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REVIEW

Hematopoietic Stem Cell Transplantation in Children with Autoimmune Connective Tissue Diseases

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Abstract Autoimmune connective tissue diseases (ACTDs) are heterogeneous disorders associated with different manifestations, clinical course of disease and prognosis among patients. Although recent advances in understanding the pathogenesis have led to major progress in target-oriented therapy, they still remain incurable. Novel biological drugs, cellular therapy and hematopoietic stem cell transplantation (HSCT) are real hopes for treatment development in the future. The concept of both autologous and allogeneic HSCT in children with autoimmune diseases is developing energetically since 1996, when the first HSCT was performed. Nowadays, after 17 years of clinical experience, both types of HSCT remain attractive and powerful salvage methods of treatment. However, there are still many doubts and unclear issues, which need further investigation. In the present review, we provide an overview of the knowledge concerning actual data on HSCT in a pediatric group of patients with different ACTDs, focused on juvenile idiopathic arthritis, systemic lupus erythematosus and systemic sclerosis.

Keywords Autoimmune connective tissue diseases · Children · Treatment · Hematopoietic stem cell transplantation

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Introduction

Autoimmune connective tissue diseases (ACTDs) are a heterogeneous group of disorders, which include rheumatoid arthritis in adults, and juvenile idiopathic arthritis (JIA) in children, systemic lupus erythematosus (SLE), dermatomyositis, systemic vasculitis and systemic sclerosis (SSc). Particular ACTDs differ between each other with regard to the clinical course, depending on the type of the disease-accompanying organ injuries. Although, the symptoms in the majority of patients are mild, such as skin changes or arthralgia, in a considerable number of children the disease tends to be progressive with severe or even life-threatening organ involvement.

Although the exact pathogenesis of ACTDs is still unknown, it is generally characterized as an abnormality in antigen recognition and presentation, which leads to enhanced production of proinflammatory cytokines and autoantibodies, eventually causing damage to specific organs and tissues. It is believed that there is a complex individual susceptibility to develop autoimmunity due to genetic, environmental and microbial agents. ACTDs are often accompanied by immune deficiency, especially with decreased IgA levels (Yel 2010). Faulty immune system is also due to long-term, intensive treatment with different immunosuppressive drugs. Disturbed immunoregulation and development of autoreactive T and B cells targeting self-antigens usually lead to organ impairment (Kowal-Bielecka et al. 2009; Kumar et al. 2003; Raj et al. 2002).

During the last few decades, many new therapeutic approaches for patients with ACTDs have appeared. Today, not only disease-modifying drugs, but also biologic-specific targeting cytokines have been successfully introduced into clinical use (Kumar et al. 2003). Although major progress has been made, still, there is no therapy

effective enough to obtain complete remission in the majority of patients (Kowal-Bielecka et al. 2009; Raj et al. 2002). So far, the standard of care consists of symptomatic treatment that depends on the type and advancement of organ involvement. Although the overall prognosis for the majority of patients is favorable, up to 30 % of children do not achieve even part remission in data collected from randomized controlled trials (Redlich et al. 2003). The disease in such cases is refractory to conventional treatment and leads to severe joint or other organ damage and reduced quality of life. In the whole group, the estimated mortality rate was 2–4 % (Petty 1999).

Despite new treatment strategies developed lately for patients with ACTDs, the course of diseases tends to be progressive and refractory to therapy in a considerable number of children. Promising results of hematopoietic stem cell transplantation (HSCT) were reported initially on animal models, which suggested a potential therapeutic option in the resistant group (Zeher et al. 2011). Moreover, complete remission of concomitant autoimmune disease was also observed in patients undergoing HSCT to hematological abnormalities (Meloni et al. 1997). In this paper, we review the state of art on both autologous (auto-HSCT) and allogeneic HSCT (allo-HSCT) in resistant/relapsed group of children with the most common ACTDs.

Standard and Newer Treatment Strategies for the Most Frequent ACTDs in Children

Juvenile Idiopathic Arthritis

JIA is a very frequent chronic illness and the most common of all rheumatic disease observed among pediatric patients. The prevalence rate for chronic arthritis under 16 years of age is 16–50/10,000 (Ravelli and Martini 2007). The rate of resistance to therapy in this group varies depending on the type of onset of the disease, including the use of both disease-modifying anti-rheumatic drugs (DMARDs) and biologic agents. The rate of death is 0.23 % (Hashkes et al. 2010). JIA is caused by inflammation of the synovium, which as a result leads to significant pain, swelling, joint deformity and growth impairment, with progressive destruction of joints. This term describes a heterogenous group of arthritis lasting more than 6 weeks, with the first disease symptoms appearing before 16 years of age (Kahn 2012). The etiology of JIA still remains unknown. So far, the most probable disease-relating factors are mentioned environmental exposures such as infections and genetic predisposition. A key to their pathogenesis is regarded as an increased production of proinflammatory cytokines, responsible for secreting metalloproteinases, which leads to the destruction of articular cartilage (El Bahri et al. 2007; Kahn 2012).

