Hügle T, van Laar JM. Allogeneic stem cell transplantation for rheumatic autoimmune diseases. F1000 Med Rep 2010;2:22.

[87] Bohgaki T, Atsumi T, Koike T. Autoimmune disease after autologous hematopoietic stem cell transplantation. Autoimmun Rev 2008;7:198-203.

[88] Snarski E, Snowden JA, Oliveira MC, Simoes B, Badoglio M, Carlson K et al. Onset and outcome of pregnancy after autologous haematopoietic SCT (AHSCT) for autoimmune diseases: a retrospective study of the EBMT autoimmune diseases working party (ADWP). Bone Marrow Transplant 2015;50:216-20.

Tables

Autoimmune disease	Number of treated patients
Multiple sclerosis	801
Systemic sclerosis	433
Crohn's disease	155
Systemic lupus erythematosus	113
Juvenile chronic arthritis	89
Rheumatoid arthritis	85
Vasculitides	49
Immune thrombocytopenic purpura	31
Chr. inflamm. demyelinating polyneuropathy	31
Autoimmune hemolytic anemia	25

Table 1. The list of the top 10 autoimmune diseases treated with AHSCT in Europe between 1995 and 2015, according to the latest annual report on EBMT database [19].

Trial	Disease	Status	Treatment	Trial number	Reference
ASSIST (Autologous Stem Cell Transplantation for Refractory Systemic Lupus Erythematosus)	Systemic sclerosis	Completed	ASCT vs. Cyclophosphamide	NCT00750971	[29]
ASTIC (Autologous Stem Cell Transplantation for Crohn's Disease)	Crohn's disease	Terminated	Early vs. Late ASCT	NCT00297193	[55]
ASTIMS (Autologous Stem cell Transplantation International Multiple Sclerosis)	Multiple sclerosis	Completed	ASCT vs. Mitoxantrone	Eudract 2007 - 000064-24	[48]
ASTIS (Autologous Stem cell Transplantation International Scleroderma trial)	Systemic sclerosis	Completed	ASCT vs. Cyclophosphamide	NTR338	[30]
MIST (Stem Cell Therapy for Patients With Multiple Sclerosis Failing Alternate Approved Therapy- A Randomized Study)	Multiple sclerosis	Ongoing	ASCT vs. Standard therapy	NCT00273364	[49]
SCOT (Scleroderma: Cyclophosphamide or Transplantation)	Systemic sclerosis	Completed	ASCT vs. Cyclophosphamide	NCT00114530	[31]

Table 2. Prospective randomized controlled studies on AHSCT in autoimmune diseases.