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Refractory juvenile idiopathic arthritis: using autologous stem cell transplantation as a treatment strategy

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Cellular immune therapy for severe autoimmune diseases can now be considered when such patients are refractory to conventional treatment. The use of autologous stem cell transplantation (ASCT) to treat human autoimmune diseases has been initiated following promising results in a variety of animal models. Anecdotal observations have been made of autoimmune disease remission in patients who have undergone allogeneic bone marrow transplantation as a result of coincidental haematological malignancies. The possibility of inducing immunological self-tolerance by ASCT is particularly attractive as a means for treating juvenile idiopathic arthritis (JIA). In this disease, ASCT restores self-tolerance both through a cell-intrinsic mechanism, involving the reprogramming of autoreactive T cells, and through a cell-extrinsic mechanism, involving a renewal of the immune balance between $CD4^+CD25^+$ regulatory T cells and other T cells. This review describes the clinical results of ASCT performed for this disease and the possible underlying immunological mechanisms.

Juvenile idiopathic arthritis (JIA) is a heterogeneous autoimmune disease characterised by chronic inflammation of one or more joints (Ref. 1). As defined by the International League of Associations for Rheumatology, JIA is defined as beginning before 16 years of age and having a duration of arthritis >6 weeks (Ref. 2). Although a childhood-onset disease, JIA may persist into adult life. The prevalence of JIA has been estimated to be about 1 in 1000 for children who are less than 16 years of age. Symptoms of JIA are chronic arthritis characterised by stiffness, pains, swelling and limitation of movement. In addition, more-systemic complaints include anorexia, weight loss and growth failure. Ongoing disease activity invariably induces bone and joint deformities.

Several different forms of JIA have been defined (Table 1). These vary in severity and are mainly distinguished by the presence or absence of systemic symptoms that present during the first 6 months. Of these, systemic onset disease is usually the most severe subtype and is associated with spiking fever, rash, pericardial

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Table 1. Subtypes of juvenile idiopathic arthritis

Subtype	Frequency	Special feature
Oligoarthritis-persistent	30–40%	Fewer than five joints are affected; good prognosis; high incidence of uveitis
Oligoarthritis-extended	20%	Gradual increase in the number of joints affected (>5) within the first 3 months of disease
Polyarthritis RF negative	15%	More than five joints are affected; higher incidence of permanent destructive changes
Polyarthritis RF positive	5%	More than five joints are affected; chronic disease course mimicking adult RA
Systemic arthritis	5–10%	Spiking fever, exanthema (rash), arthritis; has the worst prognosis, often with severe complications such as MAS
Enthesitis-related arthritis	5%	Spinal column often affected (spondylarthropathy); often occurs in HLA-B27-positive individuals
Psoriatic arthritis	3–5%	Arthritis and dactylitis, nail pitting, or a positive family history of psoriasis in a first-degree relative
Unclassified	1–2%	

Abbreviations: MAS, macrophage activation syndrome; RA, rheumatoid arthritis; RF rheumatoid factor.

effusions, myocarditis, interstitial pulmonary fibrosis, hepatomegaly, splenomegaly and lymphadenopathy. Laboratory investigations show an increase in the parameters of chronic inflammation and occasionally haemophagocytic lymphohistiocytosis [also called macrophage activation syndrome (MAS)], which involves engulfment of blood cells by phagocytic cells, leading to cytopaenias, clotting disorders and very high ferritin values. The overall mortality rate for JIA is approximately 1% but can be as high as 10–15% in the systemic subtype. Death can result from infections, haemophagocytosis, renal or cardiac amyloidosis, or myocardial infarction.

The treatment of JIA has been intensified considerably in the past 10 years, particularly as some subtypes of the disease have a poor prognosis. Potent immunosuppressive drugs have been introduced early in attempts to suppress joint inflammation in those children that do not respond rapidly to non-steroidal anti-inflammatory drugs (NSAIDs) (Ref. 3). The use of a variety of treatments such as high-dose intravenous methylprednisolone, methotrexate, cyclophosphamide and anti-tumour necrosis factor receptor (TNFR) has produced remarkable success in the control of disease activity and better quality of life. However, early experience with the anti-TNFR drugs also suggests that a significant proportion of children with systemic arthritis are likely to remain resistant to these therapies (Refs 4, 5). Furthermore, these treatments can be associated with severe side-effects, which are mostly seen in the most severely affected children who use combinations of the drugs (for example prolonged use of corticosteroids induces many side-effects). Children with refractory disease not only develop severe morbidity and significantly impaired quality of life, both from the disease and from drug toxicities, but they also have a significantly increased mortality rate (Ref. 6).