The most important feature of JIA is systemic manifestation of the disease, with involvement of large joints, oligoarticular onset, as well as several developmental abnormalities regarding JIA. Also, a rarer presence of the rheumatoid factor and anti-cyclic citrullinated peptide antibodies or later appearance of radiological changes is characteristic for JIA (Adib et al. 2005; Kahn 2012).

The concept of the current therapy mainly concentrates on aggressive approach from the beginning to prevent long-term damage. Treatment of JIA should be complex, including not only pharmacotherapy adjusted to the specific type of disease, but also with physical and occupational therapy with surgical interventions if needed. JIA is mainly treated with a combination of non-steroidal anti-inflammatory drugs (NSAIDs), steroids, DMARDs such as methotrexate (MTX), sulfasalazine, hydroxychlorochine, leflunomide or immunosuppressive agents (cyclosporine A, azathioprine, chlorambucil or cyclophosphamide) (Kahn 2012; Niehues and Lankisch 2006). Despite toxicity of chronic treatment mentioned above, such as hepatotoxicity or pneumonitis induced by MTX, their safety and tolerability are mostly favorable. Of importance is the fact that if the therapy is administered in the early stage of the disease, it may improve long-term outcomes, including reduction in disability, higher quality of life and longer life expectancy. Recently, interesting results have been observed while biological therapies, including inhibitors of tumor necrosis factor (TNF)-α pathway (anti-TNF drugs; infliximab, etanercept, adalimumab, golimumab, certolizumab), anti-interleukin (IL)-1 receptor antibody (anakinra, canakinumab), anti-IL-6 receptor antibody (tocilizumab), anti-CD20 monoclonal antibody (rituximab), anti-costimulatory molecules (abatacept), as well as JAK signaling pathway inhibitors (tofacitinib), are being further investigated. Novel drugs are much more effective, especially in patients already refractory to treatment with DMARDs (Huang 2012; Kahn 2012; McMahan et al. 2012). Unfortunately, those novel agents may on the other hand increase the risk of serious infections, including tuberculosis (Toussirot et al. 2007). Some of them have been already approved by the Food and Drug Administration and/or European Medicines Agency. Several new biological drugs are currently under investigation in the randomized clinical studies. Despite the already proven effectiveness of these new therapies, there is still a group of JIA cases that relapse or is resistant to this treatment. These children can possibly benefit from more aggressive approach including HSCT.

Juvenile SLE

Another common childhood ACTD is juvenile SLE (jSLE). The prevalence of this disease is difficult to estimate

because there are very few studies focused on pediatric population. Approximately, 15–20 % of SLE cases begin before the age of 16 years. Data suggest a prevalence of jSLE from 6 to 18.9/100,000 (Malleson et al. 1996). The overall 5-year survival in recent studies has shown the rate to be >95 %. The percentage of death is 16 % and depends on the kind of organ involvement (Hari et al. 2009). The etiology of jSLE is still unclear; however, different hormonal, genetic, environmental and infectious factors are considered to play a role in its pathogenesis. The disease is characterized by widespread immune dysregulation, due to overproduction of autoantibodies and immune complexes, resulting in chronic inflammation and possible injury of different organs. Moreover, there is observed overproduction of several inflammatory cytokines, along the impaired T-cell function and enhanced apoptosis. There are notable differences among the clinical manifestations of the disease between children; however, the onset is usually rapid, with fever, weakness, weight loss and symptoms connected with organ involvement. In more severe cases, life-threatening renal and neurologic damage are observed (Habibi et al. 2011).

Treatment for jSLE should be tailored according to the disease activity, severity, types of organ involvement as well as number of observed flares. Different therapies available nowadays include NSAIDs, antimalarial agents, corticosteroids (high dose of methylprednisolone in high disease activity), high-dose intravenous immunoglobulins and cytotoxic immunosuppressive agents such as azathioprine, cyclophosphamide (CY), MTX or mycophenolic acid. Although these strategies can be moderately effective, a new, specific, B cell-targeted therapy has been developed (rituximab). Moreover, belimumab, a monoclonal antibody against B-lymphocyte stimulator B-cell activating factor; a member of the TNF (ligand superfamily), a key factor in maturation and survival of B cells, approved in treatment of adult SLE patients, is currently under investigation in jSLE (Bezalel et al. 2012; Gurevitz et al. 2013; Habibi et al. 2011). The agent is targeted to reduce autoantibody production and by prevention of antigen presenting to T cells. However, therapy remains challenging in children with refractory and relapsed disease course. In this group of patients, HSCT could be a promising therapeutic opportunity.

Systemic Sclerosis

SSc is a chronic, multisystem ACTD connected with immune dysregulation, which leads to increased fibrosis in skin and internal organs and vasculopathy. The prevalence of SSc in adult patients is estimated at 27.6 cases per 100,000. Children younger than 10 years account for <2 % of all cases, and patients between 10 and 20 years of age for only 1.3–9 %. Survivorship has not been determined in any large series of children because of the rarity of this disease. The survival rate of childhood onset SSc at 10 year after diagnosis was 75 % (Scalapino et al. 2006).

