Well over 1000 HLA-identical marrow transplantations have been performed since the early 1980s in patients with severe aplastic anemia [1], a disease that can result from immunological suppression of the bone marrow. Therefore, many transplantation centers already have considerable experience in treating immune-mediated disorders with high-dose therapy and allogeneic marrow transplantation. In the last 5 to 6 years, new investigational autologous transplantation protocols have been developed for treatment of nonhematological autoimmune diseases. A number of technological advances gave impetus to this development, including methods of peripheral blood stem cell collection and T-cell purging. Equally important, preclinical studies of certain animal models of autoimmunity suggested that, in addition to allogeneic transplantation, high-dose
immunosuppressive therapy with autologous hematopoietic stem cell transplantation (HSCT) support might also be an effective treatment [2].

Influenced by these preclinical studies and anecdotal reports of patients who underwent marrow transplantation for hematological malignancy and were cured of autoimmune disease, transplantation physicians and rheumatologists organized an autoimmune disease meeting in October 1995 at Fred Hutchinson Cancer Research Center in Seattle [3]. As interest and experience grew, A. Gratwohl and A. Tyndall set up biennial conferences in Basel beginning in October 1996 under the sponsorship of the European Group for Blood and Marrow Transplantation (EBMT) and the European League against Rheumatism (EULAR). Reports from these Basel meetings have been published [4-6]. On alternate years, R. Burt and R. Emmons hosted meetings in Worcester, Massachusetts.

More than 70 centers from 20 countries have contributed cases to the EBMT registry. In North America, transplantations have been performed at 20 centers, although approximately two thirds have been carried out with common protocols developed by either the Northwestern or the Seattle groups. Early in 2001, to avoid duplication in the registries of the cases from North America, data were transferred from EBMT to the International Bone Marrow Transplant Registry (IBMTR).

Figure 1 shows a breakdown of transplantations by year in the EBMT registry (data courtesy of Dr. Alan Tyndall for EBMT). The largest number of transplantations has been for multiple sclerosis (MS), although the number decreased in 2000, possibly in anticipation of planned controlled trials in MS. The number of transplantations for rheumatoid arthritis (RA) also decreased in 2000, whereas the number for systemic sclerosis (SSc), systemic lupus erythematosus (SLE), and juvenile idiopathic arthritis (JIA) remained approximately the same. Other diagnoses for which more than 5 patients were reported to the EBMT registry include idiopathic thrombocytopenic purpura (9 patients), polymyositis (7 patients), and autoimmune hemolytic anemia (6 patients). The North American experience has been mostly with MS and SSc; very few patients with RA or JIA have been treated.

The data in Figure 1 are from autologous HSCT. There have been rare syngeneic transplantations performed for autoimmune diseases [7], but with the strong genetic influence on autoimmunity, the advantage of syngeneic over autologous transplantations may be modest. Nonmyeloablative allogeneic transplantation with mixed chimerism [8] has theoretical appeal because of the reduced risk of regimen-related morbidity and mortality compared to allogeneic transplantations and the potential for a graft-versus–autoimmune immune cell effect. Concern about risks from graft-versus-host disease has delayed activation of allogeneic protocols, at least until there is a better idea of the effectiveness of autologous transplantations.

This review, written in preparation for the October 2001 conference on Stem Cell Therapy in Autoimmune Diseases, held in Los Angeles, summarizes clinical reports and abstracts of open-label, pilot studies published up to mid-2001.

