Workshop Report

Autologous Stem Cell Transplantation for Pediatric Rheumatic Diseases

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ABSTRACT. The National Institute of Allergy and Infectious Disease, National Institutes of Health, convened a workshop entitled The Next Step: Protocol Development for Autologous Stem Cell Transplantation for Pediatric Rheumatic Disease, June 2000, co-chaired by Drs. Karyl Barron and Carol Wallace. The goal of the workshop was to focus on the scientific rationale for stem cell transplantation therapy in the pediatric diseases, unique aspects of this therapy in the pediatric rheumatic diseases, transplantation issues and options, regulatory issues, and development of a DNA repository for these diseases. (J Rheumatol 2001;28:2337–58)

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INTRODUCTION

The National Institute of Allergy and Infectious Disease, National Institutes of Health, convened a workshop entitled The Next Step: Protocol Development for Autologous Stem Cell Transplantation for Pediatric Rheumatic Disease, June 2000, co-chaired by Drs. Karyl Barron and Carol Wallace. The goal of the workshop was to focus on the immunology and science of pediatric rheumatic disease and stem cell transplantation therapy, unique problems of the pediatric rheumatic diseases, transplantation issues and options, regulatory aspects, and development of a DNA repository for these diseases. The participants were also divided into workgroups to discuss: development of specific protocols, disease-specific inclusion criteria, and optimal standard therapy as comparator arms for future randomized trials. The following are summaries of the reports.

PRESENTATIONS

Pediatric Autoimmune Diseases: Why New Treatments Are Needed: Ronald M. Laxer

We have entered a new era in the treatment of the rheumatic diseases. Would the proverbial "man in the moon," in looking at this new era, say that with respect to current treatments, the glass looks half empty or half full? Despite significant advances in the management of patients with rheumatic diseases over the last decade, current treatments remain inadequate for a large number of children, because

of either poor disease control, excessive toxicity of the treatment, or a combination of the two. This review will focus on current evidence suggesting that treatment for children with juvenile idiopathic arthritis (JIA, previously juvenile rheumatoid arthritis, or JRA), systemic lupus erythematosus, and juvenile dermatomyositis remains inadequate.

Juvenile idiopathic arthritis. Longterm observational studies have documented that active disease persists in a significant percentage of patients with JIA, and that functional class also deteriorates with time[1]. More recently, Zak and Pedersen[2] have shown that disease activity persists in 37% of patients with JIA followed for 26 years, and that the Steinbrocker functional class deteriorates with time, correlating with disease duration, erosive disease at 10 year followup, JIA subtype, systemic steroid treatment, and Steinbrocker functional class at 10 year followup. These data were generated from patients who were evaluated and managed in the pre-methotrexate and biologic era, and it is hoped (and presumed) that the longterm outcomes over the next decade will show better results.

Children with systemic onset JIA (sJIA) can have significant ongoing morbidity, in part due to their systemic disease, arthritis, potential medication toxicity, and possibility of developing macrophage activation syndrome. Most mortality associated with JIA occurs in this subset of patients[3]. A number of studies have looked specifically at the role of methotrexate (MTX) in sJIA. Halle and Prieur reported that in a series of 10 patients with sJIA, MTX did not result in a significant reduction of fever, number of active joints, early morning stiffness, or ability to taper prednisone[4]. Similarly, Speckmaier, *et al* showed an improvement in only 4 of 12 patients with sJIA who were treated with MTX[5]. Ravelli, *et al* reported that in a series of 19 children with sJIA, 12 were responders[6]. Compared to the nonresponders, these patients had milder disease; it is unclear whether the MTX had an effect or their observation was merely the natural course of patients with milder disease. One criticism from these studies is that the doses of MTX used were lower than those currently used. Two studies looked at increasing doses of MTX in children with JIA[7,8]. Wallace, *et al* treated 5 children with sJIA who had failed to respond to a standard dose of MTX with doses ranging from 0.86 to 1.1 mg/kg/week[7]. Only one patient entered remission. Reiff, *et al* used doses of MTX ranging from 0.46 to 1.2 mg/kg/wk with a mean followup of 15 months[8]. Only 5 of 13 patients were considered responders. Radiologic progression occurred even in patients who were responders. In another study, of 25 patients with sJIA treated with 0.3–0.9 mg/kg/wk of MTX, only 10 had what the authors defined as a complete response[9]. After stopping the drug in 4 patients, 2 quickly relapsed. Similarly, 10 of 16 patients with sJIA went into remission taking 7.1–10.7 mg/m^2/wk of MTX; 4 of those 10 quickly relapsed when the MTX was stopped[10]. These patients may have been those of the early responder group described by Ravelli, *et al*[6]. Early institution of MTX in children with sJIA and prognostic indicators of poor functional outcome did not alter the course[11]. These data suggest that MTX, the agent with the best proven track record for the treatment of children with JIA, is inadequate treatment for a significant number of children with JIA.

In a recent randomized trial, etanercept (a potent biologic agent requiring twice weekly subcutaneous injections) resulted in improvement in a significant number of children with polyarticular course JIA who had failed or been intolerant of MTX[12]. The percentage of patients overall demonstrating core set improvement[13] of 30%, 50%, and 70% were 74%, 64%, and 36%, respectively. Alternatively, one could say that despite treatment with etanercept, 36% of patients improved by less than 50%, and 64% of patients improved by less than 70%. While sJIA patients in this trial who flared taking etanercept were fewer than patients taking placebo, 44% (4/9) of patients flared. Fifty percent of patients who required steroids prior to starting etanercept flared while receiving this agent. These data suggest that patients with more severe disease have a greater tendency to flare. While etanercept clearly has an important role to play in the management of children with JIA, there remains a large percentage of children who require additional treatment. Additionally, the next few years will likely reveal toxicity with this and other biologic agents as results emerge from postmarketing surveillance studies.

Systemic lupus erythematosus (SLE). The incidence of SLE in the pediatric population is approximately 10–20 new cases per 100,000 per year. Over the last 3 decades, there has been a significant improvement in the mortality rate, largely due to earlier recognition and better supportive management. However, ongoing as well as longterm morbidity remain significant clinical issues. Morbidity from SLE must be considered in terms of (1) the disease, (2) the treatment, and (3) a combination of the two. The major cause of disease related morbidity and mortality is related to renal disease. Three large series of children with lupus nephritis all suggest that diffuse proliferative glomerulonephritis (WHO Class IV) is a significant predictive factor for endstage renal disease and death[14-16]. Clinical factors predictive of progression to endstage renal disease include the presence of hypertension, elevated serum creatinine, and increasing levels of proteinuria at the time of diagnosis. Over the last 15 years, the use of cyclophosphamide has been proposed to result in better outcomes[17]. A recent series of 16 pediatric patients treated with the US National Institutes of Health (NIH) protocol of intravenous (IV) cyclophosphamide monthly for 6 months, and then every 3 months for a total of 3 years, resulted in significant improvement in the histology, ability to reduce prednisone and normalize serology, and normalize serology and SLE Disease Activity Index (SLEDAI) scores[18]. Complications

of IV cyclophosphamide were minimal. However, another series of patients examined retrospectively received treatment with only high dose steroids prior to 1985, and high dose steroids plus IV cyclophosphamide according to a protocol similar to the NIH protocol subsequent to 1985[16]. The administration of IV cyclophosphamide did not appear to influence the progression to endstage renal disease. While the complications in studies to date have been minimal, there are no longterm outcome data in pediatric lupus patients who have been treated with cyclophosphamide. Concerns remain regarding bladder toxicity, alopecia, and risk of infection. In the long term, the risks of malignancy and infertility are potentially significant and likely related to the overall dose of cyclophosphamide given. Mok, *et al*[19] have shown that older age at treatment and total dose predispose to ovarian failure. However, 2 of 10 patients less than 30 years old who had received between 10 to 20 g of cyclophosphamide had ovarian failure.

Ioannidis, *et al* have recently examined risk of relapse in patients with lupus nephritis treated with IV cyclophosphamide and noted that, of 85 patients (33 Class III, 52 Class IV) treated with IV cyclophosphamide, only 63 went into remission[20]. Twenty-one of the 63 patients relapsed with median time to relapse of 79 months. Predictors of early relapse were co-existent central nervous disease and the time taken to reach the first remission. Chronic renal damage on initial biopsy and time to reach first remission both predicted time to reach a second remission. The authors conclude that patients with adverse prognostic factors for a second remission should be considered for alternative therapies. Therefore, while IV cyclophosphamide may offer the best current hope for prevention of endstage renal disease in children with Class IV lupus nephritis, there is clearly a need for improved therapies both in terms of efficacy and potential toxicity.

In addition to short and medium term morbidity, longterm morbidity remains a significant concern for patients with lupus. Adult studies have shown that about 40% of female lupus patients have subclinical atherosclerotic disease[21]. We have described a significant incidence of coronary artery disease in a small cohort of patients[22]. This is likely due to a combination of coronary artery vasculitis, renal disease with hypertension, and effect of corticosteroids. Better immunosuppressive therapies are required to prevent this. Other steroid induced morbidity includes skin disease (striae), bone disease (avascular necrosis and osteoporosis), eye disease (cataracts and glaucoma), risk of infection, gastrointestinal disease (gastritis, pancreatitis), hypertension, and concern of cerebral dysfunction. A combination of disease and drug induced morbidities affect the vast majority of children and adolescents with SLE[23].

To date, there is no clearly effective therapy for manifestations of the antiphospholipid antibody syndrome. Current recommendations from adult studies include life-long anticoagulation at levels that are potentially dangerous for growing active children who are frequently exposed to minor trauma and risk of bleeding[24].

Juvenile dermatomyositis (JDM). The mortality of JDM has been reduced significantly over the last several decades to less than 5 to 10%. However, the quality of life in patients with JDM is significantly affected by the disease and its treatment. Patients at most risk for poor outcomes include those with dysphagia and ulcerative skin disease at onset, severe vasculopathy on initial muscle biopsy, and relative "undertreatment" with high dose corticosteroids[25-27]. As with SLE, there is concern with the ongoing morbidity both from the disease and from corticosteroids. Corticosteroid related morbidity is similar to that associated with SLE. Disease related morbidity includes manifestations of severe skin disease, including poikiloderma and chronic skin infection. Recently, the syndrome of lipoatrophy (insulin resistant diabetes, hyperlipidemia, acanthosis nigricans, and amenorrhea) has been reported in about 10% of patients with JDM. Cutaneous calcinosis has been reported to occur in 20–60% of different series of patients with JDM. Early treatment with high doses of corticosteroids seems to reduce, but not prevent, this complication[27]. One of the most important side effects of corticosteroid treatment is growth delay, and in a series of patients recently reported, 14 of 33 patients with a continuous form of JDM were noted to be at least 1 standard deviation shorter than the mean midparental height at a mean of 7.7 years of followup[28]. In this series, a full 2/3 of patients were moderately or not at all satisfied with the longterm outcome. Forty percent of patients still had rash, 27% of patients were still weak, and 39% of patients remained on medications. Again, this indicates that current treatments do not result in cure, patients require ongoing treatment to control disease activity, and significant morbidity continues both from the disease manifestations and the treatment of the disease.