In children, the main clinical manifestation includes skin changes, Raynaud's phenomenon, pulmonary fibrosis, pulmonary arterial hypertension and other visceral organ involvement. Moreover, advanced changes in motional organs can lead to disability (Balbir-Gurman and Braun-Moscovici 2012; Torok 2012; Zulian and Martini 2007). First-line treatment in SSc includes MTX, d-penicillamine, piascledine and, in systemic disease, drugs that expand the blood vessels and steroids. In more severe cases, mainly in lung involvement, immunosuppressive treatment (cyclosporine A, CY) is used. Newer T cell-targeted therapies (sirolimus and anti-CD2 antibody, alefacept) as well as monoclonal anti-B-cell antibody, rituximab, showed encouraging results in a preliminary studies in adult patients (Balbir-Gurman and Braun-Moscovici 2012). Clinical efficacy and safety of antifibrotic treatment, including Abl/Bcr inhibitor, imatinib, have to be confirmed in further studies (Manno and Boin 2010).

The Role of Stem Cell Transplantations in Children with ACTDs

HSCT is a widely accepted procedure, in which hematopoietic stem cells of any donor type and source are given to the recipient after appropriate preparation. Depending on the donor type, HSCTs are classified into two groups: auto-HSCT (stem cells collected from the patient) and allo-HSCT (stem cells collected from related or unrelated donor). Moreover, stem cells for both types of transplantations can be obtained from bone marrow or mobilized from peripheral blood (the most common source of stem cells). Finally, an umbilical cord blood can be the source of stem cells for HSCT, especially for the pediatric group. Originally, transplantation procedures were reserved mainly for patients with congenital or acquired hematopoietic system disorders or malignant tumors, which require high-dose chemotherapy. Nowadays, with major evolution in HSCT methodology, there are many new indications for transplantations, both autologous and allogeneic. These indications, according to UK Pediatric Bone Marrow Transplantation Group (http://bsbmt.org), which are revised annually, are presented in Table 1. The development of knowledge about biology of hematopoietic stem cell provided more profound understanding of HSCT techniques and biological implications for the recipients. As a result, we can more accurately manipulate the immune system, providing the possibility to cure a wide variety of new diseases.

Table 1 Indications for autogenous and allogeneic HSCT in children (according to the UK Pediatric Bone Marrow Transplantation Group)

	Disease	Auto-HSCT	Allo-HSCT
Hematologic malignancy	Acute myeloid leukemia	S	S
	Acute lymphoblastic leukemia	CO	S
	Chronic myeloid leukemia	S	CO
	Myelodysplastic syndrome	GNR	S
	Non-Hodgkin's lymphoma	S	CO
	Hodgkin's lymphoma	S	CO
Bone marrow failure	Acquired aplastic anemia	GNR	S
	Diamond-Blackfan anemia	GNR	S
	Dyskeratosis congenita	GNR	S
	Fanconi anemia	GNR	S
	Constitutional monocytopenia	GNR	S
Immunodeficiencies	Severe combined immunodeficiency	GNR	S
	Chediak–Higashi syndrome	GNR	S
	Wiskott–Aldrich syndrome	GNR	S
	Chronic granulomatous disease	GNR	S
	Leukocyte adhesion deficiency	GNR	S
	X-linked lymphoproliferaltive syndrome	GNR	S
	Leukocyte adhesion deficiency	GNR	S
Hemoglobinopathies	Thalassemia	GNR	S
	Sickle cell disease	GNR	S
Solid tumor	Neuroblastoma	S	CO
	Medulloblastoma	S	GNR
	Ewing's sarcoma	S	GNR
	Wilms tumor	CO	GNR
	Germ cell tumor	CO	GNR
	Soft tissue sarcoma	CO	GNR
	Brain tumors	CO	GNR
Metabolic disease	Mucopolissacaridose	GNR	S
	Mannosidosis sphingolipidosis	GNR	CO
	Adrenoleukodystrophy	GNR	CO

S standard of care, *CO* clinical option after careful assessment of risks and benefits, *GNR* generally not recommended

Both types of HSCTs are highly invasive procedures, associated with many side effects leading to morbidity and treatment-related mortality (TRM). This issue is the most important limitation for widespread transplantations among children with ACTDs. The TRM ratios and side effects are different for both HSCT types, being much higher in allo-HSCT. In a study by Locatelli et al. (2005), the 5-year TRM after allogeneic transplantation was 13 %, while for auto-HSCT it is reported to be under 5 % (Marmont 1998). It is crucial that side effects after auto-HSCT are not as severe as after allo-HSCT. Both types of transplantations are connected with well-known acute toxicity like infection and bleeding during the aplastic period and late toxicity, i.e., infection during the T-cell reconstitution period. Some other complications emerged during the program; the most common were secondary neoplasms, endocrine or renal dysfunctions and immunodeficiencies (Cohen et al. 2008). What makes allo-HSCT more dangerous is mainly graft-versus-host disease (GVHD) that is unique to this procedure. It may be extensive or more limited, while the donor T cells attack recipient tissues, mainly the liver, skin and gastrointestinal tract.