**RATIONALE OF AUTOLOGOUS HSCT IN AUTOIMMUNE DISEASE**

**Introduction**

Figure 2 presents a simplified time line for the development of an autoimmune disease and progression to target-tissue injury. The framed section shows 2 possible mechanisms of high-dose immunosuppression and hematopoietic stem cell transplantation: an anti-inflammatory effect decreasing target-tissue injury and a more durable immunosuppressive effect restoring self-tolerance.
injury. Genetic makeup and environmental exposure play critical roles [9,10]. An individual’s susceptibility to clinical autoimmunity depends on genetic makeup or, more specifically, the balance of immune-enhancing and immune-protective genes. These genes affect cytokines, HLA expression, costimulatory molecules, apoptosis pathways, antigen receptor and signaling, regulatory cell level, immune complex clearance, and other functions [9]. Whether and when a genetically predisposed individual develops an autoimmune disease and possibly the nature of the autoimmune disease—organ specific or generalized—may depend on contact with environmental agents, infectious and noninfectious. Evidence for these still-uncharacterized environmental agents include greater risk in temperate climates, point epidemics, and lack of 100% concordance in monozygotic twins [11]. Moreover, retrospective studies in patients who had migrated from high- to low-prevalence areas suggest that there is a latent period, ie, a delay of many years between contact with a hypothetical environmental agent and clinical onset of the disease. The concepts of an environmental trigger and a latent period are important in the rationale of autologous HSCT as treatment for autoimmune diseases. If genetic predisposition alone is sufficient for development of clinical autoimmunity, then the predisposition for the disease resides solely in the hematopoietic stem cells, and the best result that can be hoped from autologous HSCT would be a temporary anti-inflammatory effect from the high-dose immunosuppression. In contrast, if particular environmental exposures at critical times are important, then high-dose immunosuppressive therapy with autologous HSCT has the potential to “time shift” the clinical autoimmune disease line to an earlier period, analogous to the latent period, restoring self-tolerance. This rationale assumes that responses on reexposure to even the same self-antigens will be sufficiently different that clinical autoimmunity will not recur.

Animal Models of Autoimmunity and HSCT

As shown in Table 1, there are 2 types of autoimmune disease models: (1) autoimmune-prone animals that spontaneously develop either generalized autoimmunity, such as the classic model of SLE in NZB×NZW F1 mice, or organ-specific autoimmunity, such as the model of diabetes mellitus NOD mice and (2) antigen-induced models of autoimmune diseases, such as adjuvant arthritis and experimental allergic encephalomyelitis (EAE). In cases of spontaneous autoimmune diseases, syngeneic bone marrow transplantation early in life has not prevented clinical or pathological autoimmunity; however, allogeneic transplantations from an autoimmune resistant strain have prevented and in some instances, when given early after disease onset, ameliorated the autoimmune manifestations [12]. These results have lead Good and Ikehara to conclude that autoimmunity derives from hematopoietic stem cells [13]. In contrast, studies of antigen-induced autoimmune diseases by van Bekkum and his colleagues have shown a therapeutic response from syngeneic or pseudoautologous transplantations [2]. For example, recovery from EAE-induced paresis was more rapid in animals treated with total body irradiation (TBI) and syngeneic transplantation compared to that in untreated animals, although allogeneic transplantations were superior in preventing spontaneous relapses and induced relapse from reimmunization of myelin protein [14,23]. Timing of the transplantation is important. For example, with EAE in SJL mice, treatment was effective only if given early in the course of the disease, before significant target-tissue injury [15].

### Implications of Immunological Reconstitution

The strongest rationale justifying autologous HSCT concerns the effect of high-dose chemotherapy on T-cell recovery. Non–T-cell immune recovery, with maturation through the marrow rather than the thymus, is more rapid than T-cell recovery, although full functional recovery of all immunoglobulin (Ig) isotypes may take up to 2 years [24]. In general, the number of CD3 cells normalizes 3 months after high-dose chemotherapy, but reduced numbers of CD4 cells and an inverted CD4/CD8 cell ratio persist for 12 months along with predominance of CD45RO+ cells, deficiency of naive CD45RA+ cells in thymus-deficient adult patients, and