If a child with JIA continues to have poorly controlled joint inflammation despite consistent pharmacological interventions, the patient is a candidate for experimental therapies (Ref. 6). Current research has focused on tailor-made approaches such as immunotherapy using epitope-specific T cells (Ref. 7). The challenge lies in achieving immunological tolerance without the requirement for severe and prolonged

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immunosuppression. The focus of this review is the use of autologous stem cell transplantation (ASCT) to treat patients with JIA and the possible immunological basis for its effectiveness.

Use of stem cells to treat human autoimmune diseases

The use of intensive immunosuppressive treatment coupled with SCT to treat human autoimmune diseases follows extensive research in animal models, as well as anecdotal observations of remissions of autoimmune disease in patients who have undergone allogeneic bone marrow transplantation because of coincidental haematological malignancies (Refs 8, 9). Animal studies have shown that transplantation of normal allogeneic bone marrow prevented and ameliorated, or cured, both spontaneous and induced autoimmune disease (Refs 7, 10, 11, 12, 13). Furthermore, a high incidence of remission, which was often durable, was also observed following autologous bone marrow transplantation in adjuvant-induced arthritis (Ref. 14).

SCT has been applied in patients with autoimmune disease since 1995. By 2004, almost 800 patients had been transplanted [as registered in databases created by the European and North American stem cell transplant organisations EBMT and CIBMTR (see http://www.EBMT.org and http://www.CIBMTR.org)] (Refs 8, 9, 15, 16). The majority of the patients received autologous (derived from the patient themselves) rather than allogeneic (derived from a matched, healthy donor) stem cells because the use of autologous cells is associated with a lower mortality and avoids the problem of graft matching and graft-versus-host disease. However, allogeneic haematopoietic stem cell (HSC) transplantation, by providing stem cells from a disease-resistant donor, will also alter the patient's genetic predisposition to disease susceptibility. The mechanism of efficacy in the allogeneic setting is presumed to reflect a reduction in the burden of self-reactive lymphocytes by the conditioning regimen, together with eradication of residual immune cells by a postulated graft-versus-autoimmune effect. The surprising efficacy of ASCT is thought to be the result of a similar ablation of self-reactive lymphocytes during conditioning followed by induction of self-tolerance by the 're-education' of HSC-derived lymphocytes.

The procedure of ASCT for resistant JIA

In children, ASCT has been applied in a large series of JIA patients and incidental cases of other rheumatic diseases such as systemic lupus erythematosus (SLE) and juvenile dermatomyositis. JIA is the most common rheumatic disease in childhood and a major cause of disability. Although the overall prognosis for most children with chronic arthritis is good, the disease is refractory to conventional therapies in 5–10% of children with the systemic and polyarticular onset forms (Refs 3, 4, 6, 17). The first results of a pilot study conducted in 1997 and 1998 to analyse the clinical efficacy of ASCT for JIA were promising (Ref. 18) and since then more than 52 cases have been reported and registered in the EBMT database (Ref. 19). Since there is potential high morbidity and mortality associated with SCT, it is imperative that children eligible for ASCT are carefully selected. Guidelines on inclusion criteria, the conditioning regimen and manipulation of the graft were recently reviewed (Ref. 20).

The procedure for ASCT in patients with JIA is described in Fig. 1. HSCs used in ASCT may be obtained either from bone marrow or by inducing mobilisation into the peripheral blood using a single infusion of cyclophosphamide (between 1.5–3.0 g/m^2) and granulocyte colony-stimulating factor (G-CSF; 10 μg/kg/d for 4 days). The harvested cells can be purified by T-cell depletion with anti-CD2 and anti-CD3 antibodies or by direct stem cell selection using a CD34$^+$ cell separation device (see Fig. 1).