Recently, the rate of morbidity and mortality related to transplantation procedures has been decreasing, mainly due to progress in HSCT techniques. Not only conditioning regimens are much safer, but also antibiotics and antifungal drugs are more efficient. Moreover, experience in facing post-transplant complications has still been improving. Unfortunately, the risk of allo-HSCT-related side effects is still high. A key factor is that after both auto- and allo-HSCT, proper procedures must be accomplished. The most important is the awareness about preventive and supportive programs as well as about detailed screening investigations.

The first investigations that have proven that auto-HSCT and, in some indications, allo-HSCT may be beneficial in ACTDs were made on animal models. The experimental data suggested the opportunity of changing the course of autoimmune disease after both types of HSCTs (Knaan-Shanzer et al. 1991; van Bekkum et al. 1989). Moreover, there were significant advances in the recognition of the potential mechanism of those therapeutic methods. It was observed that allo-HSCT was more beneficial in disease control than auto-HSCT. However, there was no statistical difference in long-term survival between the auto-HSCT and allo-HSCT groups, while allo-HSCT is strictly associated with higher morbidity and mortality rates (Ikehara 2002; van Bekkum 1993, 2000, 2004).

Crucial for further development were incidental findings in patients who received HSCT due to hematological indications, with coexistence of ACTD. Collected data confirmed that transplantation procedure can stop the inflammation associated with a disease. Complete remission of autoimmune disease was observed both after auto-HSCT (Meloni et al. 1997) and allo-HSCT (Baldwin et al. 1977). In a work published by Marmont (2004) in the majority of patients, remission was observed even 20 years after auto-HSCT or allo-HSCT procedures. Every relapse was strictly connected with recurrence of hematological disorder. The theory that autoimmune disease can be caused, at least in some part, by damage of stem cell was also supported by clinical data in which ACTD was transmitted after allo-HSCT from donor to the recipient (Bargetzi et al. 1997; Berisso et al. 1999; Marazuela and Steegman 2000).

Since 1996, when the first auto-HSCT in severe ACTD has been performed, more than 159 transplantations have been accomplished in pediatric patients (119 autologous and 40 allogeneic). Each case was registered in the European Group for Blood and Marrow Transplantation (EBMT) database. Autoimmune diseases can be treated by both auto- and allo-HSCT depending on indications. Both methods have their advantages and disadvantages and should be precisely considered before being selected.

The efficacy of auto-HSCT has been already confirmed by the data from the largest observational study by Farge et al. (2010). It is for sure a valid therapeutic option for children with ACTD if the disease is progressive, in spite of standard treatment. It is especially recommended after the failure of biological agents, or if they are not available for specific autoimmune disease. It is extremely important to analyze each patient separately according to not only the type of autoimmune disease, but also clinical stage. Appropriate inter-disciplinary center should be consisted of specialist in hematology as well as specialist in autoimmune disease, both with experience in transplantation procedures. Moreover, centers should provide Joint Accreditation Committee for International Society for Cell Therapy Europe and EBMT (JACIE) accreditation or equivalent certificate to perform transplantation. Each time there is a possibility, HSCT should be performed in clinical trial according to both clearly defined end points and eligibility criteria.

Although there have been prior enormous expectations associated with allogeneic transplantation, its position is still unclear. First of all, the high mortality and morbidity connected with GVHD must be considered in every patient, even if reduced dose conditioning regimens are applied. What is more, despite the complete donor chimerism, there are still cases of autoimmune disease relapse after allo-HSCT. This is a clear confirmation that minimal residual disease could survive even the graft-versus-autoimmunity (GVA) effects (Mckendry et al. 1996; Tapprich et al. 2003). Further, experience is needed to establish clear indications for allogeneic procedure in children with ACTDs. For sure, the early enthusiasm must be confronted with a realistic evaluation, until a new important turning point arises.

So far, the predominance of auto-HSCT over allo-HSCTs is clear, mainly because of lower risk of post-transplant complications. Data on children with autoimmune disease who received auto-HSCT are depicted in Table 2. Last, but not least, patients, who relapse after transplantation procedure can still be treated with standard or biological drugs to which they used to be resistant earlier.

The most common diagnosis of patients treated with HSCT in the pediatric group is JIA (61 auto-HSCTs and three allo-HSCTs), jSLE (17 auto-HSCTs and one allo-HSCTs) and SSc (nine auto-HSCTs). The immune system can be destroyed directly with stem cells replacement or by the immunomodulatory mechanism connected with mesenchymal stem cells. It is believed that even after auto-HSCT, the immune system can reset and regenerate without relapse of the disease (Rabusin et al. 2008).