### Table 1. Animal Models of Autoimmunity: Effect of Marrow Transplantation

<table>
<thead>
<tr>
<th>Pathology/Disease</th>
<th>Animal Model</th>
<th>Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous autoimmune disease [13]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Models of SLE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune complex disease</td>
<td>(NZB×NZW) F1 mice</td>
<td>Prevented and treated by allogeneic transplantation [16-20]</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>BXXSB mice</td>
<td></td>
</tr>
<tr>
<td>Coronary vascular disease</td>
<td>(NZW×BXXSB) F1 mice</td>
<td></td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>MRL/pr mice</td>
<td></td>
</tr>
<tr>
<td>Lymphoproliferative disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoantibodies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model of diabetes mellitus</td>
<td>NOD mice</td>
<td>Prevented by allogeneic transplantation [12,21]</td>
</tr>
<tr>
<td>Antigen-induced autoimmune disease [2]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant arthritis</td>
<td>Buffalo rat</td>
<td>Treated by syngeneic and allogeneic transplantation [22]</td>
</tr>
<tr>
<td>Model of RA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyarthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experimental allergic encephalomyelitis</td>
<td>Buffalo rat</td>
<td>Treated by syngeneic and allogeneic transplantation [14,23]</td>
</tr>
<tr>
<td>Model of MS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS inflammation</td>
<td>Buffalo rat</td>
<td></td>
</tr>
<tr>
<td>Demyelination</td>
<td>SjL mice</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lewis rat</td>
<td></td>
</tr>
</tbody>
</table>
restriction in the T-cell repertoire [25-28]. A greater degree of resulting immunosuppression would be anticipated in most HSCT protocols for autoimmune diseases because of both ex vivo depletion of T-cells in the graft by CD3+ cell selection and antithymocyte globulin (ATG) therapy at the time of stem cell reinfusion.

In most autoimmune diseases, the epitope of the initial target antigen is unknown. Autoreactive T-cells, eg, to myelin antigens, are found in normal individuals [29]. The immune dysregulation leading to clinical loss of tolerance in autoimmune diseases may involve an increase in the number of autoreactive cells through molecular mimicry of viral or other foreign antigens, an increase in epitope spreading as shown in Figure 2, or target-organ microenvironment changes allowing optimal cytokine and other conditions for T-cell activation [9,30-32]. Unfortunately only a few studies have monitored autoreactive T-cells after autologous HSCT in patients. In patients, marrow ablative therapy and transplantation clears encephalitogenic T-cells from the central nervous system (CNS) within 3 weeks [33]. In a limited number of MS patients followed after autologous HSCT, the anticipated general suppression of peripheral blood mononuclear cell proliferation to myelin antigens occurred after transplantation and persisted at least 20 months, but some new responses to different myelin protein epitopes also developed as early as 8 months after transplantation [34]. The clinical significance of changes in autoreactive cells after transplantation is unknown. There has been a proposal to carry out DNA marking of stem cells in the autologous graft [35], analogous to the approach used to determine the origin of relapsed hematological malignancy after transplantation [36]. There are a number of intrinsic difficulties with this approach, including limited transduction efficiency of stem cells and uncertainty in differentiating a physiologic from pathogenetic autoreactive cell. However, DNA marking in patients in whom autologous HSCT failed could theoretically make the distinction between the transfer of pathogenetic T-cells in the graft, an outcome that may be overcome by selectively modifying the graft, and the transfer of stem cells that gave rise to pathogenetic T-cells, an outcome that would argue strongly for an allogeneic transplantation approach.

**Autologous and Allogeneic Transplantations for Hematological Disease in Patients with Preexisting Autoimmunity**

Because autoimmune diseases all together afflict up to 5% of the population [9], it is likely that a considerable number of patients with preexisting clinical autoimmunity have undergone allogeneic or autologous transplantation for oncologic disease. The literature in this area, however, is mostly anecdotal and sparse, especially regarding autologous transplantation. In a review, Tyndall and Gratwohl (1999) have cautioned that the tendency to report positive results may account for the mostly favorable experiences published [37]. In a single-institution retrospective study, 11 of 909 patients were identified who had preexisting autoimmune diagnoses and had survived at least 3 years after allogeneic transplantation. Although no autoimmune activity posttransplantation was reported [38], at least 7 of these patients had diagnoses or disease stages in which progression would not be anticipated (eg, type 1 diabetes mellitus and treated Hashimoto's thyroiditis). Recently, 2 additional patients with autoimmune thyroiditis were reported whose autoantibodies decreased and whose disease remitted after allogeneic marrow transplantation for aplastic anemia [39]; and similar to an earlier case report [40], 3 additional MS patients from one center had stable neurological disability after transplantation (2 autologous and 1 allogeneic) for hematological malignancy [7]. There are, however, some failures reported. An abstract from 1998 describes an MS patient who developed new optic neuropathy 2 months after allogeneic transplantation for chronic myelogenous leukemia and whose magnetic resonance image (MRI) of the brain showed several new lesions at 1 year [41]. There are also reports of RA relapsing after allogeneic transplantation [42] and RA and SLE relapsing after autologous transplantation for oncologic disease [43]. Failure to correct coincidental autoimmunity in autologous transplantation patients could be attributed to a suboptimal preparatory regimen or lack of T-cell depletion of the graft, factors that should be optimized when transplantations are performed specifically for autoimmune diseases. On the other hand, reports of autoimmune disease progression after allogeneic transplantation, particularly when posttransplantation hematopoiesis is 100% donor-derived, as in a patient with relapsed RA [42], would suggest that autoimmune-prone genetic factors in the donor were sufficiently shared with the sibling recipient or that the target-tissue microenvironment in the recipient was so autoimmune-prone that allogeneic cells became reactive.