Summary. While current treatments for the major connective diseases of childhood have had a significant influence on mortality and on morbidity as well, a significant number of patients remain with uncontrolled disease activity and poor outcomes. Additionally, both disease and drug related morbidity remain major problems. New treatments are needed to reduce both disease related morbidity and drug related toxicity.

Does Autologous Stem Cell Transplantation Make Sense for Pediatric Rheumatic Diseases? Raphael Hirsch

The concept of autologous stem cell transplantation (ASCT) was initially developed as an aggressive treatment for malignancy. The use of this technique for the treatment of rheumatic diseases is similar. Aggressive therapy (radiation and/or high dose chemotherapy) is given with the intent to destroy the cells that are responsible for the inflammatory disease. In the process, hematologic stem cells are

destroyed, and rescue is accomplished by using the patient's own stem cells that were harvested before treatment. For the treatment of cancer, the target cell is known. It is the tumor cell. However, the target cell or cells for each of the rheumatologic diseases is not known.

Figure 1 is a simplified representation of the immune process in juvenile idiopathic arthritis synovium. The cells shown here interact in the rheumatoid synovium (in addition to other cells not depicted, such as dendritic cells and natural killer cells). Exactly what each of these cells is doing and which one of these cells should be the target of treatment is not known. The current, most popular hypothesis is that an autoantigen is presented by an antigen-presenting cell to a T cell. The T cell then becomes activated and secretes potent inflammatory mediators. These inflammatory mediators induce adhesion molecules, angiogenesis, activate fibroblasts, and inflammatory cells, such as macrophages, into the joint. The inflammatory mediators begin degradation of cartilage. While this hypothesis has been the focus of research for the last 20 years, it is problematic, as there are few data to support it. Despite intensive efforts, an autoantigen that causes arthritis has not been identified. An additional problem is that depletion of T cells, which supposedly are the cells mediating this cascade of events, does not result in abatement of arthritis (as demonstrated by the disappointing results of anti-CD4 trials). Data from collagen induced arthritis in animals reveal that although the initiation of the arthritis appears to be T cell dependent, once it is established, complete depletion of T cells (as well as B cells) has no effect on the course of the arthritis. Thus, the hypothesis that most investigators have been working with may not be true.

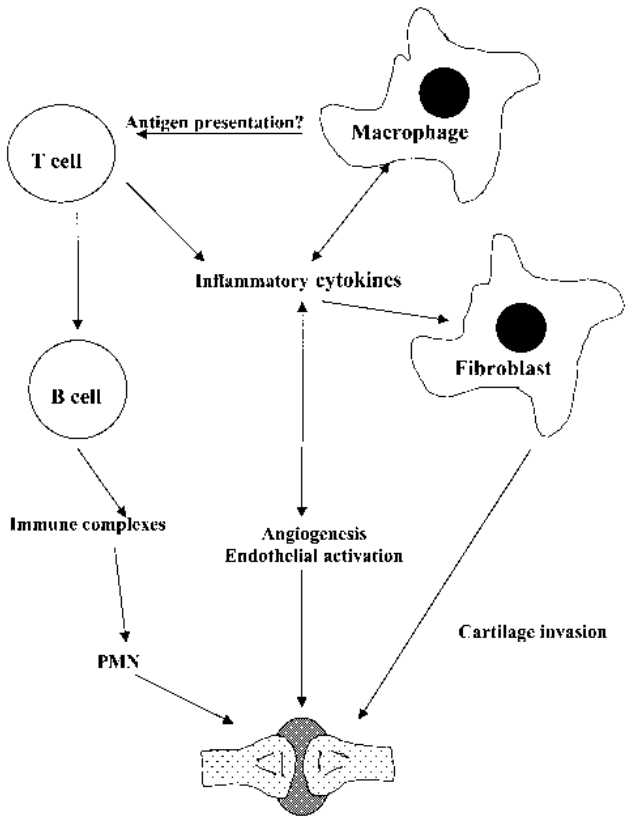

Figure 1. Proposed mechanism of joint inflammation and destruction.

There are new data in humans that support a new hypothesis, and shift focus of key affector cells to the fibroblast[29,30]. When fibroblasts from normal synovium are placed on cartilage, they are quiescent and nonreactive. On the other hand, if rheumatoid fibroblasts are placed on cartilage, even isolated from other cells and inflammatory mediators, they aggressively erode the cartilage. The fibroblasts no longer behave normally, even when removed from the inflammatory milieu of the rheumatoid synovium. The rheumatoid fibroblasts appear to have mutated and have become aggressive. A possible mechanism for this change in behavior is mutation in the site called oncogene P53[29,30].

Incorporating this information results in a new hypothesis of rheumatoid arthritis in which there is still an initiating antigen, possibly bacterial, that induces a T cell autoreactive (or crossreactive) response. This initiates inflammation in the synovium. Once inflammation has begun, the fibroblasts mutate and become aggressive. This process allows inflammation to persist in the absence of further T cell mediation and results in cytokines destructive to cartilage. If this hypothesis is true, then what needs to be targeted in arthritis, the T cell or the fibroblast?

In addition to challenging our basic ideas of important affector cells in arthritis, new information challenges current concepts of the role of synovial inflammation in cartilage destruction. The inflammatory process has recently been shown to be separate from the process of cartilage destruction. This concept is illustrated by current data on interleukin 1 receptor antagonist (IL-1RA)[31]. IL-1RA does not perform as a powerful antiinflammatory agent (in terms of reduction of joint swelling), but has significant chondroprotective effects[31-33]. Briefly, rheumatoid synovium is wrapped around cartilage and implanted into a SCID mouse. The synovium is not rejected and becomes a model where the synovium can thrive in an *in vivo* system for a couple of months, retaining its inflammatory phenotype. The fibroblast of the synovium will invade the cartilage that is enclosed within the synovium. If the synovium is treated with IL-10, the inflammation in the synovium is dramatically inhibited, but erosion of cartilage continues unabated. Conversely, if the same synovium is treated with IL-4, inflammation is not changed, but erosion is inhibited. This suggests that the fibroblasts can be inhibited without affecting the inflammatory process and vice versa.

When aggressive therapy such as stem cell transplantation is contemplated, serious consideration needs to be given

to the definition of efficacy. Is it enough to observe eradication of inflammation, or should there also be demonstrable cartilage protection? Back to the initial question: which cell should be targeted in new aggressive treatments? This becomes a critical issue if one agrees with the standard hypothesis that the T cell is the target, as most preparative regimens for stem cell therapy, such as radiation and chemotherapy, tend to spare memory T cells. Early data emerging from stem cell therapy in adult autoimmune disease indicate that the preparative regimen significantly halts inflammation (as macrophages and neutrophils are destroyed). If the memory T cell is not completely destroyed, and if this is the cell that needs to be eliminated, then these cells will recover and disease will recur. If the fibroblast is the cell that should be destroyed, this is problematic, because fibroblasts tend to be resistant to the preparative regimens commonly used. An initial antiinflammatory response, due to the depletion of macrophages and neutrophils, would most likely occur. The patient might be initially free of disease; however, erosion could continue and disease could recur if the fibroblasts are not destroyed by the preparative regimen.

For SLE, JDM, and systemic sclerosis (SSc) the same questions regarding the appropriateness of ASCT persist: what is the target cell that needs to be destroyed and will the preparative regimen destroy the target cell?

Technical Considerations in Autologous Stem Cell Transplantation: Ann Woolfrey

Rationale for stem cell transplants in autoimmune diseases. Autologous stem cell transplants offer potential to improve treatment of refractory autoimmune diseases in 3 respects. First, transplants of autologous hematopoietic stem cells (HSC) could optimize delivery of high dose immunosuppression by rescuing the patient from myeloablative side effects. In this respect, ASCT can be viewed as supportive therapy for induction of long lasting disease remission, but not necessarily curative therapy. Second, highly intensive immunosuppression followed by ASCT could be curative. In this respect, immune ablation followed by reconstitution of autologous hematopoiesis might allow "resetting" of the immune system, through induction of peripheral tolerance. Finally, complete replacement of the defective immune system after transplantation of allogeneic HSC from a healthy donor could ameliorate the disease.

Autologous and allogeneic SCT have been tested in preclinical animal models. Animals with genetic susceptibility to autoimmune states have been cured by transplantation of genetically resistant HSC. Animal models of induced autoimmune diseases have responded to both autologous and allogeneic SCT. Initial human experience was derived from anecdotal observations of disease remittance following allogeneic SCT for hematologic disorders. Over the past several years, important pilot trials have demonstrated efficacy of autologous as well as allogeneic SCT for inducing disease remission in patients with refractory autoimmune disorders.

The designs of cooperative trials to treat refractory autoimmune diseases in children depend upon an understanding of important elements involved in SCT. These include knowledge of the various types of HSC products used for transplantation and the fundamentals of high intensity therapies.

Source of hematopoietic stem cells. Theoretically, replacement of the autoreactive immune system would best be accomplished by transplantation of allogeneic HSC. Nonetheless, most initial trials in humans have studied the safety and efficacy of ASCT. One practical reason is that most patients lack an HLA identical family member donor. A second reason is that ASCT has been associated with less morbidity compared to allogeneic SCT. Comparative data derive mainly from studies of patients with solid tumors, where outcome is affected by relapse and non-relapse causes. Most comparative studies find survival advantage for autologous recipients, despite the risk for reinfusion of tumor cells[34-36]. The main additional risk from allogeneic HSC is development of graft-versus-host disease (GVHD). About 20–30% of children who receive marrow from HLA identical siblings will develop acute GVHD (grades II–IV), 15–25% will develop clinical extensive chronic GVHD, and mortality from GVHD occurs in 10–20%[37]. While initial trials have studied ASCT primarily for reasons of practicality and safety, current results support the efficacy of this approach in patients with JIA, SLE, and SSc.

Hematopoietic stem cell products. HSC may be obtained by collection of bone marrow or by mobilization and collection of peripheral blood stem cells (PBSC). Collection of each product entails different technical limitations, particularly important for pediatric donors. Marrow donors must undergo general anesthesia and 75% of pediatric donors will require homologous blood transfusion or preoperative erythropoietin injections (P. Hoffmeister, *et al*, submitted for publication). PBSC donors undergo a period of mobilization followed by 1–4 days of apheresis. Smaller donors may require insertion of a central venous catheter and may receive homologous blood for priming the apheresis machine. While there is no difference in the number or severity of adverse events experienced by marrow and PBSC donors, there are qualitative differences in types of events and pace of recovery (S. Rowley, *et al*, submitted for publication). PBSC may be mobilized by chemotherapy such as cyclophosphamide followed by cytokines such as granulocyte-colony stimulating factor (G-CSF), or cytokines alone. Both methods have been used successfully in patients with autoimmune diseases, although there have been reported disease flares associated with G-CSF alone.

The main advantage of PBSC is the large increase in number of HSC that can be obtained[38]. The benefits of high

HSC dose have been shown in a number of studies, and include reduction in transplant related mortality, shorter time to recovery of peripheral granulocyte and platelet counts, reduction of platelet and red cell transfusions, and fewer days in hospital[39]. Marrow and PBSC differ quantitatively and qualitatively in the number of CD34+ cells as well as other cell subsets, including a 10-fold increase in number of CD3 cells in PBSC. CD34+ and CD3 cells obtained by G-CSF mobilization may be functionally different, and together with differences in types of accessory cells, the 2 products may not be equivalent in types of immune cells reinfused or the kinetics of immune reconstitution (S. Heimfeld, unpublished observations).