Already three studies included pediatric patients with JIA who underwent auto-HSCT. The first retrospective analysis by De Kleer et al. (2004) included 34 children diagnosed with JIA. All of them were treated with auto-HSCT, proceeding with T-cell depletion. In 25 patients, stem cells were collected from bone marrow, and in nine mobilized from peripheral blood. There were three different conditioning regimens used in this study. First was myeloablative, composed of anti-thymocyte globulin (ATG), CY, and low-dose total body irradiation (TBI); the second was immune ablative as well without TBI, while the last one include fludarabine, ATG, CY, and methylprednisolone. It was observed that the outcome did not differ between different conditioning regimens used. After the follow-up of 29 months 53 % achieved complete remission (CR), without necessity of treatment; 20 % of them were in partial remission (PR) and needed low doses of additional regimens. The second investigation was performed on a group which consisted of 22 children (Brinkman et al. 2007). All of the patients were treated with T-cell-depleted autologous transplantation with a previous myeloablative and immunoablative conditioning consisting of CY, ATG and TBI. In the median follow-up of 80 months, 36 % achieved CR and 20 % PR. There were two deaths connected with transplant complications. An important issue is that 9 % of TRM was strictly due to infection. The last analyzed trial of auto-HSCT in children with JIA (Ferreira et al. 2006) was performed on a smaller group of seven children. All the children were conditioned with ATG and CY. Stem cells were collected from bone marrow (five patients) or peripheral blood (two patients), and after that T-cell depletion by means of positive $CD34^+$ cell selection was performed in all of them. The CR was observed in four patients, two of them relapsed and one child died 4 months after auto-HSCT due to severe infection.

So far, two studies have described a group of jSLE children in whom auto-HSCT was performed. Jayne et al. (2004) reported results in the SLE group consisting of 53 patients, including 17 children. The myeloablative and immunoablative conditioning regimen was mainly composed of CY, ATG, and TLI with positive selection of $CD34^+$ in half of the children. CR of the entire group was achieved at 50 % level. The other work by Chen et al. (2005) is a case report of two girls (aged 18 and 13 years), who obtained auto-HSCT. $CD34^+$ was collected from peripheral blood and mobilized by granulocyte-colony

Table 2 Data collected from studies of auto-HSCT performed in children with autoimmune diseases

Disease	References	*N*	Donor type	CR (%)	PR (%)	R (%)	TRM (%)	Follow-up (months)
Juvenile idiopathic arthritis	De Kleer et al. (2004)	34/34	Auto	18	6	9	5	29
	Brinkman et al. (2007)	22/22	Auto	8	7	5	2	80
	Ferreira et al. (2006)	7/7	Auto	4	2	–	–	60
Systemic lupus erythematosus	Jayne et al. (2004)	17/53	Auto	33	7	10	7	26
	Chen et al. (2005)	2/2	Auto	1	–	1	–	48
Systemic sclerosis	Vonk et al. (2008)	5/28	Auto	3	–	–	1	63
	Farge et al. (2004)	5/57	Auto	3	–	–	–	21

N number of children in the study of the total number of patients, *CR* complete remission, *PR* partial remission, *R* relapse, *TRM* transplant-related mortality in 100 days

stimulating factor (G-CSF). Both patients were conditioned by immunoablative regimen combination based on CY and ATG. One of them had a CR after 4 years of follow-up and the other relapsed after 9 months from the transplantation procedure.

As SSc is an extremely rare disease; the data collected about children treated with auto-HSCT are poor too. In clinical practice, this kind of transplantation may be especially effective for severe fibrotic skin disease, but its toxicity may be an important limiting factor. So far, there were two studies that included groups of a few SSc children treated with HSCTs. Vonk et al. (2008) reported 28 patients, with five children included in auto-HSCT. Stem cells were collected from peripheral blood achieved with CY and G-CSF, or in some cases G-CSF used alone. Three children obtained CR after more than 5 years of the observation period. The EBMT database (Farge et al. 2004) reported CR after almost 23 months of follow-up in three out of five SSc children treated with auto-HSCT. What is more, 100-day TRM was not noticed.

Most recently, Holzer et al. (2010) reported two children with dermatomyositis, treated with auto-SCT. Both cases were refractory, wheelchair dependent, although many lines of chemotherapy (for instance, metotrexate and cyclosporine A) and immunotherapy (rituximab and immunoglobulins) were given. The outcome of this study was excellent. In both cases, major improvement in everyday lifeand remission of the autoimmune disease were observed.

The main benefit from proceeding auto-HSCT is the possibility to treat with intense immune suppression induced by the conditioning regimen. This gives the possibility to destroy the immune system completely and provide an attempt to regenerate. It was discovered that the regeneration and activation of $CD4^+/CD25^+$ regulatory T lymphocytes play a main role in inducing peripheral tolerance to autoantigens by the secretion of cytokines (TGF-β and IL-10) (Bennett 2001). T-regulatory cells expressing the transcription factor Foxp3 are a key to prevent autoreactivity. Moreover, during regeneration, adaptive immune system showed normal level of the restricted T cell, replacing memory T- and B-cell subpopulations with naïve cell. For sure, the exact mechanism is still unclear: whether the auto-HSCT outcome is mainly immunosuppressive without any need of stem cell rescue or it has the role inducing immunological self-tolerance as well. It could be possible by reprogramming autoreactive cells to a tolerant phenotype and as a result restoring the $CD4^+/CD25^+$ immune-regulatory network (Seidel et al. 2006).