**Development of Pathogenetic Immune Events after HSCT**

A related consideration is induction of autoimmunity by transplantation, the process Marmont has characterized as “adoptive autoimmunity” [44]. Allogeneic stimulation has been shown to reactivate EAE [45], and scleroderma-like signs are common in chronic graft-versus-host disease [46]. Moreover, some organ-specific autoimmune diseases for which autologous HSCT have been performed—polymyositis and myasthenia gravis, for example—can themselves occur (albeit uncommonly) as complications of chronic graft-versus-host disease [47,48]. Myelitis and optic neuritis with MRI abnormalities of demyelination, identical to abnormalities seen in MS, have been reported in rare instances in transplantation patients [49]; and there have been reports of immune-mediated neuropathies, some with demyelinating features suggestive of chronic Guillain Barré syndrome, after transplantation [50]. Autologous graft-versus-host disease can be induced by cyclosporin administered early after transplantation [51], and many of the immune-mediated complications of transplantation noted in this section have been seen in autologous as well as allogeneic transplantation [50,52]. Therefore, it would not be totally unexpected if in some instances a second autoimmune disease occurs after HSCT or if paradoxical worsening of the original autoimmune disease occurs.

**Protocols for Autologous HSCT for Autoimmune Diseases**

**Eligibility**

For phase I-II studies on feasibility, investigators used selection criteria that were based on severe disease, progres-
sive despite available therapy, but without infection or organ damage that would preclude transplantation. Eligibility criteria varied according to protocol and transplantation center. In the United States, approval from the Food and Drug Administration (FDA) was required because most investigators chose to use CD34+ cell selection devices. This role of the FDA assured some uniformity in eligibility of US protocols.

For MS, the expanded disability status scale (EDSS), a standard disability scale validated for investigational studies, was used to determine eligibility [53]. Most protocols specified EDSS of 5.0 or 5.5 to 8.0 points. At this range in the EDSS, disability grading is based mainly on gait: EDSS 5.5, patients can walk 100 meters but not 200 meters without aid or rest; EDSS 6.0, patients need a cane or brace to walk 100 meters; EDSS 6.5, patients need bilateral assistance of canes or crutches to walk 20 meters; EDSS 7.0, patients are unable to walk more than 5 meters even with aids; EDSS 7.5, patients are unable to take more than a few steps and may need help with transfers; and EDSS 8.0, patients are wheelchair- or bed-bound. Documented advancement of 1 to 2 points on the EDSS in the 1 to 2 years prior to entry was required in most protocols, but MRI gadolinium enhancement as an indication of active disease has not generally been required. In SSc, proposed inclusion criteria have generally included disease duration limited to less than 3 years and diffuse cutaneous involvement with a modified Rodnan skin score (mRSS) [54] of greater than 16, together with at least 1 of the following visceral involvements: pulmonary with active alveolitis and a forced vital capacity (FVC) of less than 80%, renal involvement with proteinuria and elevated serum creatinine, and heart involvement with arrhythmias, cardiomegaly, or pericardial effusion [55]. Based on the report from the European registry [56], some investigators included patients with CREST syndrome (calcinosis cutis, Raynaud phenomenon, esophageal motility disorder, sclerodactyly, and telangiectasia) who had advanced pulmonary hypertension. To date, no single study has been reported that details specific SyS eligibility criteria. In SLE, inclusion criteria include catastrophic antiphospholipid syndrome or failed cyclophosphamide for glomerulonephritis (World Health Organization class III-IV), CNS lupus, vasculitis involving the heart or lung, or life-threatening cytopenias [57]. For RA, inclusion criteria differed slightly among published pilot studies, but all required a confirmed diagnosis of RA based on the American College of Rheumatology criteria and failure to respond to conventional therapy [58-61]. Current protocols also require failure of anti–tumor necrosis factor (TNF)-receptor treatment. For JIA, eligible subjects must have poor-prognosis disease—such as persistence of thrombocytosis, fever, and steroid dependency 6 months into the disease—and have failed all conventional therapy, including anti–TNF-receptor treatment [62].