Conditioning is performed immediately before stem cell reinfusion. The phrase 'conditioning' refers to a course of immunosuppressive and/or myeloablative drugs that are used to prepare a patient for SCT. The most common combination used to condition JIA patients has been an immunosuppressive regimen in which the patient is treated with cyclophosphamide with antithymocyte globulin (ATG) and total body irradiation (TBI; 4 Gy). The use of TBI in children remains controversial because of concerns about long-term safety. Data recently published on the follow-up of 34 transplanted JIA patients suggested that children not given TBI have an equally good outcome as those treated with irradiation. This finding led to the recommendation that TBI should be eliminated from future conditioning regimens (Ref. 20).

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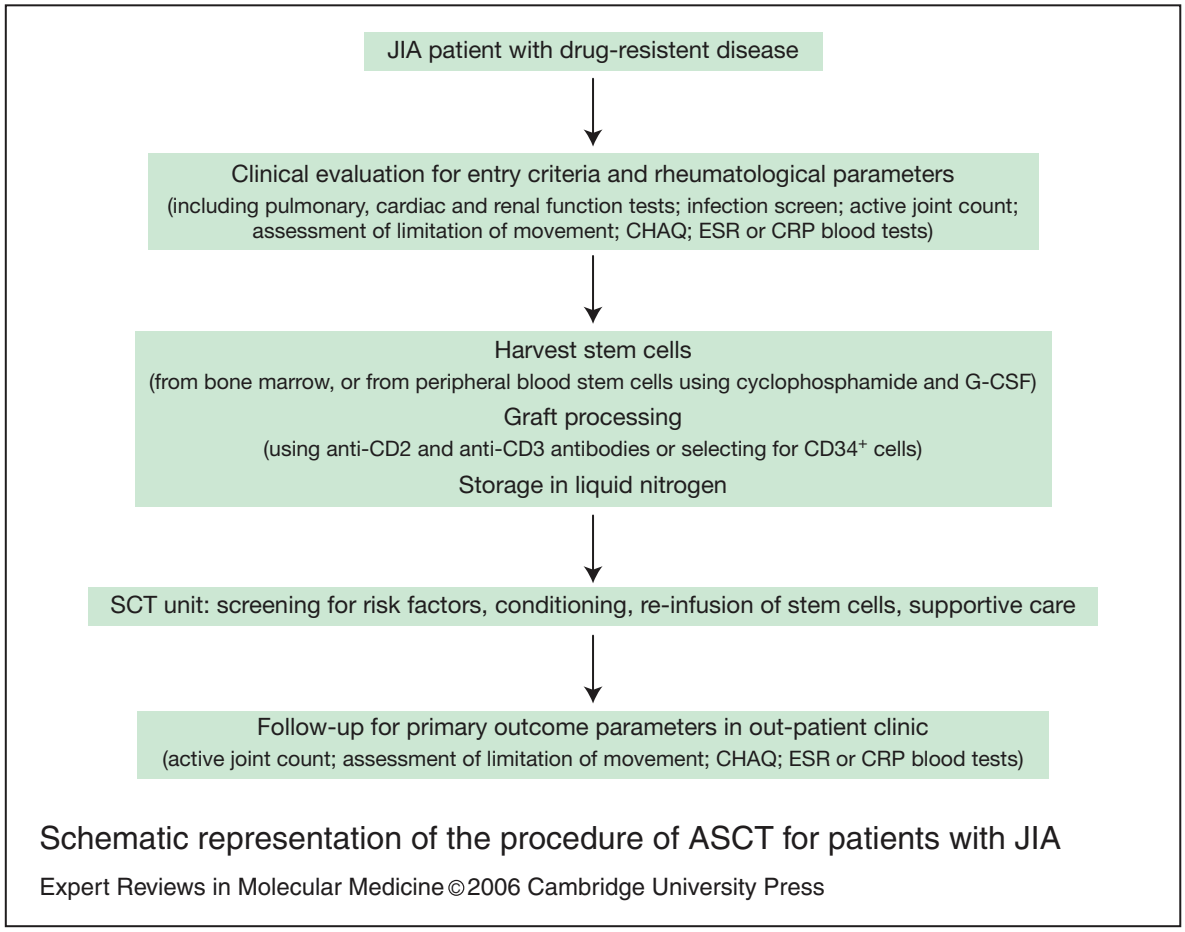