Allo-HSCT is a procedure considered to be much more effective than auto-HSCT mainly due to the possibility of replacing faulty autoimmune system by new, healthy one. There are many mechanisms that are considered to be responsible for the positive effects of allo-HSCT in autoimmune diseases, such as tolerability by T-regulatory cells, immunomodulation, and most importantly immune-mediated destruction of autoreactive cells (Sykes and Nikolic 2005). Similar to widely accepted graft-versus-leukemia effect (Falkenburg and Warren 2011), in ACTDs it was defined as a GVA effect (Appelbaum 2001). The data collected so far were from patients, who underwent HSCT for hematological disease proving that acute and chronic GVHD is strictly connected with lower relapse rate of autoimmune disease (Hinterberger et al. 2002). It is not fully discovered whether the relapse is part of a graft rejection or if the disease control is partly achieved by engraftment of the normal donor cells or as a specific GVA. Mixed chimerism after allo-HSCT may be another possible explanation for controlling autoimmune disease after allogeneic transplantation.

So far, the data that gather information about allo-HSCT performed in children with ACTDs are extremely poor. In theory, the curative result after replacing the entire immune system with a healthy one should be superior than the effect of auto-HSCT. Although it is confirmed to control the course of disease much better, still there are no reliable findings on the long-term survival difference between auto- and allo-HSCT in animal models. A retrospective analysis

by Rabusin et al. (2011) on behalf of the EMBT registry took into consideration both auto-HSCT and allo-HSCT. Unfortunately, in this study data on both types of HSCTs cannot be compared because of the small number of patients with allogeneic transplantation. It includes 24 children with the diagnosis of immune cytopenia (ten with Evans syndrome, six with autoimmune hemolytic anemia, five with immune thrombocytopenia and three with autoimmune lymphoproliferative syndrome). Altogethe,r 7 auto-HSCT (one patient received two transplantations) and 19 allo-HSCT (one after previous auto-HSCT) were performed. The percentage of TRM was high (26 %). After the follow-up that lasted 120 months, CR was noted in 13 children. In the group of six children who relapsed, two obtained allo-HSCT and four obtained auto-HSCT.

Conclusions

So far, the data published on transplantation in severe childhood autoimmune disease suggest that HSCT may be an effective therapeutic option (Pession et al. 2012). The first success of HSCT in ACTDs was accidentally reported in patients who, after transplantation procedure for a hematological indication, were cured of a coexisting autoimmune disease. According to last EMBT guidelines (Snowden et al. 2012), auto-HSCT or, in patients who have stem cell donors, allo-HSCT should be considered. It was already proved that HSCT could be a valid therapeutic option for patients who do not respond to conventional treatment and novel biological agents. It should be always taken into consideration in each patient separately in second-line treatment or beyond. It is important that the quality of life increases and regimen-related toxicity after the transplantation procedure decreases. On the other hand, morbidity and mortality related in this method are still important issues, especially if recently new biological agents are becoming more effective. Although, remission after transplantation was observed in the majority of patients, the long-term effect has still not been confirmed.

The present data are still limited and there is a need for organized clinical trials on larger cohort to dissipate all doubts. Hopefully, in future the scientific step will be made to prove the real role of auto- or allo-HSCT in the treatment of autoimmune disease. Nowadays, it cannot be a gold standard in the treatment of children with ACTDs. The decision should be made individually, after clear assessment of risk related to transplant procedures and resistance to traditional therapies. Last, but not least, patients, who relapse after transplantation procedure, can still be treated with standard or biological drugs to which they used to be resistant earlier.

The fundamental matter, which should not be omitted, is to report all patients, who underwent transplantation procedure, to international registries, for example EBMT. It will help to evaluate proper and specific recommendations, indispensable in the further development of HSCTs as a therapeutic strategy for resistant/relapsed ACTD children. Long-term, detailed follow-up of children who underwent the HSCT procedure is extremely important. It should be done by well-trained data managers with prior experience and supervised by a rheumatologist specialist. Clinical data in international registries will provide meaningful statistics which can be a great help in establishing future recommendations for HSCTs in children with ACTDs.

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References

Adib N, Silman A, Thomson W (2005) Outcome following onset of juvenile idiopathic inflammatory arthritis: II. Predictors of outcome in juvenile arthritis. Rheumatology 44:1002–1007

Appelbaum FR (2001) Haematopoietic cell transplantation as immunotherapy. Nature 411:385–389

Balbir-Gurman A, Braun-Moscovici Y (2012) Scleroderma—new aspects in pathogenesis and treatment. Best Pract Res Clin Rheumatol 26:13–24

Baldwin JL, Storb R, Thomas ED et al (1977) Bone marrow transplantation in patients with gold-induced marrow aplasia. Arthr Rheum 20:1043–1048

Bargetzi MJ, Schönenberger A, Tichelli A et al (1997) Celiac disease transmitted by allogeneic non-T cell-depleted bone marrow transplantation. Bone Marrow Transpl 20:607–609