**Peripheral Blood Stem Cell Mobilization**

Details have been published on stem cell mobilization for 187 patients who underwent transplantation at 24 centers worldwide [63]. These cases include 54 in North America and approximately 50% of the cases in the EBMT registry. Bone marrow rather than peripheral blood stem cells have been used in at least 60% of patients with JIA, whereas transplants for patients with other diagnoses have been almost exclusively peripheral blood stem cells. In Europe, granulocyte colony-stimulating factor (G-CSF) without cyclophosphamide has been uncommonly used for stem cell mobilization, except for treatment of RA; whereas some North American protocols use G-CSF alone for MS and SSc [34,64,65]. Most protocols have used cyclophosphamide at 4 g/m2 followed by daily G-CSF at 5 µg/kg per day until completion of mobilization. Generally autografts contained at least 3.0 × 106 CD34+ cells/kg, although required cell dose varied from protocol to protocol. Some centers have reported occasional patients for whom mobilization failed [66]. CD34+ cell selection with the Isolex or CellPro device has been used in the North American centers, but CD34+ cell selection was done in only about 50% of the RA patients and 60% of MS patients in the EBMT registry.

On the basis of animal studies and with reference to patients who have relapsed after autologous HSCT with unmanipulated grafts [43], van Bekkum has made a strong argument in favor of T-cell purging [2,67]. An unmanipulated peripheral blood stem cell graft generally contains 1010 T-cells, 2 logs more than the estimated number of T-cells that survive 900-cGy radiation conditioning. A total of 107/kg T-cells (obtained by CD34+ cell selection) has been suggested as the maximum number of reinfused T-cells in manipulated grafts [2].

**Preparatory Regimens**

There has been great heterogeneity in preparatory regimens used. Figure 3 gives a breakdown of the 4 most commonly used preparatory regimens for specific diseases reported to the EBMT registry through 2000. BEAM was used in approximately half the patients who underwent transplantation for MS, but in only a few patients with other autoimmune diagnoses. BEAM consists of the following: BCNU (carmustine) 300 mg/m2 on day –6, cytosine arabinoside 200 mg/m2 and etoposide 200 mg/m2 from days –5 to –2, and melphalan 140 mg/m2 on day –1 [68]. Cyclophosphamide alone was used most often in SSc, RA, and SLE. In the EBMT registry, cyclophosphamide in combination with TBI was the most frequently used preparatory regimen in

---

**Figure 3.** Preparatory regimens in transplantation cases reported to the EBMT registry for MS, SSc, RA, SLE, and JIA. BEAM indicates BCNU, etoposide, cytosine arabinoside, melphalan; Bu, busulfan; Cy, cyclophosphamide; TBI, total body irradiation. Data courtesy of Alan Tyndall, MD, for EBMT.
JIA. In North America, cyclophosphamide (120 mg/kg) combined with TBI has been used by both the Northwestern (TBI, 1200 cGy) and Seattle (TBI, 800 cGy) groups for MS, and the Seattle group has used the same regimen for SSc [64].

Some investigators have assumed that early relapses of autoimmunity after transplantation are from residual autoreactive T-cells remaining after conditioning therapy or autoreactive T-cells at too high a level in the graft. ATG treatment at the time of stem cell reinfusion is intended to deplete both reinfused T-cells and T-cells that survive conditioning. ATG has been used in approximately 80% of MS patients in the EBMT registry and is included in the Seattle but not the Northwestern MS protocols. ATG has been used in less than 10% of transplantations in RA cases, in less than 50% of transplantations in SSc cases, and in two thirds of transplantations in SLE cases in the EBMT registry. In 50% of transplantations in SSc cases, and in two thirds of transplantations in MS cases, ATG has been used [64].