Figure 1. Schematic representation of the procedure of ASCT for patients with JIA. After evaluating the patient, HSCs used in ASCT may be obtained either from bone marrow or by inducing mobilisation into the peripheral blood using a single infusion of cyclophosphamide (between 1.5–3.0 g/m^2) and G-CSF (10 μg/kg/d). Bone marrow stem cells are harvested under general anaesthesia by multiple needle aspirations from the iliac crest. The harvested cells can be purified by T-cell depletion with anti-CD2 and anti-CD3 antibodies (resulting in a mean 2.5 log depletion of T cells) or by direct stem cell selection using a CD34$^+$ cell separation device. Stem cell selection using one of the CD34$^+$ selection procedures usually results in a 4.5 log depletion of T cells. An increased yield of CD34$^+$ cells can be obtained with the Clinimacs procedure (57.9 ± 9.0%) in comparison with the Isolex procedure (40.1 ± 12.5%) (Ref. 20). In the cases of peripheral stem cell collection, these techniques yielded a final suspension with a CD34$^+$ cell count of 2.9–10.9 × 10^6 cells per kg (mean 5.2 × 10^6 cells per kg) and with a CD3$^+$ cell count of 0–1.4 × 10^5 cells per kg (mean 0.3 × 10^5 cells per kg). In the cases of bone marrow collection, these techniques yielded a final suspension with a CD34$^+$ cell count of 0.44–6.0 × 10^6 cells per kg (mean 2.2 × 10^6 cells per kg) and with a CD3$^+$ cell count of 0–3.5 × 10^5 cells per kg (mean 0.7 × 10^5 cells per kg) (Ref. 20). Although full depletion of autoreactive T cells might be desirable, profound depletion is also associated with a higher risk of opportunistic infection including EBV and CMV reactivation post-transplantation. Abbreviations: ASCT, autologous stem cell transplantation; CHAQ, childhood health assessment questionnaire; CMV, cytomegalovirus; CRP, C-reactive protein; EBV, Epstein–Barr virus; ESR, erythrocyte sedimentation rate; G-CSF, granulocyte colony-stimulating factor; HSC, haematopoietic stem cell; JIA, juvenile idiopathic arthritis; SCT, stem cell transplantation.

Clinical outcome of ASCT for resistant JIA

Since the first JIA patient was transplanted in 1997, more than 52 cases have been reported. One can find several case reports describing the clinical outcome of small groups of JIA patients treated with ASCT (Ref. 21). However, the largest study is a report of 34 cases, transplanted

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in nine different paediatric bone marrow transplantation units (Ref. 20).

In this study, all 34 children showed a polyarticular course of the disease complicated by recurrent episodes of systemic disease, severe joint erosions, osteoporosis and stunted growth. Ten of the 34 children had failed treatment with anti-TNFR therapy. The results of using ASCT to treat these children were impressive: ASCT induced a drug-free complete remission in 18 severely ill JIA patients (53%), even after prolonged withdrawal of anti-rheumatic drugs. Six patients (18%) achieved a partial response (30–70% improvement) and showed a remarkable improvement in most core set criteria (these criteria include active joint count, limitation of motion, physician and patient/parent global assessments, functional assessment and erythrocyte sedimentation rate), indicating a profound improvement in general well being. No response was noted in seven patients (21%) and four patients (12%) died of a transplant-related cause. Altogether, using the preliminary definition of improvement in JIA developed by Giannini et al. (Ref. 22), 50% of the patients showed a drug-free improvement of more than 50% after 4–60 months of follow-up (Ref. 20). However, an evaluation of the range of motion of the joint (EPM-ROM) showed that the limit of movement did not change, illustrating that erosive joint destruction that existed prior to ASCT is not reversed by this treatment (during this follow-up of up to 5 years). Younger children in particular had significant catch-up growth, which was less notable in older children.