Over the past decade PBSC have replaced marrow as the preferred product for reconstitution of autologous hematopoiesis, primarily due to more rapid recovery of peripheral blood counts. The only major randomized study comparing autologous marrow to PBSC found significant differences in time to recovery of neutrophils and platelets, number of platelet and red blood cell transfusions, and number of hospital days (Table 1)[40]. These differences were similar to findings in other studies including pediatric patients receiving autologous PBSC or marrow grafts[39,41,42]. Improvement in recovery of peripheral blood counts has been associated with fewer days of antibiotics and blood component, fewer infections, and earlier hospital discharge. The advantage of PBSC recently was made evident in a randomized study of HLA-identical related SCT, where a 1.9–fold ($p = 0.02$) reduction in mortality was seen for PBSC recipients[43].

T cell depletion. Both marrow and PBSC contain T lymphocytes with the potential to reintroduce the autoreactive state. Direct depletion of T cells from the HSC product, or negative selection, involves immunologic or physical methods that target T cells for removal (Table 2)[44]. Used separately or in combination, these methods result in 2 $\log_{10}$ to 3 $\log_{10}$ depletion of T cells. Negative selection methods are more difficult to perform technically in PBSC products than marrow, due to the greater numbers of cells, particularly T cells, generated by the mobilization procedure. Positive selection of the relatively small numbers of hematopoietic progenitor cells is more feasible, and results in a highly purified product that is depleted significantly of contaminating T cells[45,46]. Alternatively, T cell depleting agents, such as anti-thymocyte globulin (ATG), can be given to the patient after reinfusion of HSC as a means to prevent reconstitution of autoreactive T cells. While it is difficult to measure the degree of T cell depletion after ATG, it produces profound reduction in circulating T lymphocytes.

Table 1. Effect of stem cell source on recovery after ASCT.

	PBSC	Marrow
Neutrophil recovery, median days	11	14
Platelet recovery, median days	16	23
Platelet transfusions, median days	6	10
Red blood cell transfusions, median number	2	3
Hospitalization, median days	17	23

PBSC: peripheral blood stem cells.

Table 2. Common methods of T cell depletion.

Methods of T Cell Depletion		Log_{10} T Cell Depletion
Negative selection		2.0–3.0
Monoclonal antibody (Mab)	Plus complement	
	Conjugated to toxin	
	Conjugated to magnetic beads	
Physical separation	E-rosette	2.5–3.0
	Soybean lectin agglutination	
	Counterflow elutriation	
Positive selection	Selection of CD34+ cells	1.0–3.0
In vivo depletion	Anti-thymocyte globulin or anti-CD3 Mab	?

While methods to deplete T cells from the reinfused stem cell product may reduce the chances of reintroducing autoreactive T cells, they are also associated with increased risks for opportunistic infections after transplant. Although uncommon after ASCT, reactivation of cytomegalovirus and Epstein-Barr virus have been reported more frequently after transplants of T cell depleted HSC[47,48]. An increase in opportunistic infections following T cell depleted ASCT may be explained by delayed immune reconstitution. Limited data from autologous CD34+ selected SCT in adult patients with autoimmune disease suggest prolonged delay in reconstitution of T cells, particularly naive CD4 cells (J. Storek, unpublished observations).

Conditioning regimens. Conditioning regimens for autologous transplants are designed to eliminate the underlying disease. Because marrow function is rescued by transplantation of HSC, maximum intensity of the regimen is dictated by dose-limiting toxicity of nonhematopoietic organs. Delivery of intensive immune suppression has been the basis behind conditioning regimens for autoimmune disorders. Potent immunosuppressive agents commonly used in ASCT regimens include ATG, alkylating agents such as cyclophosphamide or fludarabine, and total body irradiation (TBI) or total lymphoid irradiation.

For a given agent, the intensity of an immunosuppressive agent must be balanced against its short and longterm toxicities. Because lymphocytes are highly sensitive to irradiation, higher levels of immune suppression can be achieved with TBI compared to an equivalently toxic dose of another agent[49,50]. This is best exemplified in allogeneic ASCT, where addition of TBI to the regimen abrogates the high rates of graft rejection found in recipients of HLA mismatched allogeneic grafts or in presensitized aplastic patients.

The main disadvantage of TBI is the increased incidence of longterm complications including development of cataracts, sterility, hormonal deficiencies, and secondary malignancies. The degrees to which these sequelae occur depend on the dose of TBI. Most data regarding risks of TBI are derived from patients who received ≥ 12.0 Gy and there are comparatively few data among patients who received lower doses (4.0–8.0 Gy, doses used in protocols of ASCT for autoimmune diseases). Risk for secondary malignancy is significantly higher among patients treated with ≥ 12 Gy fractionated or ≥ 10 Gy single dose TBI (1.8–4.4 relative risk), but not in those who received less (1.2 relative risk)[51]. Similarly, 77% of children undergo normal pubertal development after TBI doses of ≥ 2.0 Gy, compared to 94% among those given less[52].

Implications for trial design. The endpoints of safety and efficacy must be considered when designing a trial of ASCT, regardless of the target disease. Patients with refractory autoimmune disorders and their rheumatologists are best suited to decide what degree of risk is acceptable when undergoing these experimental procedures. The most effective procedures will undoubtedly entail the most risk. The role of pilot studies is to establish the safety for a given ASCT procedure. To answer questions regarding the effectiveness of each element, for example, whether TBI or T cell depletion is required for successful ASCT, there will need to be cooperative group studies that address each question in a meaningful way.

Minimum Center Requirements for Autologous Stem Cell Transplantation Protocols: Mitchell Horwitz

I will discuss the 4 primary components of autologous stem cell transplantation: stem cell collection, cell processing and storage, the conditioning regimen, and supportive care.

Stem cell collection. Historically, stem cells used for ASCT were collected directly from the bone marrow. A minor operative procedure was required to collect the graft. Patients received general anesthesia and multiple aspirations from the posterior superior iliac crest were performed until 10–20 ml/kg of marrow was collected. The overall complication rate for this procedure was low. When complications arose, they were usually a consequence of general anesthesia. Excessive bleeding or pain at the aspiration site have also been described.

During the 1990s, peripheral blood replaced bone marrow as the favored source for stem cells. Since few stem cells are present in the circulation at steady state, hematopoietic growth factors such as G-CSF are administered to "mobilize" stem cells. Following a 5 to 6 day course of cytokine therapy, large numbers of peripheral blood stem cells can be collected from peripheral circulation by apheresis. Many large academic medical centers have an apheresis unit that can be adapted for PBSC collection. If not, regional blood centers may be able to provide this service. The advantage of PBSC collection is that the patient need not receive general anesthesia, thereby reducing the risk. Further, a larger stem cell collection is usually feasible from mobilized peripheral blood compared to the bone marrow.

Cell processing. Depending on protocol design, processing of the autograft ranges from simple cryopreservation to complex engineering such as CD34 selection and T cell depletion. Since we are considering ASCT for autoimmune diseases, some form of T cell depletion may hold some appeal. Non-antibody based methods of T cell depletion include E-rosetting, soybean lectin agglutination, and centrifugal elutriation. Each of these methods has been adapted for clinical use. Positive selection for hematopoietic stem cells may be accomplished by using anti-CD34 antibodies and immunomagnetic beads. (See also section by Drs. Siegel and Rider, below.)

Conditioning regimens. Whether one is treating a malignancy or an autoimmune disorder, the conditioning regimen will determine disease response. The conditioning regimen may consist of chemotherapeutic agents, radiation therapy, or new generation biologic agents such as monoclonal antibodies. Most pediatric oncology wards are capable of providing the equipment and the expertise required for safe administration of these agents.

Supportive care. Most experts would agree that given the brief period of neutropenia observed when PBSC are used for transplantation, patient rooms with laminar air flow or high efficiency particulate air (HEPA) filtration is unnecessary. The medical care team must be well versed in management of neutropenic patients. This includes rigorous investigations of patients who develop fever and administration of empiric broad spectrum antibiotics while investigations are under way. Appropriate prophylaxis against pneumocystis pneumonia and herpes zoster or herpes simplex infections is recommended, especially when potent immunosuppressive conditioning regimens are combined with T cell depleted autografts.

The extent of blood product support is dependent on the myelosuppressive activity of the conditioning regimen. Blood and platelet support for 7 to 14 days may be necessary following some high dose conditioning regimens, particularly for patients who have been heavily pretreated with alkylating agents prior to the transplant. All blood products should be leukocyte depleted to prevent transfusion associated graft-versus-host disease. Adequate leukodepletion of all blood products should also serve to prevent patients who are seronegative for cytomegalovirus from primary exposure to this virus from the transfusion.

In summary, minimum center requirements for protocols involving ASCT require expertise in PBSC collection, cell processing and storage, administration of chemotherapeutic conditioning regimens, and supportive care of immunocom-

promised patients. With the exception of expertise and equipment necessary for complex manipulation of the autograft such as CD34 selection, most large academic centers have the capability of supporting such an endeavor.

Issues in Drug Development of Stem Cell Selection Devices in Autologous Stem Cell Transplantation for Pediatric Autoimmune Diseases: Jeffrey N. Siegel and Lisa G. Rider

The Food Drug and Cosmetic Act grants the US Food and Drug Administration (FDA) the authority to regulate unapproved devices including CD34+ stem cell selection devices used in SCT. The FDA reviews clinical trials involving the use of unapproved devices under applications called investigational device exemptions (IDE). Devices approved for a specific indication that are being studied for indications that are not approved, particularly where the use involves significant risk, are also regulated by the FDA (21 CFR 812.2). New cell selection devices become marketed or new indications become approved for already marketed cell selection devices through the pre-market approval (PMA) process. The device manufacturer submits a PMA application to the FDA, which contains the results of clinical trials designed to show the device is safe and effective for its intended use.

Two CD34+ stem cell selection devices, the Nexell Isolex 300i and the AmCell CliniMACS, have been used in SCT studies to deplete autologous sources of stem cells of contaminating T cells in patients with autoimmune disease. The Isolex device is approved in the United States "for hematopoietic reconstitution after myeloablative therapy in patients with CD34-negative tumors," but not for the treatment of autoimmune disease. The AmCell device has not been approved for use in the US. Thus, clinical studies of SCT for autoimmune diseases that utilize either of these devices require an IDE from the FDA.

Generally, clinical development proceeds according to progressive phases; initially, small studies are the first or early human exposure to a product, followed by larger multicenter trials designed to establish safety and efficacy. Early in development, when the device is being used along with a new conditioning regimen or where there is a novel safety issue, a small study is appropriate to gain some preliminary safety experience before exposing a larger number of patients.

Currently, there are a number of active IDE for autoimmune disease indications using stem cell selection devices. Most studies using these devices are single arm, single center studies of adult patients. The most common indications under study are SLE, RA, SSc, and multiple sclerosis. One pediatric protocol includes patients with JIA and other autoimmune diseases.