There have been concerns about the risk of late-onset malignancies from the preparatory regimens, especially TBI regimens. Another argument against TBI, at least for MS, includes a concern that CNS irradiation may exacerbate the neurologic disability. In the EAE model, transient worsening of paresis has been seen after TBI of Buffalo rats [14]. The mechanism is unknown, but it could be related to TNF-α—a proinflammatory cytokine known to be increased in active MS [71] and shown to be induced in astrocytes and microglial cells after even low-dose irradiation [72]. There have been reports of a worsening of clinical inflammatory demyelinating polyneuropathy after transplantations in patients with hematological malignancies who have been conditioned with TBI [73]. Some protocols have added prednisone during TBI conditioning [74] or cyclosporin during BEAM conditioning in an attempt to modulate cytokine release [75]. There have also been concerns regarding growth retardation with TBI in children with JIA [76] and the worsening of skin and subcutaneous fibrosis in SSc. However, neither MS flares nor worsening of fibrosis has been seen in more than 50 transplantations performed in North America, demonstrating the safety of TBI with lung shielding in these patients. As with any agent, dose and schedule of administration influence risks. In general, TBI-containing protocols for autoimmune disease have used doses lower (eg, 800 cGy) than those employed in treating malignant diseases (usually ≥1200 cGy) and doses that were not associated with an increased risk of late malignancies [77].

An analysis of EBMT registry cases showed a statistically significant higher transplantation-related mortality with the higher intensity conditioning regimens (busulfan combined with cyclophosphamide or other drugs and cyclophosphamide plus TBI) [78]. However, as can be seen in Figure 3, the various preparatory regimens were not evenly distributed across the 5 diseases shown, and differences noted in transplantation-related mortality may reflect the disease treated rather than the preparatory regimen used. Overall, the choice of preparative regimens for these initial studies has been based largely on experience, known side effects, and the projected effects of the regimens together with the philosophies of the investigators. It is unlikely that distinguishing between regimens will be a major short-term objective of studies in the near future, because more fundamental questions of efficacy must first be addressed.

### Assessment of Clinical Results

Table 2 lists endpoints that have been used or proposed for transplantation studies in autoimmune diseases. For MS, potential efficacy has been evaluated by stabilization or a decrease in disability as indicated in the EDSS scores, the same scale used to determine eligibility. Attack frequency has not been a useful indicator because most protocols exclude patients with the remitting and relapsing form of the disease. The Scripps Neurological Rating Scale (NRS) has been used as a second indicator by some centers. NRS is designed as a way of quantitating the standard neurological examination [79]. Recent protocols have also included the composite scale [80], although composite scale results for transplantation patients have not yet been published. This scale includes an ambulatory index, pegboard test for upper extremity functioning, and the paced auditory serial addition test for information processing. MRI has been used mainly to record gadolinium enhancement as an indicator of disease activity and T2 abnormalities, registering new lesions and total lesion load. With one exception [75], MRIs have generally been obtained infrequently; and newer, unconventional techniques to increase sensitivity and objectivity, such as assessment of axonal loss by hypointense lesions on T1 scans (black holes), measurement of atrophy, and computer assisted technique to measure lesion load [81,82], have not generally been applied to transplantation patients.

SSc patients enrolled in autologous transplantation studies have generally been treated for advanced pulmonary disease, and high skin scores have generally been present. The lack of previously demonstrated effective therapies for
SSc may have limited the development of elaborate scoring systems for quantifying responses. To date the effects of treatment have been reported as changes in organ function in conjunction with effects on skin scores and health assessment questionnaires. Studies of organ function have generally focused on FVC, diffusion capacity, left ventricular ejection fraction, and pulmonary artery pressure. The mRSS is a validated tool for measuring skin sclerosis [54]. It relies on physical examination, assessing 17 anatomic sites on a 0-to-3 scale with a composite score between 0 and 51, with 0 being normal. Interobserver variability is greater than intraobserver variability, and changes of 25% over baseline or greater in mRSS are considered significant. Although the mRSS has important prognostic value for survival in untreated patients, whether changes in mRSS arising from therapy change prognosis is uncertain. The modified health assessment questionnaire disability index (mHAQ-DI) is a tool for measuring quality of life [83]. Despite its subjective nature, the mHAQ-DI has been shown to have prognostic value and utility in measuring disease activity. The mHAQ and mRSS are important secondary endpoints being used in the currently planned prospective randomized studies of autologous transplantation for SSc.