Transplant-related complications and mortality

Infectious complications were common in the study described above, with 24 of the 34 children (71%) developing at least one infection. Varicella zoster virus (VZV), Epstein–Barr virus (EBV) and cytomegalovirus (CMV) reactivations were seen frequently, mainly during the aplastic period before the stem cells have reconstituted the immune system. Furthermore, four of the 34 children (12%) died 10 days to 16 months post-ASCT, which is an unexpected high mortality rate. Death was in all cases principally the result of infection following bone marrow suppression and immunosuppression. In three of the four fatal cases, MAS haemophagocytosis was present (Refs 19, 23, 24). This complication was preceded by infections with EBV, adenovirus and disseminated toxoplasmosis.

MAS is a well-recognised and frequently fatal complication of systemic JIA. Of interest, such episodes often seemed to be induced by drugs such as salazopyrin, methotrexate or intramuscular gold. Why patients with systemic JIA are at risk for episodes of reactive haemophagocytosis is unknown. The marked macrophage activation seems to reflect a loss of T-cell control and perhaps an underlying abnormality of macrophage function is also present. The unexpected occurrence of MAS after ASCT also remains unexplained. This complication resembles the active phases of familial haemophagocytic lymphohistiocytosis (FHL), in which an immunological imbalance between regulatory T cells and macrophages has been postulated. FHL is an autosomal recessive disorder characterised by uncontrolled activation of T cells and macrophages, and excessive production of inflammatory cytokines. Recently, a defect in the gene encoding perforin, whose product is involved in the immunoregulatory process of target cell killing, was described as the underlying cause of FHL (Refs 25, 26). Perforin expression often appears to be severely reduced in systemic JIA. Prolonged immunosuppression and dysregulation of perforin expression on cytotoxic effector and natural killer (NK) cells and a defective NK-cell function during early immune reconstitution after ASCT might explain the development of MAS (Refs 27, 28, 29). Since MAS accounts for such a significant part of mortality in systemic JIA patients and is clearly the most dangerous complication after ASCT, careful monitoring for early signs of MAS (fever, hepatomegaly, cytopaenias, clotting disorders, high ferritin values) and institution of early treatment with steroids and cyclosporin is mandatory; exclusion of patients with active disease just before the transplant (in particular with persistent fevers) has been added to current protocols to avoid MAS.

What is the underlying immunological mechanism inducing this prolonged disease remission?

The induction of immune tolerance requires target antigens and competent immune cells. In JIA, the causative antigen is by definition unknown. However, heat shock proteins (HSPs) have been proposed as putative autoantigens.

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In several experimental autoimmune models, T cells responding to HSPs have an important role in the regulation of peripheral tolerance and the suppressing of pathogenic immune responses. HSPs are evolutionarily highly conserved proteins that are present in the cells of virtually all living organisms and play an important role in various cell processes. Most evidence for a regulatory role of HSP-specific T cells has been gathered in experimental models of arthritis. In the experimentally induced adjuvant-induced arthritis (AIA) model, pre-immunisation with HSPs protected animals from arthritis (Ref. 30), and protection was shown to result from the induction of T cells that were crossreactive with self-HSP60 and were capable of downregulating inflammation.

In humans, an increased expression of endogenously produced HSP60 in the membranes of synovial lining cells of patients with JIA was described (Ref. 31). Subsequently, T-cell reactivity to mycobacterial and human HSP60 was documented in patients with JIA (Ref. 32). In a separate study, peripheral blood mononuclear cells (PBMCs) and synovial fluid mononuclear cells (SFMCs) from patients with oligoarticular JIA were cultured in various media and stimulated with human HSP60 for 3 days (Ref. 33). On day 3, the cells were counted and tested for expression of CD30 and other cell-surface markers. In addition, cytokine analysis was performed by lymphocyte intracellular staining and flow cytometry. CD30 expression on $CD4^+$ T cells was determined before (on day 0) and after two rounds of activation in vitro with HSP60 in the presence of interleukin (IL)-2 and IL-4 (on day 3). HSP60 was found to induce a significant increase in $CD4^+CD30^+$ cells in PBMCs from patients with oligoarticular JIA compared with unactivated PBMCs, and compared with cells from patients with polyarticular JIA (Refs 33, 34). Intracellular cytokine analysis showed a high ratio of IL-10 to interferon (IFN)-γ in oligoarticular JIA patients, but not in polyarticular JIA patients. This T-cell reactivity occurred very early in the course of oligoarticular JIA and patients lacking early responsiveness to HSP60 later developed a polyarticular course of the disease.