To date, outcomes from these early studies of ASCT, although mixed, suggest some potential for benefit[53]. In studies of ASCT in RA, SLE, and SSc, some patients appear to have a marked reduction in disease activity in the absence of concomitant disease modifying therapies or induction of remission for up to 3 years following transplantation. However, late relapses, including increases in autoantibody titers without clinical relapse, have also been observed 6 months to 2 years after the procedure[53-57]. Transplant related mortality has been reported to be about 9% overall in autoimmune diseases[57]. In some studies of SSc, however, mortality has been estimated to be as high as 25%, perhaps partly attributable to the selection of the most seriously ill patients with more long-standing disease. Fatal pulmonary toxicity has been reported in SSc patients who received total body irradiation without lung shielding, and preliminary data suggest that pulmonary toxicity may be diminished when lung shielding is used during radiation[57].

The FDA may disapprove a clinical trial of a new device if "there is reason to believe that the risks to the subjects are not outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained...." [US *Code of Federal Regulations* (CFR), 21 CFR 812.30(b)(4)]. Once the pilot studies are performed, the limited information that can be obtained from additional single arm, uncontrolled studies may not justify the substantial risks of ASCT for autoimmune diseases.

Randomized controlled clinical trials, adequately powered to establish effectiveness, are needed to determine whether ASCT provides clinical benefit for the treatment of autoimmune diseases. However, prior to conducting a definitive, large, multicenter, randomized controlled efficacy trial, a moderate size randomized controlled trial of ASCT in autoimmune disease could be carried out, in which patients who meet the eligibility criteria described above are randomized to either ASCT or optimal medical management. Such trials would have the distinct advantage over non-concurrently controlled studies in that the safety profile and potential benefits in patients who received an ASCT procedure can be directly compared to outcomes in patients who do not receive a transplant. A moderate size randomized, controlled phase 2 trial could help provide estimates of the effect size in order to determine the appropriate sample size of a subsequent pivotal trial. However, it is important to be aware that such phase 2 studies cannot ultimately substitute for an adequately powered phase 3 trial.

Pediatric patients represent a special situation. When the course of the disease and the effects of the therapy are thought to be similar in adults and children, such as might be the case with SSc or SLE, and effectiveness is demonstrated through adequate and well controlled trials in adults, it may be appropriate to extrapolate efficacy results from adult studies to children, as may be done for labeling of certain drugs and biologics for pediatric use [21 CFR 201.57(f)(9)(iv)]. In these cases, even if separate efficacy trials are not necessary for the device to be labeled for use in pediatric patients, it would still be important to obtain

some safety experience with the device in children and to assess response rates. This could be accomplished in open label studies. In contrast, for indications where the pediatric disease is not comparable to an adult condition (e.g., systemic JIA), determination of effectiveness may ultimately require a separate efficacy trial.

Design issues of particular relevance to ASCT. Informed consent documents for patients entering ASCT protocols should include an adequate description of the risks, including the potential transplant related mortality and failure to engraft, as well as a frank discussion of the risks of secondary malignancy, sterility, growth retardation, and secondary infections, either from the procedure or from adjunctive agents used in the conditioning regimens[58]. In patients with multiple sclerosis, flares in disease activity have been associated with use of G-CSF in the mobilization regimen[59]. Of note, cases of Epstein-Barr virus associated lymphoproliferative disease, some fatal, have been observed in patients who received rabbit anti-thymocyte globulin (ATG) instead of the more commonly used horse ATG.

A number of factors need to be considered when defining inclusion criteria for ASCT protocols in pediatric autoimmune disease. Due to the current risks associated with ASCT, patients selected for enrollment should be at high risk of death or severe disability from the underlying disease. Commonly used criteria include a high degree of active disease despite treatment with all currently available therapy and the presence of poor prognostic factors that justify the risks of this therapy. Patients should be excluded from enrollment in ASCT protocols if they have features placing them at unacceptable risk from the transplant itself. Patients with ongoing infections should be excluded. Patients unable to withstand the rigors of a transplant procedure due to a poor functional status or organ system compromise, such as irreversible or endstage disease defined by significant impairment in left ventricular ejection fraction, DLCO, or creatinine clearance, and patients who have received prior total lymphoid irradiation should be excluded from these trials.

Patients with autoimmune disease enrolled in trials should be closely monitored for short and longterm toxicity. There should be vigilant baseline screening and monitoring for occult infections, particularly in those patients who have already received immunosuppressive therapies. It is important to use a standardized toxicity assessment scale, such as the National Cancer Institute's Common Toxicity Criteria (http://ctep.info.nih.gov/CTC3/ctc.htm) or the OMERACT toxicity criteria (http://www.ilar.org/_interface/frsetsearch.asp), to systematically assess the frequency and severity of adverse events. The protocol should specify a threshold for the number, types, and severity of adverse events that would lead to discontinuation of enrollment. These might include unexpectedly high rates of engraftment failure or mortality, a prespecified number of grade 3 or 4 nonhematologic toxicities, or transplant related mortality exceeding a specified rate. Adequate mobilization of autologous stem cells should be a prerequisite to the initiation of the conditioning regimen.

For patients with systemic JIA who receive ASCT, European experience suggests there may be an increased risk of macrophage activation syndrome (MAS) and associated mortality in patients with active systemic disease at baseline[60]. These data suggest that JIA patients with ongoing fever or evidence of MAS at baseline should be excluded from ASCT protocols. Patients should be closely monitored for the development of MAS during and after ASCT through such laboratory tests as fibrinogen, D-dimer, transaminases, and complete blood count. Corticosteroid therapy should be tapered slowly, and when infectious etiologies are excluded, additional steroids may need to be given following the transplant procedure if MAS develops.

Public confidence in experimental trials depends on complete and accurate reporting of adverse events. Investigators are required to report unanticipated adverse device effects [ADE 21 CFR 812.3(s)] to their institutional review board and to the sponsor of the investigation device exemptions (IDE) within 10 working days [21 CFR 812.150(a)(1)]. The sponsor of an IDE is required to immediately conduct an evaluation of any unanticipated ADE [21 CFR 812.46] and report results to the FDA, to the institutional review boards of all participating sites, and to participating investigators within 10 working days after the sponsor of the IDE received notice of the adverse event [21 CFR 812.150(b)(1)].

Sponsors should be aware of other FDA requirements, including the necessity of submitting all protocol changes to the FDA prior to, or in some cases within 5 days of, implementation [21 CFR 812.35 (1)(3)(ii and iv)]. Progress reports for IDE submissions should be filed with the FDA at least annually and should generally include the current status of the trial, all adverse events observed to date, and any changes in the protocol.

In conclusion, uncontrolled pilot studies of ASCT suggest a potential for this treatment to be effective for patients with severe autoimmune disease, but these potential benefits must be confirmed and weighed against significant morbidity and mortality associated with the procedure. In designing clinical trials of ASCT in children with autoimmune disease, every effort should be made so that patients are not subjected to unreasonable risk. There are special safety considerations in ASCT protocols for autoimmune diseases, particularly for pediatric patients with systemic JIA. Finally, there is a critical need for well designed, randomized controlled trials of stem cell therapy of autoimmune diseases for advancement to occur in the overall assessment of the efficacy and safety of ASCT for these conditions.

The Case for a Multi-Institutional Repository of Biologic Materials for the Study of Pediatric Rheumatic Diseases Treated with Autologous Stem Cell Transplantation: Lisa Filipovich

The establishment of a repository of biologic materials from children with severe autoimmune disorders would provide a unique and highly valuable resource for the future discovery of genes etiologic to pediatric rheumatoid disorders, as well as a clearer understanding of which genes are specifically engaged and upregulated as the symptomatic consequence of the underlying genetic program. Materials to be collected would include DNA, RNA, viably cryopreserved T cells (both resting and activated), and, most important, EBV transformed B cell lines.

With the advent of major clinical interventions, such as autologous hematopoietic stem cell transplantation, that are currently being applied to severe cases of rheumatoid diseases, an unprecedented opportunity exists to elucidate pathogenic mechanisms responsible for clinical disease, by studying gene expression during active disease (e.g., pretransplant) and remission of disease (e.g., after transplant) in the same patient. Comparison of gene expression between patient groups with different disease phenotypes by microarray techniques could reveal common or divergent pathologic pathways amenable to new targeted therapies.

Animal models of autoimmune disorders have taught us that the etiology is often polygenic, and that a null mutation in a gene seemingly critical on a given genetic background may not prove as pathogenic in another murine strain. Further, genetic skewing of type 2 versus type 1 cytokine balance and sex (differences in the sex hormone milieu) predispose to symptomatic autoimmunity in murine models.

I hypothesize that children who develop severe, systemic, or multiple autoimmune complications are more likely to carry a stronger genetic predisposition for these problems than patients who develop autoimmune disorders as adults, where environmental exposure is required, as well as hereditary predisposition, to express the "acquired" disease.

Severe and multiple autoimmune complications are well recognized complications in a number of genetically determined immunodeficiencies with symptomatic onset in childhood. Indeed, as better antibiotics have been developed to prevent and treat opportunistic infections and children with certain immunodeficiencies are surviving longer, more autoimmune complications are being observed. Autoimmune complications are seen in human disorders where the T cell repertoire is limited and/or skewed, and when defects in the normal balance of lymphoid proliferation versus apoptosis occur. A partial list of primary immunodeficiencies associated with autoimmune complications, and arthritis in particular, is shown in Table 3. For some of these immunodeficiency and immunoregulatory disorders the underlying gene defects are known — such as mutations resulting in abnormal expression of MHC genes, CD40 ligand and FAS, defects in RAG genes responsible for rearrangement of immunoglobulin and T cell receptor genes, and microdeletions on chromosome 22 seen in the DiGeorge anomalad. Other immunodeficiencies such as common variable immunodeficiency may be polygenic in etiology. For still others, the gene responsible remains elusive.

Table 3. Arthritis as a complication of genetic immune disorders.

Disorder	Inheritance/Gene Defect	Autoimmune Complication
CVID	Unknown, polygenic	AIHA, ITP, RA, IBD, Th
MHC deficiency	AR (several)	AIHA, RA, IBD
SCID (Omenn's S.)	AR, RAG1	AIHA, RA
XHIM	X, CD40 ligand	ScCh, RA
ALPS Type 1a	AD, FAS	AIHA, ITP, RA
ALPS Type 2	AR, Caspase 10	AIHA, ITP, RA
DiGeorge anomalad	Microdeletion 22	AIHA, ITP, RA

CVID: Common variable immunodeficiency; MHC: major histocompatibility complex; SCID: severe combined immunodeficiency; XHIM: X-linked hyper IgM syndrome; ALPS: autoimmune lymphoproliferative syndrome; AIHA: autoimmune hemolytic anemia; ITP: immune thrombocytopenic purpura; RA: rheumatoid arthritis; Th: autoimmune thyroid disorder; ScCh: sclerosing cholangitis.

It is also possible, indeed probable, that mutations leading to partial expression of genes responsible for severe immune/inflammatory disorders or a carrier state could predispose to autoimmune complications in humans. A provocative example is provided by our recent study of perforin gene expression in a patient with JIA who developed life-threatening macrophage activation syndrome — a complication symptomatically reminiscent of the autosomal recessive genetic disorder HLH, hemophagocytic lymphohistiocytosis. Recently, mutations in the perforin gene have been reported to be linked with the development of HLH in a subset of children with that diagnosis. FACS analysis of cytotoxic cells in carrier parents of the perforin mutation causing HLH reveal decreased protein expression in these cell types compared with healthy adult controls. A very similar abnormal (decreased) pattern of perforin expression was detected in the JIA patient with MAS.