Bennett CL (2001) The immune dysregulation, polyendocrinopathy, enteropathy, X linked syndrome (IPEX) is caused by mutations FOXP3. Nat Genet 27:20–21

Berisso GA, van Lint MT, Bacigalupo A et al (1999) Adoptive autoimmune hyperthyroidism following allogeneic stem cell transplantation from an HLA-identical sibling with Graves' disease. Bone Marrow Transpl 23:1091–1092

Bezalel S, Asher I, Elbirt D et al (2012) Novel biological treatments for systemic lupus erythematosus: current and future modalities. Isr Med Assoc J 14:508–514

Brinkman DM, de Kleer IM, ten Cate R et al (2007) Autologous stem cell transplantation in children with severe progressive systemic or polyarticular juvenile idiopathic arthritis: long-term follow-up of a prospective clinical trial. Arthr Rheum 56:2410–2421

Chen J, Wang Y, Kunkel G et al (2005) Use of CD^{34+} autologous stem cell transplantation in the treatment of children with refractory systemic lupus erythematosus. Clin Rheumatol 24:464–468

Cohen A, Békássy AN, Gaiero A et al (2008) Endocrinological late complications after hematopoietic SCT in children. Bone Marrow Transpl 41(Suppl 2):S43–S48

De Kleer IM, Brinkman DM, Ferster A et al (2004) Autologous stem cell transplantation for refractory juvenile idiopathic arthritis: analysis of clinical effects, mortality, and transplant related morbidity. Ann Rheum Dis 63:1318–1326

El Bahri DM, Meddeb N, Sellami S (2007) Rheumatoid arthritis: current status of therapy. Tunis Med 85:1–8

Falkenburg JH, Warren EH (2011) Graft versus leukemia reactivity after allogeneic stem cell transplantation. Biol Blood Marrow Transpl 17:33–38

Farge D, Passweg J, van Laar JM et al (2004) Autologous stem cell transplantation in the treatment of systemic sclerosis: report from the EBMT/EULAR registry. Ann Rheum Dis 63:974–981

Farge D, Labopin M, Tyndall A et al (2010) 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 95:284–292

Ferreira RA, Vastert SJ, Abinun M et al (2006) Hemophagocytosis during fludarabine-based SCT for systemic juvenile idiopathic arthritis. Bone Marrow Transpl 38:249–251

Gurevitz SL, Snyder JA, Wessel EK et al (2013) Systemic lupus erythematosus: a review of the disease and treatment options. Consult Pharm 28:110–121

Habibi S, Saleem MA, Ramanan AV (2011) Juvenile systemic lupus erythematosus: review of clinical features and management. Indian Pediatr 48:879–887

Hari P, Bagga A, Mahajan P et al (2009) Outcome of lupus nephritis in Indian children. Lupus 18:348–354

Hashkes PJ, Wright BM, Lauer MS et al (2010) Mortality outcomes in pediatric rheumatology in the US. Arthr Rheum 62:599–608

Hinterberger W, Hinterberger-Fischer M, Marmont A (2002) Clinically demonstrable anti-autoimmunity mediated by allogeneic immune cells favorably affects outcome after stem cell transplantation in human autoimmune diseases. Bone Marrow Transpl 30:753–759

Holzer U, van Royen-Kerkhof A, van der Torre P et al (2010) Successful autologous stem cell transplantation in two patients with juvenile dermatomyositis. Scand J Rheumatol 39:88–92

Huang JL (2012) New advances in juvenile idiopathic arthritis. Chang Gung Med J 35:1–14

Ikehara S (2002) Bone marrow transplantation: a new strategy for intractable diseases. Drugs Today 38:103–111

Jayne D, Passweg J, Marmont A et al (2004) Autologous stem cell transplantation for systemic lupus erythematosus. Lupus 13:168–176

Kahn P (2012) Juvenile idiopathic arthritis: an update for the clinician. Bull NYU Hosp Jt Dis 70:152–166

Knaan-Shanzer S, Houben P, Kinwel-Bohré EP et al (1991) Remission induction of adjuvant arthritis in rats by total body irradiation and autologous bone marrow transplantation. Bone Marrow Transpl 8:333–338

Kowal-Bielecka O, Landewe R, Avouac J et al (2009) EULAR recommendations for the treatment of systemic sclerosis: a report from EULAR Scleroderma Trials and Research Group (EUSTAR). Ann Rheum Dis 68:620–628

Kumar A, Marwaha V, Grover R (2003) Emergencies in rheumatology. J Indian Med Assoc 101:520–524

Locatelli F, Nöllke P, Zecca M et al (2005) Hematopoietic stem cell transplantation (HSCT) in children with juvenile myelomonocytic leukemia (JMML): results of the EWOG-MDS/EBMT trial. Blood 105:410–419

Malleson PN, Fung MY, Rosenberg AM et al (1996) The incidence of pediatric rheumatic diseases: results from the Canadian Pediatric Rheumatology Association Disease Registry. J Rheumatol 23:1981–1987

Manno R, Boin F (2010) Immunotherapy of systemic sclerosis. Immunotherapy 2:863–878