Altogether, these data suggest that T cells responding to human HSP60 exert a regulatory function and subsequently contribute to disease remission. These findings strongly support the hypothesis that, in oligoarticular JIA patients, human HSP60-specific $CD4^+$ T cells are T regulatory (Treg) cells that contribute to disease remission (Ref. 35). Indeed, recently published data have shown that a decreased number of $CD4^+CD25^+$ Treg cells in the synovial fluid of children with JIA is correlated with the development of a less-favourable clinical course of the disease (Ref. 36). Treg cells are now believed to play a key role in mediating tolerance and inhibiting the induction of tumour immunity. This concept of therapeutic immunoregulation aimed at treating autoimmune pathology has been validated in many animal models (Ref. 37).

ASCT induces immunological tolerance

It is possible that $CD4^+CD25^+$ Treg cells induce a durable remission after ASCT. The initial clinical effect is likely to be attributable to the eradication of autoreactive lymphocytes and memory cells as a result of the high-dose conditioning regimen. Subsequently, there may be a significant contribution from altered immune reconstitution that occurs after autologous transplantation. Furthermore, foetal animal work is supportive of the hypothesis that exposure of the developing immune system to neoantigens, in a period when the immune system is developing its repertoire, leads to tolerance (Ref. 38). Altogether, these observations suggest that the success of ASCT is not only based on the loss of autoreactive T-cell clones, but also on the complete re-assignment of imbalanced cellular and soluble networks, including Treg cells (Fig. 2). The most important group of Treg cells is currently identified by the expression of CD25 and the transcription factor FoxP3 (Ref. 39). Expression of FoxP3 distinguishes $CD4^+$ Treg cells from recently activated, non-regulatory $CD4^+CD25^+$ T cells. Such $CD4^+CD25^+$ Treg cells play a key role in the maintenance of immunological tolerance to both self- and foreign antigens by suppressing aggressive T-cell responses. Indeed, in multiple experimental animal models, it has been shown that, in the absence of these so-called $CD4^+CD25^+$ Treg cells, the risk of developing autoimmunity is significantly increased (Ref. 40). As early as 6–8 weeks post-transplant, the transplanted patient group showed a significant increase in the relative number of $CD4^+CD25^{bright}$ T cells (Ref. 41).

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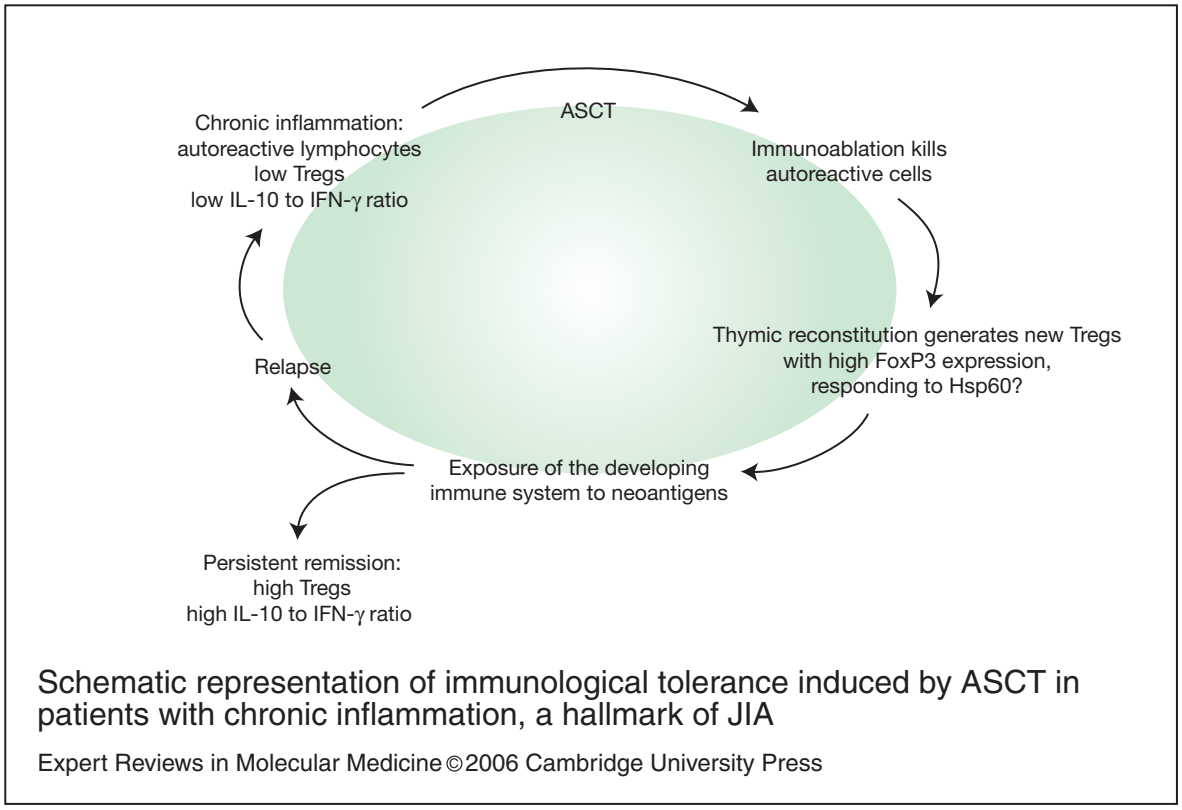