In light of the considerations described above one can propose a battery of immune studies that could be performed as part of the "pretransplant" gene-finding protocol for children with severe autoimmune disease who are potential candidates for autologous or allogeneic transplantation. These are listed in Table 4.

Biologic samples to be collected both pretransplant and at intervals afterwards include EBV transformed B cell lines, cryopreserved DNA (PBMC), viably cryopreserved PBMC, cryopreserved mRNA (resting PBMC), and cryopreserved mRNA (activated PBMC).

Finally, most proposed protocols for ASCT in autoimmune disease that have been piloted in the adult setting as

Table 4. Proposed pretransplant immunologic evaluation for children with autoimmune diseases undergoing ASCT.

Lymphocyte subsets
CD3 4/8, CD16/56, CD19/5
Proportional distribution of naïve/memory T cells
Proportional distribution of T cells expression α/ß or γ/Δ TCR
MHC Class I and II expression
Proportional distribution of Th1 and Th2 cells
T cell repertoire diversity (V beta families, TREC)
Studies of cell mediated immunity
Lymphocyte activation and proliferation to mitogens and antigens
In vitro cytokine synthesis (proinflammatory, T cell derived)
Natural killer cell cytolysis and perforin expression
Quantitative immunoglobulins

TCR: T cell receptor. TREC: T cell receptor excision circles.

"resetting the immunoregulatory clock" involve extensive *in vivo* and *in vitro* immune depletion aimed at ablating acquired autoimmune clones. Such immunoablation, however, is broadly immunosuppressive and has resulted in an unacceptably high risk of opportunistic viral infections with some protocols. For this reason, monitoring immunoreconstitution across protocols and patient groups could prove instructive both for monitoring post-transplant recovery of desirable immune responses and for maintenance of remission of clinical autoimmunity. Suggested studies for tracking immunoreconstitution are listed in Table 5.

Autologous Stem Cell Transplantation for Refractory Juvenile Idiopathic Arthritis: Current Results and Perspectives: Nico M. Wulffraat

A small proportion of children with systemic or polyarticular juvenile idiopathic arthritis (JIA) are refractory to combinations of nonsteroidal antiinflammatory drugs (NSAID) and immunosuppressive drugs such as methotrexate (MTX), cyclosporine (CsA), prednisone, and anti-tumor necrosis factor (TNF) treatment[6,61-63]. These children challenge the pediatric rheumatologist to look for new possible treatments. In the evaluation of such new treatments one needs to balance a possible significant improvement of the quality of life with risk of severe side effects. The first children with severe JIA treated with ASCT were reported earlier[64,65]. We report an extension of this study in the Netherlands, which at present includes 14 children with JIA, with a followup of 3 to 40 months.

Table 5. Proposed post-transplant studies of immune reconstitution for children with autoimmune diseases undergoing ASCT.

Lymphocyte subsets
CD3 4/8, CD16/56, CD19/5
Proportional distribution of naïve/memory T cells
Proportional distribution of T cells expression α/ß or γ/Δ TCR
Proportional distribution of Th1 and Th2 cells
T cell repertoire diversity (V beta families, TREC)
Studies of cell mediated immunity
Lymphocyte activation and proliferation to mitogens and antigens
In vitro cytokine synthesis (proinflammatory, T cell derived)
Quantitative immunoglobulins
Response to immunizations

TCR: T cell receptor. TREC: T cell receptor excision circles.

Patients. In the Dutch study, started in 1997, we included 14 patients with a followup of 3 to 40 months (median 20). The clinical characteristics are given in Table 6. The inclusion criteria for this trial were failure to respond to high dose MTX intramuscularly (1 mg/kg/wk), failure to respond to at least 2 disease modifying antirheumatic drugs (DMARD), anti-TNF treatment (for patients enrolled after October 1999), steroid dependency (> 0.3 mg/kg/day needed to control symptoms), and unacceptable toxicity of DMARD or steroids. Exclusion criteria were cardiorespiratory insufficiency, chronic active infection such as EBV, CMV, toxoplasmosis, spiking fever despite steroids, endstage disease (Steinbrocker IV), or poor compliance.

We studied 10 children with systemic JIA and 4 with polyarticular JIA, all with progressive disease activity for more than 5 years despite the use of NSAID, prednisone (maintenance dose and pulses), cyclophosphamide pulses (750 mg/m^2), intramuscular MTX up to 1 mg/kg/wk, and CsA (2.5 mg/kg/day). The clinical characteristics in all children were a polyarticular course with erosions, osteoporosis, and stunted growth; and in those with systemic onset disease, periods of spiking fever and exanthema. Most suffered from steroid related side effects. The mean time interval between diagnosis and transplant was 6 years (range 13–137 mo).

Outcome measures. We used the core set of outcome variables for clinical trials in childhood arthritis as proposed by Giannini and the Pediatric Rheumatology International Trials Organisation group (PRINTO)[13,66-69], which consists of physician's and parent/patient global assessment of disease activity, functional ability as measured by the Childhood Health Assessment Questionnaire (CHAQ), the number of joints with active arthritis (Fuchs Swelling Index, FSI), the number of joints with limited range of motion, and the erythrocyte sedimentation rate (ESR)[66-68]. The evolution of disease in our patients was followed at 3 month intervals.

Bone marrow harvest and T cell depletion. Unprimed bone marrow was harvested under general anesthesia at least 1 month prior to ASCT. In Patients 1 to 7 and Patients 12 to 14, the graft was purged by 2 cycles of T cell depletion with CD2 and CD3 antibodies, yielding a final suspension with a CD34 positive stem cell count of 0.5 to 6.5 $\times$ 10^6/kg and less than 5 $\times$ 10^5 CD3 cells/kg, and which was stored in liquid nitrogen[70]. In Patients 8 to 11 the graft was purged by positive selection of CD34 positive stem cells using the Clinimacs device. Thus a suspension was obtained containing 0.5 to 4 $\times$ 10^6 CD34 cells/kg and less than 0.3 $\times$ 10^5 CD3 cells/kg and it was stored in liquid nitrogen.

Conditioning for ASCT. The conditioning regimen included 4 days of anti-thymocyte globulin (IMTIX, Pasteur-Merieux, France) in a dose of 5 mg/kg daily from Day –9 to –6, cyclophosphamide 50 mg/kg daily from Day –5 to –2, and low dose total body irradiation (4 Gy, single fraction) on Day –1. At Day 0 the frozen stem cell suspension was thawed and infused. MTX and CsA were stopped before ASCT and prednisone was tapered after 2–6 months.

Hematological reconstitution. Neutrophil recovery (> 0.5 × 10^9/l) occurred at Day +20 to +30 and the platelet count reached 20 × 10^9/l after 16 to 35 days post-ASCT. Five to 9 months after ASCT the numbers of circulating T cells were normal (> 1000/ml) with normal *in vitro* mitogenic responses at 3 to 8 months after ASCT. CD4 lymphopenia (< 500/ml) lasted 6 to 9 months, while the CD8 T cells returned to normal values after 3 to 4 months. Interestingly, in both CD4 and CD8 subsets the first cells to return after ASCT were CD45RO (memory) T cells. Nine months after ASCT the majority of T cells were of the CD45RA (naive) phenotype.

Rheumatological followup. Seven patients showed a drug-free followup of 4 to 36 months, with a more than 50% decrease in the scores of the CHAQ, the physician global assessment, and joint swelling (Figures 2–4). Two patients with followup of 3 and 4 months are clinically in remission while the steroids have been gradually tapered.

ESR and C-reactive protein returned to near-normal values within 6 weeks but were often increased during

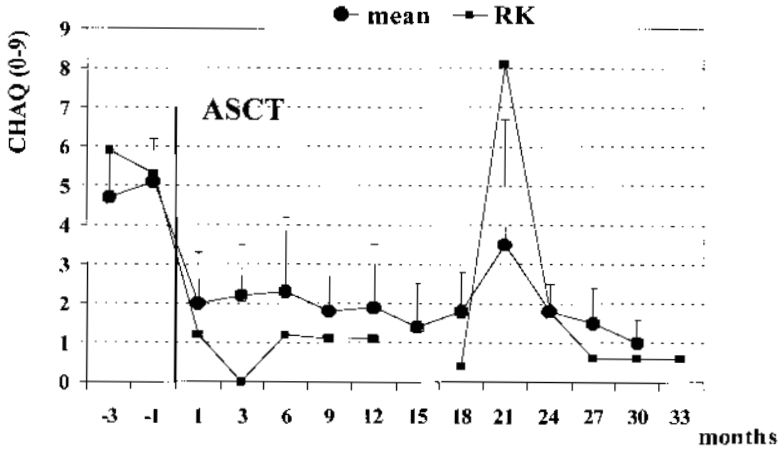

Figure 2. The mean parent/patient assessment of overall well being (the Child Health Assessment Questionnaire, CHAQ) before and after autologous SCT. The CHAQ contains 3 domains: severity, pain, and disability. The total score (0–9) of these 3 domains is given. Only patients with followup of at least 12 months are given (Patients 1–8). The total score is decreased > 50% in 7 of 8 patients after ASCT; in one patient (Patient 3) the score is decreased by 30%. Note that individual scores of Patient RK show transient relapses, associated with infections.

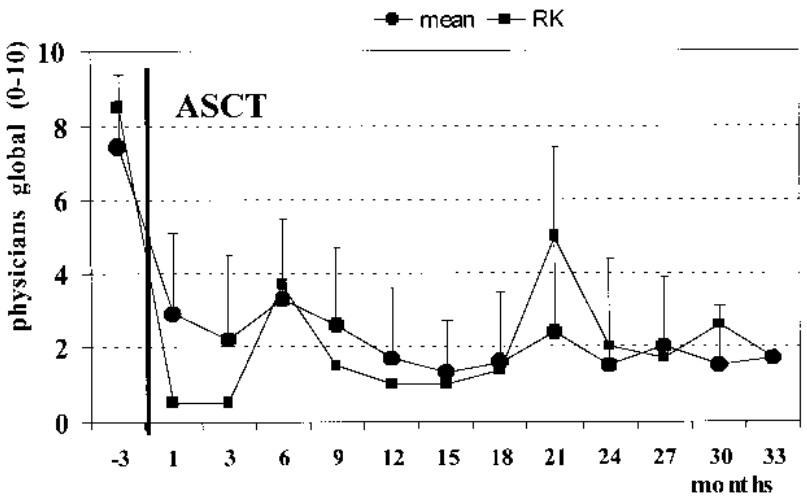

Figure 3. The mean score of the physician's global assessment of disease activity, before and after ASCT based on visual analog scale scores (0–10). Only patients with followup of at least 12 months are given (Patients 1–8). The score is decreased > 50% in 7 of 8 patients after ASCT; in Patient 3 the score is decreased by 30%.