Marazuela M, Steegman JL (2000) Transfer of autoimmune hypothyroidism following bone marrow transplantation from a donor with Graves' disease. Bone Marrow Transpl 26:1217–1220

Marmont MA (1998) Stem cell transplantation for severe autoimmune diseases: progress and problems. Haematologica 83:733–743

Marmont MA (2004) Stem cell transplantation for autoimmune disorders. Coincidental autoimmune disease in patients transplanted for conventional indications. Best Pract Res Clin Haematol 17:223–232

Mckendry RJ, Huebsch L, Leclair B (1996) Progression of rheumatoid arthritis following bone marrow transplantation. A case report with a 13-year follow-up. Arthr Rheum 39: 1246–1253

McMahan R, Balfe LM, Greene L (2012) Summary of AHRQ's comparative effectiveness review of disease-modifying antirheumatic drugs for children with juvenile idiopathic arthritis. J Manag Care Pharm 18(1 Suppl B):1–16

Meloni G, Capria S, Vignetti M et al (1997) Blast crisis of chronic myelogenous leukemia in long-lasting systemic lupus erythematosus: regression of both diseases after autologous bone marrow transplantation. Blood 89:4659

Niehues T, Lankisch P (2006) Recommendations for the use of methotrexate in juvenile idiopathic arthritis. Paediatr Drugs 8:347–356

Pession A, Zama D, Masetti R et al (2012) Hematopoietic stem cell transplantation for curing children with severe autoimmune diseases: is this a valid option? Pediatr Transpl 16:413–425

Petty RE (1999) Prognosis in children with rheumatic disease: justification for consideration of new therapies. Rheumatology 38:739–742

Rabusin M, Andolina M, Maximova N et al (2008) Haematopoietic SCT in autoimmune diseases in children: rationale and new perspectives. Bone Marrow Transpl 41(Suppl 2):S96–S99

Rabusin M, Andolina M, Maximova N (2011) Haematopoietic stem cell transplantation with refractory autoimmune cytopenia: a retrospective analysis from EBMT registry. Bone Marrow Transpl 46:377

Raj R, Murin S, Matthay R et al (2002) Systemic lupus erythematosus in the intensive care unit. Crit Care Clin 18:781–803

Ravelli A, Martini A (2007) Juvenile idiopathic arthritis. Lancet 369:767–778

Redlich K, Schett G, Steiner G et al (2003) Rheumatoid arthritis therapy after tumor necrosis factor and interleukin-1 blockade. Arthr Rheum 48:3308–3319

Scalapino K, Arkachaisri T, Lucas M et al (2006) Childhood onset systemic sclerosis: classification, clinical and serologic features, and survival in comparison with adult onset disease. J Rheumatol 33:1004–1013

Seidel MG, Ernst U, Printz D et al (2006) Expression of the putatively regulatory T-cell marker FOXP3 by $CD4^+$ $CD25^+$ T cells after pediatric hematopoietic stem cell transplantation. Haematologica 91:566–569

Snowden JA, Saccardi R, Allez M et al (2012) Haematopoietic SCT in severe autoimmune diseases: updated guidelines of the European Group for blood and marrow transplantation. Bone Marrow Transpl 47:770–790

Sykes M, Nikolic B (2005) Treatment of severe autoimmune disease by stem-cell transplantation. Nature 435:620–627

Tapprich C, Feuk R, Schneider P et al (2003) Early recurrence of rheumatoid arthritis after nonmyeloablative allogeneic blood stem cell transplantation in a patient with multiple myeloma. Bone Marrow Transpl 32:629–631

Torok KS (2012) Pediatric scleroderma: systemic or localized forms. Pediatr Clin North Am 59:381–405

Toussirot E, Streit G, Wendling D (2007) Infectious complications with anti-TNFalpha therapy in rheumatic diseases: a review. Recent Pat Inflamm Allergy Drug Discov 1:39–47

van Bekkum DW (1993) BMT in experimental autoimmune diseases. Bone Marrow Transpl 11:183–187

van Bekkum DW (2000) Stem cell transplantation in experimental models of autoimmune disease. J Clin Immunol 20:10–16

van Bekkum DW (2004) Stem cell transplantation for autoimmune disorders. Preclinical experiments. Best Pract Res Clin Haematol 17:201–222

van Bekkum DW, Bohre EP, Houben PF et al (1989) Regression of adjuvant-induced arthritis in rats following bone marrow transplantation. Proc Natl Acad Sci USA 86:10090–10094

Vonk MC, Marjanovic Z, van den Hoogen FM et al (2008) Long-term follow-up results after autologous haematopoietic stem cell transplantation for severe systemic sclerosis. Ann Rheum Dis 67:98–104

Yel L (2010) Selective IgA deficiency. J Clin Immunol 30:10–16

Zeher M, Papp G, Szodoray P (2011) Autologous haemopoietic stem cell transplantation for autoimmune diseases. Expert Opin Biol Ther 11:1193–1201

Zulian F, Martini G (2007) Childhood systemic sclerosis. Curr Opin Rheumatol 19:592–597