Figure 2. Schematic representation of immunological tolerance induced by ASCT in patients with chronic inflammation, a hallmark of JIA. For more details, see Refs 32, 33, 34, 36, 37, 42, 43. Abbreviations: ASCT, autologous stem cell transplantation; HSP60, heat shock protein 60; IFN-γ, interferon γ; IL-10; interleukin 10; JIA, juvenile idiopathic arthritis; SCT, stem cell transplantation; Treg, regulatory T cell.

Taken together, experiments from de Kleer et al. show a severely reduced frequency of $CD4^+CD25^{bright}$ Treg cells in the peripheral blood of systemic JIA patients, which in all but one patient was completely restored by ASCT (Ref. 41). This patient was one of two who showed a complete relapse of the disease; all the others gained a partial or complete remission of the disease after ASCT. Since ASCT obviously is not successful in the restoration of genetic defects, it can now be concluded that the low frequency of $CD4^+CD25^{bright}$ Treg cells found in systemic JIA patients is the result of either environmental factors acting before the onset of disease, or the disease itself, or the immunosuppressive drugs the patients received in an attempt to control the disease.

After ASCT, the $CD4^+CD25^+$ Treg cells reconstitute by clonal expansion and a thymic-dependent de novo regeneration (Refs 42, 43). In addition to such preferential proliferation, the $CD4^+CD25^+$ Treg cells might also have selectively survived the conditioning regimen (Ref. 44). After the first period of clonal proliferation, the first naive, thymus-derived T cells appear. These naive T cells show an intermediate expression of CD25, but also have extremely high levels of mRNA for FoxP3, reaching levels even ten times higher than found in $CD4^+CD25^{bright}$ T cells of healthy children (Ref. 36). Such $CD25^{bright}FoxP3^+$ T cells induce an anti-inflammatory cytokine profile and the suppression of reconstituting $CD4^+CD25^-$ T cells, and are thought to effectively suppress the chronic inflammation in vivo. The fact that the observed impaired in vitro proliferation could partly be abrogated by depletion of Treg cells suggests that these Treg cells suppress newly reconstituting $CD4^+CD25^-$ T cells after ASCT (Ref. 45). In other words, the rapidly reconstituting $CD4^+CD25^+$ Treg cells seem to provide a tolerant environment in which reconstitution of the rest of the immune system subsequently takes place.

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To investigate whether ASCT induced permanent changes in autoreactive T cells (i.e. changes that persist at time points when no additional suppressive effect of homeostatic proliferation can be expected), a newly developed technique was used to capture peptide-specific T cells. Using this technique, it was found that the same autoantigen-specific T cells show a clear deviation to a more regulatory phenotype during the tolerant period induced by ASCT. Thus, in addition to restoring the $CD4^+CD25^+$ regulatory network, ASCT also brought about persistent changes in autoreactive T cells (Ref. 36).

Results in adults with autoimmune diseases show more relapses after ASCT compared with the paediatric series (Refs 8, 46, 47). It has been shown that children recover faster and have a better reconstitution of their T-cell repertoire than adults (Refs 42, 49). This observation may be attributed to the age-related involution of thymic tissue.