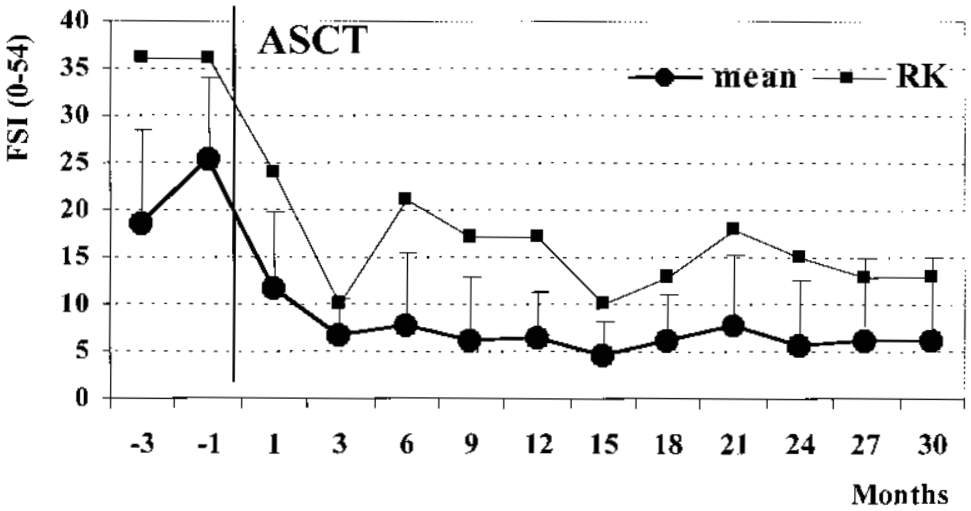

Figure 4. Number of joints with active arthritis (Fuchs Swelling Index, FSI) before and after ASCT. The FSI refers to 18 joints, with a cumulative score of 0–3 for each joint (minimal 0, maximal 54). Only patients with followup of at least 12 months are given (Patients 1–8). The score is decreased > 50% in 7 of 8 patients after ASCT; in Patient 3 the score is decreased by 30%.

infections. In 2 patients ESR increased again after 3 months, with mild and transient synovitis of the hip and knee, following varicella zoster virus (VZV) and tonsillitis. This relapse was very mild, with oligoarthritis and sporadic fever, and was controlled easily with a 3 month course of low dose prednisone and NSAID.

With regard to improvement as determined by the core set criteria, 2 children showed only a partial response, with a 30% improvement of their disease. One child did not show any response and in 2 the followup is only 3 to 4 months. The remaining 7 all showed more than 50% improvement. Two patients died of macrophage activation syndrome (see below).

Growth after auto-SCT. For each age, a mean length and standard deviations have been described. A given length can thus be expressed as a standard deviation score (SDS) of height for age[71]. Prior to the onset of their disease, the children in this study had length between –0.2 and +2 SD of the mean length for their age. During the course of their disease these children lost 3–5 SDS (Figure 5). After ASCT some of the younger children (such as Patients 1 and 2, Figure 5) show a catchup growth of 1 to 2 SDS, but the oldest children with the longest disease duration did not show catchup growth (Patients 3 and 4, Figure 5), but their SDS did not decrease further.

Table 6. Clinical characteristics of the JIA patients before ASCT (The Netherlands).

Patient	Onset Age, yrs	Onset Form	Treatment	ASCT, age	Followup, mo	Complications
1	1	Sys	NSAID, CS, IVIG, MTX, CsA	6 yrs, 7 mo	35	VZV, strep tonsillitis
2	3	Poly	NSAID, CS, MTX, CsA	7 yrs, 9 mo	33	VZV
3	3	Sys	NSAID, CS, MTX, CsA	11 yrs, 2 mo	27	VZV, EBV reactivation, HSV-hepatitis
4	5	Sys	NSAID, gold, SZ, AZA, MTX, CsA, oral and pulse CS	11 yrs	24	VZV
5	4	Sys	NSAID, Cy, AZA, CS, MTX, CsA	10 yrs, 6 mo	18	Atypical MB
6	5	Sys	NSAID, CS, MTX, CsA	9 yrs, 4 mo	15	VZV
7	3	Sys	NSAID, AZA, CS, MTX, CsA	14 yrs, 2 mo	5	CR but fatal MAS
8	5	Poly	NSAID, SZ, MTX, CS	12 yrs, 2 mo	12	VZV
9	4 yrs, 1 mo	Sys	NSAID, MTX, CS, SZ, AZA, Gold	13 yrs, 6 mo	22	CMV reactivation
10	3 yrs, 1 mo	Poly	NSAID	5 yrs, 7 mo	18	VZV, CMV primo infection
11	3 yrs, 2 mo	Sys	NSAID, CS, CsA, MTX	4 yrs, 3 mo	18 days	Fatal MAS
12	7 yrs, 7 mo	Sys	NSAID, CS, MTX, CsA	10 yrs, 7 mo	3	
13	1 yr, 2 mo	Sys	NSAID, CS, MTX, CsA, AZA, Enbrel	5 yrs, 1 mo	4	Catheter related thrombus
14	2 yrs, 2 mo	Poly	NSAID, CS, MTX, CsA	8 yrs, 4 mo	3	

NSAID: Nonsteroidal antiinflammatory drugs; CS: corticosteroids; IVIG: intravenous immunoglobulins; MTX: methotrexate; CsA: Cyclosporin A; SZ: sulfasalazine; AZA: azathioprine; MAS: macrophage activation syndrome; VZV: varicella zoster virus; CMV; cytomegalovirus; CR: complete remission.

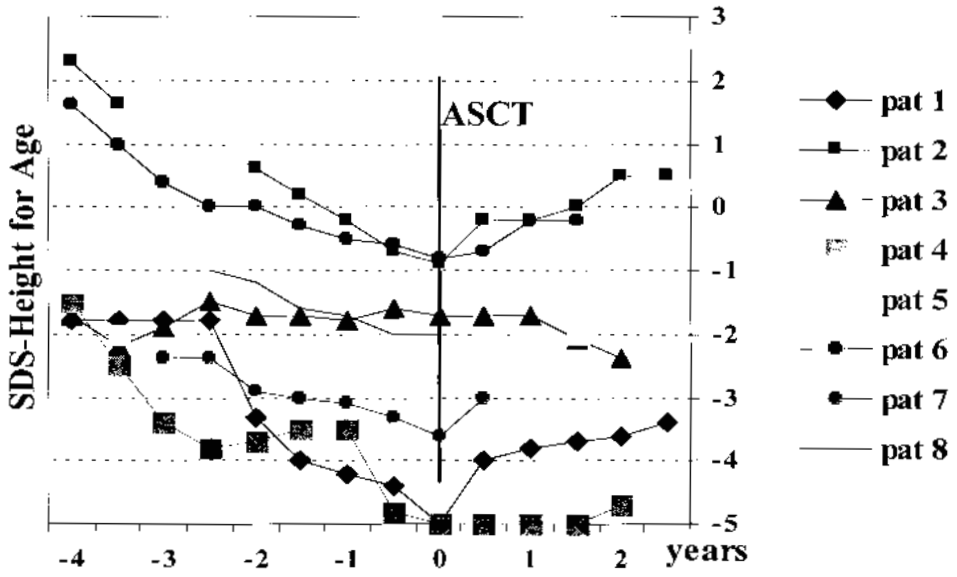

Figure 5. Growth curves of children with prolonged and severe JIA before and after ASCT expressed as standard deviation score (SDS) height for age. Note the marked loss growth velocity of –1 to –3 SDS during the disease prior to ASCT and the catchup growth after ASCT, especially in the younger children.

Complications. All children developed chills, fever, and malaise during infusion of ATG. During the aplastic period, blood cultures were positive for *Staphylococcus epidermidis* in 2 children. They responded favorably to IV antibiotics. Seven patients developed a limited VZV eruption 3 to 18 months after ASCT, which was treated by acyclovir. One developed a localized atypical mycobacterial infection. Two patients died of MAS (also known as infection associated hemophagocytic syndrome). The first case (Patient 9) was induced by EBV 4 months after ASCT. At the time of the

Table 7. Results after ASCT for 29 patients with JIA in European and North American centers.

Patients	Center	Age at Diagnosis, yrs	Age at ASCT, yrs	TCD (Y/N)	Conditioning	Followup, mo	Outcome	Present Antirheumatic Drugs
1–11	Utrecht, NL	1–7	7–14	CD2/3 (6) CD34 (3)	Cy, ATG, TBI (4 Gy)	4–36	8 remission, 2 partial remission, 1 fatal MAS	Low dose steroids (2) NSAID (1)
12–14	Leiden, NL	2–10	4,6,14	CD2/3 (1) CD34 (2)	Cy, ATG, TBI (4 Gy)	12–15	1 remission, 1 partial remission, 1 fatal MAS	Salazopyrin (1)
15	Paris, France	8	9	CD34	Cy, ATG	—	Day 18 disseminated toxoplasmosis and fatal MAS	
16–17	Goteborg, Sweden		4–9	CD2/3	Cy, ATG, TBI (4 Gy)	3–10	Both remission	Low dose steroids in 1
18–22	Trieste, Italy	3–15	8–20	VCR	Cy, ALG (3) Flu, ALG (2)	12–36	Remission 3, relapse 2	Etanercept (1) NSAID (1)
23	Portland, USA	2	10	CD34	Cy, ATG, TBI (4 Gy)	7	Remission	None
24–25	Brussels, Belgium	1–7	8, 17	CD34	Cy, ATG	7–19	Remission	None
26	Brussels	7	15	CD34	Cy, ATG	—	Sepsis and fatal cardiac toxicity	—
27–28	Osaka, Japan	1–5	3–8	CD34	Cy, ATG (1) VP16, TT (1)	4–11	No response (1), remission (1)	Low dose steroids None
29	Newcastle, UK	3	10	CD34	Cy, ATG	2	Remission	Low dose steroids

CD2/3: negative selection by monoclonal antibodies to CD2 or CD3 positive lymphocytes; CD34: positive selection of CD34+ stem cells; ATG; anti-thymocyte globulin; TBI: total body irradiation; TCD: T cell depletion; Cy: cyclophosphamide; VCR: vincristine; ALG: anti-lymphocyte globulin; MAS: macrophage activation syndrome. Data were obtained from: M. Abinun and H. Foster, Newcastle, England; D. Brinkman, Leiden, Netherlands; A. Fasth, Goteborg, Sweden; A. Ferster, Brussels, Belgium; K. Keisei, Osaka, Japan; T. Moore, Portland, USA; A.M. Prieur and P. Quartier, Paris, France; M. Rabusin, Trieste, Italy; N. Wulffraat, Utrecht, Netherlands.

EBV infection, her JIA was in remission. The other MAS fatality (Patient 11) occurred 18 days post-transplant, while he was still in complete aplasia. The occurrence of MAS in systemic JIA after ASCT may be caused by the T cell depletion resulting in inadequate control of macrophage activation. However, there was no difference in the number of reinfused T cells after CD34 selection compared to children that did not develop MAS. At a pediatric session of the EULAR conference held in June 1999 in Glasgow these cases were discussed in detail. It was agreed that the graft must contain not less than 1–5 $\times$ 10^5 T cells/kg. Further, it was suggested that patients with active disease (fever), not controlled by steroids, also be excluded from study and that immune suppression after autologous SCT should be tapered more slowly. In case of unexplained fever > 39°C for 48 hours, MAS must be considered and treatment with methylprednisolone 20 mg/kg/day (in 4 divided dosages) and cyclosporine 2 mg/kg/day should be started immediately. If no effect is seen within 48 hours, reinfusion of stored autologous T cells should be considered.

Other EBMT/ABMT centers. Including our 14 patients with JIA, at present 29 patients with childhood onset JIA have been transplanted and registered in the database of the Working Party for Autoimmune Diseases of the European Blood and Marrow Transplantation group (EBMT) from 12 centers in 10 countries (Table 7)[72]. Clearly, these children represent the most severe and drug resistant forms of JIA. Of the reported 29 children, following transplantation, 16 were reported as in "drug-free remission," 8 were in partial remission or relapse for which NSAID or low dose steroids were prescribed, and one was a nonresponder. Data pertaining to followup after ASCT in these 29 children are limited and do not permit a detailed analysis of the changes of the core set criteria. Regarding safety outcomes, 4 patients have died. The cause of death was primarily infection associated with aplasia. In 3 of these, hemophagocytosis, a well known complication of systemic JIA, was also present. This was preceded by infections such as EBV reactivation and disseminated toxoplasmosis, which may also induce hemophagocytosis.

Conclusion. In our study, ASCT induced a substantial clinical benefit in all children with severe and drug resistant juvenile idiopathic arthritis. Prolonged prednisone-free growth catchup and general well being is a major therapeutic gain in such children. Since this approach was introduced only 4 years ago, the current experience includes only case reports of selected patients and a single open label study. The results of this limited number of patients treated with ASCT do not permit firm conclusions about the optimal conditioning regimen, including the necessity of low dose TBI, or the effect of T cell depletion of the graft. We chose a combination of cyclophosphamide and low dose TBI since this was most effective in an animal model for arthritis[49].

It is to be noted, however, that this therapy in patients with systemic JIA carries a significant risk of developing fatal MAS. Factors that may predispose an individual to MAS, such as viral infections, must be identified and less profound T cell depletion, control of systemic disease prior to transplant, and slow tapering of steroids after ASCT are advised. One of the most difficult aspects is to carefully weigh the risks of the prolonged immunosuppression of "conventional" treatment against those of the short but intense immunosuppression of ASCT. Further, this new approach must be confirmed by randomized controlled studies in multicenter trials. For this purpose we propose a randomized trial with 3 arms, including a control arm with continuation of conventional therapy, ASCT with a T cell depleted graft, and ASCT with a full (nondepleted) graft. With a predicted response rate of 70% in the ASCT arms and 35% in the control arm, a total of 36 patients must be included in each arm. Given the rarity of such treatment resistant disease, such a trial should include 10 to 15 participating centers. For such a trial, registry forms have been developed by joint effort of ABMT and EBMT.

WORK GROUPS

Below are reports from individual working groups. Members of the pediatric transplantation group discussed protocol development for studies beyond pilot investigations. Simultaneously, participating pediatric rheumatologists were divided into small work groups with instructions to develop entry and exclusion criteria for autologous stem cell transplantation for studies beyond pilot investigations and to determine the optimal standard therapy for comparison in future randomized, controlled studies.

Protocol Development: Consensus Meeting: Murray Passo, Moderator

Four pediatric rheumatologists met with the transplanter participants to develop protocol (or protocols) for SCT for pediatric autoimmune disease to be used in the next phase of investigations in randomized controlled trials. An interactive, collaborative process known as the nominal group technique was employed to generate a list of specific components of the SCT process to establish consensus on a defined national protocol. In total, there were 21 participants suggesting questions and ideas that were discussed in detail.

Multiple protocols were discussed during the first day of this workshop. These protocols were based on individual transplanter beliefs and experiences, resources, prior protocol development, and institutional factors. Several assumptions were made prior to consensus development:

1. There exists a paucity of children with autoimmune disease who will require SCT for refractory disease management.

2. Given Point 1, there needs to be a consensus on the design of the protocol for SCT to conduct a meaningful study for safety and efficacy.

Several procedural aspects emerged during presentations the first day. Questions derived from those procedures set the format for discussion prior to generating a consensus. These questions included:

1. Graft source: peripheral blood stem cells versus bone marrow stem cells.

2. Mobilization of the stem cells with G-CSF with or without cyclophosphamide.

3. T cell depletion/CD34 selection, specific methodology.

4. Conditioning/preparative phase, including aspects such as total body irradiation, fludarabine, BuCy, and cyclophosphamide dosage (120–200 mg/kg).

5. Other transplant issues, such as supportive care issues, data collection, case report forms, etc., were presented as potential issues for discussion.

The format above was presented to spawn the consensus meeting, whereupon participants quickly decided that we were not ready to embark on protocol development. Numerous questions needed to be discussed before the group could invest in discussion of a specific nationwide protocol.

Utilizing the nominal group technique, we elicited ideas, generating discussion of these, for clarification and evaluation. Each participant ranked ideas anonymously, thus generating 5 leading questions, before we could embark on a protocol, on how to:

1. Define achievement of disease remission, including duration and event-free survival. This was emphasized in regard to ASCT.

2. Establish the safety, both morbidity and mortality, of SCT.

3. Reach uniform agreement on 2 specific features, (a) reporting using the same forms, and (b) tracking eligible patients (with or without transplantation). This was notable since we do not have a control group built into the current protocols, which was mandated as essential by the US FDA participants. A control group would be patients who either did not receive transplantation or received a different treatment.

4. Consider biologic questions, including the basic pathophysiology of the autoimmune diseases and the effects of SCT. A subcategory of this question included development of a data and tissue repository.

5. Compare autologous bone marrow transplantation versus allogeneic. Which is more efficacious? Can the morbidity/mortality of allogeneic transplantation be reduced to an "acceptable" level (especially as viewed by the pediatric rheumatologists)?

In summary, ideas were generated that required more discussion before a specific protocol (or protocols) could be developed and accepted nationwide. Due to time limitation it was suggested that a Delphi technique be employed to seek consensus. This is a similar consensus technique done by serial questionnaires through the mail and would be conducted within the next several months. This process is being developed and will be reported separately.

Juvenile Idiopathic Arthritis Criteria for Study Comparing Autologous Stem Cell Transplantation and Best Standard Therapy: Carol Wallace, Moderator

This workshop used the nominal group technique for discussion and development of appropriate inclusion and exclusion criteria for JIA for use in potential future randomized controlled trials of ASCT. In addition, a definition of "best standard therapy" was discussed and developed that could serve as the control arm in future studies. As for inclusion and exclusion criteria, there was discussion of the ideal time for ASCT and the number of agents to be tried, keeping in mind both the progressive joint destruction and possible cumulative toxicities from therapy. If mortality from ASCT could become < 3%, patients could potentially receive ASCT earlier in their course. Given the intensity of the conditioning regimens, and the agents usually involved, there was consensus that in future studies ASCT could be an alternative to cyclophosphamide therapy. From this discussion, the "best standard therapy" for JIA to compare to ASCT then evolved to include cyclophosphamide. The conclusions of this workshop follow.

INCLUSION CRITERIA: JIA

1. Diagnosis of systemic onset or polyarticular course disease according to American College of Rheumatology (ACR) criteria

2. Duration of disease of at least one year

3. Evidence of active inflammatory disease during at least the last 6 months despite aggressive treatment. Evidence of active inflammatory disease is defined by either a or b:

a. Evidence of active inflammatory disease in at least 5 joints, including 2 critical joints. Critical joints are defined as neck, shoulders, elbows, wrists, hips, knees, and ankles. Active inflammatory disease is defined as joint swelling or effusion OR limitation of range.

b. Evidence of inflammatory disease in at least 4 joints including 2 critical joints *and* 2 of the following:

- 6 months of active systemic features requiring corticosteroid therapy of ≥ 0.25 mg/kg/day — defined by at least 2 of the following: fever, growth failure, serositis, pericarditis/myocarditis, lymphadenopathy, hepatosplenomegaly, or interstitial pneumonitis
- Elevated erythrocyte sedimentation rate ≥ 1.5 times upper limit of normal
- CHAQ score ≥ 0.75
- Presence of erosive disease assessed by radiologic imaging study
- Rheumatoid factor positive disease. Previous episode of severe macrophage activation syndrome requiring hospitalization.

4. There must be evidence of unresponsiveness to or unacceptable toxicity (defined below) from aggressive therapy. Evidence for unresponsiveness includes continued disease activity despite ALL the following:

a. Inability to taper below ≤ 0.25 mg/kg/day of prednisone, or unacceptable toxicity.

b. Methotrexate (1.0 mg/kg/week subcutaneous or intramuscular, up to 40 mg/week) for at least 3 months or until unacceptable toxicity.

c. Combination therapy consisting of: steroid pulse 30 mg/kg/week (1 g maximum) or daily oral prednisone ≥ 0.25 mg/kg/day, and TNF antagonist, and either MTX and CsA or MTX and FK506.

Evidence for unacceptable toxicity includes at least 2 of the criteria defined below.

1. Failure to grow (dropping 2 SD or < 3% for height) related to corticosteroid use
2. Severe osteoporosis (e.g., vertebral or pathologic fractures) related to corticosteroid use
3. Avascular necrosis
4. Severe corticosteroid induced psychiatric disease
5. Increased serum creatinine > 30% over baseline on at least 2 separate occasions related to CsA use
6. Hypertension requiring treatment related to medication use. Diastolic or systolic pressure persistently higher than the acceptable range for a given age
7. Elevation of liver enzymes > 5 times the upper limit of normal on at least 2 separate occasions related to MTX use
8. Intractable gastrointestinal toxicity from DMARD or MTX unresponsive to antiemetics
9. Recurrent serious infections due to treatment
10. Steroid induced diabetes or pancreatitis

EXCLUSION CRITERIA: JIA

1. Patients with fever > 39°C
2. Cytopenia — absolute neutrophil count < 1000 or platelet count < 100,000 *and* bone marrow aspirate or biopsy consistent with production defect (depletion of neutrophil precursors or megakaryocytes) OR myelodysplasia
3. Serious central nervous system damage precluding significant functional recovery
4. Endstage glomerulonephritis or renal disease. Creatinine clearance < 40 ml/min/1.73 m^2
5. Patients with DLCO < 70% who have pulmonary disease caused by processes other than the primary autoimmune disorder, as documented by chest radiograph or chest computerized tomography, including infectious pneumonia or aspiration pneumonia
6. Endstage cardiopulmonary disease (including any of the following):

a. DLCO < 45%

b. Severe pulmonary hypertension (PAP > 50) without potential for significant improvement

c. Uncontrolled malignant arrhythmia

d. Clinical evidence of congestive heart failure (New York Class III–IV) or ejection fraction < 50%

7. Severe liver dysfunction within one month prior to transplantation. Bilirubin > 2.5 mg/dl or AST > 300 U/l on 2 sequential tests. Patients with myositis and AST > 300 U/l are not excluded if it can be demonstrated that elevated AST is not due to intrinsic liver dysfunction (enzyme profile, hepatic ultrasound, or liver biopsy not compatible with hepatitis or liver dysfunction)
8. Active viral hepatitis, including hepatitis A, hepatitis B, and hepatitis C
9. Patients with positive serology for toxoplasmosis
10. HIV positive patients are excluded due to high risk for acceleration or reactivation of viral replication
11. Active life-threatening infections not responsive to therapy
12. Other disease or organ dysfunction that would limit survival to less than 30 days
13. No potential for improvement in function of affected organ systems
14. Known hypersensitivity to murine or equine proteins or to *Escherichia coli* derived products
15. Known primary immunodeficiency disease.