Novel therapies and concluding remarks

ASCT still remains a toxic treatment, and novel strategies for cellular immunotherapies in children with severe autoimmune disease should be sought (Ref. 7). It is possible that such induction of immunological tolerance might be achieved by new vaccination strategies employing HSPs as antigenic targets. What is the current evidence for such novel treatment options?

Small sequences within HSP60, called epitopes, were found to induce T-cell reactivity. In a recent study, this epitope-specific reactivity was correlated with a favourable disease course (Ref. 7). In vitro major histocompatibility complex (MHC)-binding studies were carried out with such peptides, and patients with JIA were HLA class II typed. The peptides yielded proliferative T-cell responses in 50–70% of mononuclear cells from patients with JIA irrespective of MHC genotype, but not in healthy or disease controls. Although such mononuclear cells from patients with JIA and healthy controls produced IFN-γ in response to these peptides, only mononuclear cells from patients with the disease produced IL-10. Therefore, this T-cell induction in JIA is tolerogenic. In patients with oligoarticular disease, the immune responses to the HSP60 epitopes could contribute to disease remission. Hopefully, this might favour vaccination strategies using selected HSP epitopes to induce immunological tolerance. Phase I/II studies with such vaccines are currently being performed in adults with rheumatoid arthritis (Ref. 50). However, one must realise that these responses were seen mainly in the rather mild subset of oligoarticular JIA and so far not in the more severe systemic JIA.

Recently, much attention has focused on a possible role for mesenchymal stem cells (MSCs) as a tool of regenerative medicine (Refs 51, 52, 53, 54, 55). Such cells can be derived from bone marrow, adipose tissue and synovial fluid. MSCs can still differentiate into a variety of precursor cell lines and this ability has initiated research on their future application for immunosuppression and tissue repair such as cartilage, bone, and possibly even myocardial and nervous tissues (Refs 56, 57). Of this development, much remains speculative and detailed studies on the characterisation of MSCs and their application in animal models are clearly needed. However, it is of note that MSCs have already been used for their immunosuppressive properties in children with acute graft-versus-host disease following allogeneic SCT that was refractory to conventional immunosuppression, and early successes have been reported (Ref. 58).

To conclude, ASCT for refractory JIA appears to induce immunological self-tolerance by reprogramming arthritis-related autoimmune T cells and restoring the $CD4^+CD25^+$ regulatory network. These observations could guide the design of new protocols for ASCT aiming at higher remission rates. The data suggest that dose intensification, or new preparative regimens that cause a further depletion of T cells, is not the answer to improving outcomes. Rather, directing the reconstitution and/or activity of Treg cells during the first 9 months of immune reconstitution might provide a mechanism by which a higher incidence of patients can be cured. In other words, tailor-made immunotherapy instead of prolonged, intense immunosuppression seems a promising possibility.

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Further reading, resources and contacts

The European Group for Blood and Marrow Transplantation (EBMT) is a non-profit organisation established in 1974 and based in Maastricht, The Netherlands. It provides a forum for cooperation between scientists and physicians involved in clinical bone marrow transplantation, and promotes 'basic and clinical research, education, standardisation, quality control and accreditation for transplant procedures'. The website provides links to current established standards in HSC transplantation and information on clinical trials:

http://www.EBMT.org

The Center for International Blood and Marrow Transplant Research (CIBMTR), based at the Medical College of Wisconsin (Milwaukee, WI), brings together the expertise and resources of the National Marrow Donor Program and the International Bone Marrow Transplant Registry and Autologous Blood and Marrow Transplant Registry. CIBMTR collects patient data on allogeneic blood and marrow transplants performed worldwide, and autologous blood and marrow transplants performed in North and South America. The website lists more than 450 transplant centres from 48 countries that provide detailed information regarding transplant recipients:

http://www.CIBMTR.org

Features associated with this article

Figures

Figure 1. Schematic representation of the procedure of ASCT for patients with JIA.
Figure 2. Schematic representation of immunological tolerance induced by ASCT in patients with chronic inflammation, a hallmark of JIA.

Table

Table 1. Subtypes of juvenile idiopathic arthritis.

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