BEST STANDARD THERAPY

1. Solumedrol 30 mg/kg/week (1 qm maximum)
2. Daily steroid ≥ 0.25 mg/kg/day prednisone
3. MTX 1 mg/kg subcutaneous (or intramuscular or IV) weekly (40 mg/kg/week maximum)
4. Cyclophosphamide 500–1000 mg/m^2 IV monthly

Systemic Sclerosis and Juvenile Dermatomyositis/ Polymyositis: Lisa G. Rider, Moderator

This work group was devoted to developing appropriate inclusion criteria for a potential future randomized controlled trial of autologous stem cell transplantation in pediatric patients with systemic sclerosis and juvenile dermatomyositis (DM)/polymyositis (PM). In addition the group discussed a potential design for a randomized trial and appropriate outcome criteria for such patients. Using the nominal group technique to derive consensus, the participants first agreed that SSc patients with interstitial lung disease (ILD), pulmonary hypertension, or active, progressive cutaneous disease would be potentially appropriate subgroups to include in trials of SCT, due to their established poor prognoses and the current absence of fully efficacious therapies for these complications[73-75]. As previously adapted by adult ASCT protocols, the participants agreed to maintain general inclusion criteria for patients with SSc as those with disease duration ≤ 3 years from the first non-Raynaud's symptom[73]. In addition, the group agreed to include patients with one of 3 possible organ-specific criteria as follows.

INCLUSION CRITERIA: SSc

1. ILD with a DLCO ≤ 70% predicted with a decline in DLCO of > 10%, despite receiving ≥ 3 months of optimal cyclophosphamide therapy[73]. Optimal cyclophosphamide therapy was considered to be 500–1000 mg/m^2 monthly administered IV or 2 mg/kg/day orally[76,77].

2. Pulmonary hypertension. Preliminary criteria: pulmonary artery pressure > 10% of the upper limit of normal for age (further refinement of this criterion is needed pending input from pediatric cardiologists).

3. Active, progressive cutaneous disease, with a Rodnan skin score > 16 and/or > 10% progression in skin scores over a 3 month interval and concomitant evidence of internal organ involvement[73], despite treatment with at least MTX in a dose of 1 mg/kg/week parenterally, and prednisone 1 mg/kg/day.

One potential design of a randomized controlled trial in scleroderma was discussed: to randomize patients to receive ASCT or to continue best standard therapy. The participants felt that a patient randomized to best standard therapy should potentially continue to receive this for ≥ 3 additional months, and if he then met the above inclusion criteria, he would be declared a treatment failure and offered open label ASC. A patient with ILD related to SSc could be randomized to ASCT or continue receiving cyclophosphamide therapy. If the DLCO worsened to ≤ 50% predicted, participants felt the patient could be a candidate for early escape from best standard therapy and then offered ASCT. For pulmonary hypertension, appropriate best standard therapy was agreed to be vasodilator therapy, including epoprostenol (Flolan), which has recently been approved for the treatment of pulmonary hypertension associated with scleroderma[78]. However, the group felt it would be appropriate to terminate patients from best standard therapy (the placebo arm) if left ventricular ejection fraction declined below a certain level (not determined at this meeting), but remained > 50%, which would be an absolute exclusion criterion[73]. For patients with cutaneous disease, participants agreed best standard therapy was to be MTX and prednisone. Early escape from this therapy was not considered appropriate for skin disease.

The group agreed with the current exclusion criteria for subjects with scleroderma for ASCT. These included signs of endstage disease, including DLCO < 45% predicted or left ventricular ejection fraction < 50%[73].

Assessment of outcome measures for a trial of patients with pediatric SSc was also addressed. Discussion was limited by the fact that fully validated measures do not currently exist for scleroderma. The participants felt appropriate outcome measures may include pulmonary function testing (forced vital capacity, DLCO) and high resolution computerized tomographic scan, with a quantitative scoring system for patients with ILD. For patients with pulmonary hypertension, pulmonary artery pressures would be an appropriate primary outcome in a trial. In patients with skin disease, Rodnan skin scores were considered a validated primary outcome measure[79]. Similar to current protocols for ASCT in adult SSc, the group adopted secondary outcome assessments for all patients with scleroderma as physician and parent/patient global assessments of disease activity, as well as a validated measure of physical function, such as the CHAQ[80].

The group briefly considered appropriate inclusion criteria for a randomized controlled trial of ASCT in pediatric patients with JDM or JPM. Consensus was reached that such patients would be appropriate candidates for a randomized trial if they have evidence of one of the following complications indicative of poor prognosis or severe, recalcitrant disease activity[81].

INCLUSION CRITERIA: JDM/JPM

1. ILD with DLCO ≤ 70% predicted with decline in DLCO of > 10% over a 3 month period. Failure to respond, or development of serious or unacceptable toxicity to optimal doses of prednisone and/or MTX, as well as cyclophosphamide or cyclosporine, prior to entering a randomized ASCT protocol[82].

2. Severe gastrointestinal or cutaneous ulcerations. Failure to respond, or development of serious or unacceptable toxicity to optimal doses of prednisone, MTX, and cyclophosphamide, administered for ≥ 3 months each, prior to entering a randomized ASCT protocol[81].

3. Severe myositis resulting in Steinbrocker functional Class 3 or 4, with disease duration ≥ 6 months and persistent active disease based upon evidence from serum muscle enzymes, magnetic resonance imaging, electromyography, or muscle biopsy. Patients with severe myositis should have received several agents for 4 months' duration for each agent or have experienced serious or unacceptable toxicity to these agents, prior to entering a ASCT protocol. This included prior receipt of optimal prednisone therapy in combination with at least 2 of the following: MTX, intravenous gammaglobulin, cyclosporine, cyclophosphamide, and tacrolimus[81].

For pediatric patients with JDM or JPM, a similar potential design for a randomized controlled trial of ASCT was discussed: to randomize patients to receive ASCT or to receive best standard therapy. The participants felt it was appropriate for those randomized to best standard therapy to continue this for ≥ 3 additional months and then if a patient met the above inclusion criteria, to declare him a nonresponder and offer open label ASCT. For patients with severe myositis, randomization could be to a different immunomodulatory agent, rather than continuing the same agent for 3 additional months, and an appropriate duration was felt to be 4 months prior to declaring the patient a treatment failure. For JDM/JPM patients with ILD, criteria for early escape from best standard therapy were agreed to be similar to SSc.

In summary, randomized controlled trials of ASCT in

pediatric patients with SSc or JDM/JPM were thought to be optimally performed in patients with poor prognostic factors who also have recalcitrant disease activity despite adequate courses of standard of care therapy currently available for such complications. A potential trial design for such patients is to randomize patients to receive ASCT versus continued background therapy at a time point 3–4 months after currently available optimal therapy has been initiated. A patient who continued background therapy and continued to deteriorate 3–4 months after randomization could be declared a nonresponder and then offered open label ASCT. In patients receiving background therapy, early escape could be possible sooner if disease activity progressed during background therapy.

Systemic Lupus Erythematosus: Ronald M. Laxer, Moderator

The work group developed draft consensus guidelines regarding appropriate inclusion criteria for patients with SLE undergoing autologous stem cell transplantation and discussed "best treatment" to use as a control arm. The group stressed that longterm studies are needed to assess the effect of such treatment and that it would be critical to ensure that patients have reversible disease before undergoing ASCT.

INCLUSION CRITERIA: SLE

1. At least 4 out of 11 ACR classification criteria for diagnosis of SLE
2. Disease for at least 6 months' duration
3. Evidence of unresponsiveness to or unacceptable toxicity from "standard aggressive" therapy (see below). There must be evidence of active disease (versus progressive chronic change) for at least the previous 6 months despite standard aggressive treatment. Evidence of active disease can include at least one of the following:
   a. Active glomerulonephritis, Class IV, biopsy proven (we did not agree on the required time frame for biopsy to define active/irreversibility)
   b. Active central nervous system SLE (cerebritis, seizures, organic brain syndrome, psychosis not related to prednisone)
   c. Active hematologic cytopenia, i.e., thrombocytopenia, or hemolytic anemia not supportable by transfusion therapy and failing IV immune globulin, anti-D, danazol
   d. Thrombotic thrombocytopenic purpura that is plasmapheresis dependent
   e. Active pulmonary disease, defined by high resolution computerized tomographic scanning, bronchoalveolar lavage, or pulmonary function testing, including pulmonary hemorrhage, pulmonary hypertension, ILD
   f. Transverse myelitis
   g. Antiphospholipid antibody syndrome with organ infarction

While standard aggressive therapy is debatable for many of the clinical scenarios, we agreed that patients must fail high dose daily corticosteroids (2 mg/kg/day in 3 divided doses for 6–8 weeks followed by consolidation and a slow taper) with 6 month IV monthly cyclophosphamide (500–1000 mg/m^2) to enter ASCT protocols. The debates about "standard aggressive therapy" centered upon the role of azathioprine, mycophenolate mofetil (MMF), cyclosporine, and additional cyclophosphamide. The recent data on MMF suggest that it may be effective for lupus nephritis[83], but its place in the treatment of SLE is not yet defined. Some members felt that failure of cyclophosphamide might suggest changing to MMF; others felt MMF should be used before cyclophosphamide and that failing cyclophosphamide, whenever it was used, was to be considered "treatment failure." This is an evolving field; criteria will change as we learn more about MMF and other new treatments for SLE. We did not feel that plasmapheresis had to be attempted.

Evidence for unacceptable toxicity includes:

1. Steroid induced diabetes or pancreatitis
2. Severe osteoporosis related to corticosteroid use
3. Avascular necrosis
4. Treatment related leukopenia and/or thrombocytopenia
5. Hemorrhagic cystitis
6. Recurrent serious infections due to treatment

One potential design of a randomized controlled trial in SLE would be to randomize patients either to ASCT or to continue best standard therapy. The participants felt that patients randomized to best standard therapy should potentially continue to receive this for up to 6 months, and then if they met the above agreed-to indications, they would be declared a treatment failure and be eligible for open label ASCT. Patients not randomized to the ASCT group who continue to deteriorate over the 6 months could be declared nonresponders and offered open label ASCT. In patients randomized to best standard therapy, early escape could be possible sooner if disease activity progressed during therapy.

Although the randomization arm for treatment failure was not agreed upon, the following options were discussed:

1. Continuing 6 months of IV cyclophosphamide
2. Changing to oral cyclophosphamide 1.5–2.5 mg/kg/day
3. MMF
4. Increasing prednisone, assuming that the reason to change therapy was *not* steroid toxicity.

While treatment outcomes were not discussed, they should include:

1. Organ-specific outcomes (e.g., improvement in renal function, improvement in mental status, improvement in hemoglobin and platelet count)

2. Disease activity measures (e.g., SLEDAI, SLAM, BILAG, all of which may be used in SLE in children and adolescents)

3. Disease damage measures

4. Quality of life and health related quality of life measures.

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