In patients with SLE, organ-specific measurements of function together with autoantibody titers have been used as objective measures of disease response. Because of the emphasis on renal disease in transplantations to date, measurements of serum creatinine together with anti–double stranded (ds)DNA have been parameters reported as showing major response in SLE [84]. Although the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [85] has been used for determining entry into a study in some instances, its utility has not been established for assessing disease responses. For this purpose, concern exists that the SLEDAI overemphasizes some organ systems. More balanced and potentially more useful is the BILAG (British Isles Lupus Assessment Group) score, which appears to provide accurate measures of current disease activity in SLE [86].

For RA, response has been documented with the American College of Rheumatology (ACR) core set used to evaluate changes in RA [88]. These outcome parameters include the number of joints with swelling, child health assessment questionnaire (CHAQ), physician’s global assessment, limitation of range of motion, erythrocyte sedimentation rate, and evaluation of morning stiffness. Complete remission was defined as a 70% or greater improvement of at least 3 of 6 core-set criteria with, at most 1 parameter worsening [88].

**RESULTS OF AUTOLOGOUS TRANSPLANTATION FOR AUTOIMMUNE DISEASE**

**Introduction**

Autoimmune diseases are different, one from the other, and it is reasonable to suppose that the best HSCT approach for one disease may not be best for another. Patients with SLE or SSc who are eligible for HSCT face a significant risk of mortality from their disease with or without transplantation, but this is not the case for MS, RA, and JIA patients. Also, multiple organ involvement in SLE and SSc means a greater transplantation risk than that for the other autoimmune diseases. Another obvious difference is the objectivity of inflammatory signs. Inflammatory signs and the effect of treatment on these signs are directly observable in the number of swollen painful joints in RA and JIA and skin scores in SSc. But evaluation of an anti-inflammatory effect is usually indirect in SLE, although measurable in organ-function tests and even harder to track in MS. Autoimmune diseases also differ in what is accepted as the best medical therapy, the therapy to which HSCT ultimately will have to be compared in clinical trials. Since the initiation of HSCT protocols for autol-
mune diseases, there have been new therapies approved for RA (anti-TNF drugs) and MS (mitoxantrone). There continues to be no standard therapy recognized for SSc.

Multiple Sclerosis

Mortality in 85 MS patients reported to the EBMT registry was 8%: 2 patients died from progressive disease and 6 from transplantation complications [6]. Two deaths have been reported with busulfan and cyclophosphamide conditioning, 1 from influenza pneumonia 21 days after transplantation and 1 from pneumococcal sepsis 19 months after transplantation [34]. With BEAM conditioning, 1 of 24 patients in the most active center died from cerebral aspergillosis on day 65 [68]; 2 other deaths reported to the registry from other centers occurred in the first month from cardiac and infectious complications, but no deaths occurred in 23 other patients reported from the Czech Republic, Spain, and Italy [66,75,90]. In North American reports, no deaths in 11 patients occurred in 1 center, although 1 patient had a traumatic CNS hemorrhage after transplantation and was inevaluable in terms of MS neurological progression [74], and 1 death in 26 patients treated at the other major center occurred from Epstein-Barr virus (EBV) lymphoproliferative disease (attributed to rabbit ATG) [65].

Four of 23 patients who underwent mobilization of stem cells with G-CSF alone in different centers experienced neurological flares attributed to G-CSF [63,91]. One of these patients, a woman with a high cervical cord demyelinating lesion died after mobilization. These observations lead to protocol modifications adding either cyclophosphamide (the Northwestern protocol) or prednisone (the Seattle protocol) to the G-CSF therapy. Both of these modifications appear to be effective in preventing neurological flares. More than 85 patients in the EBMT data base [6] have undergone mobilization with cyclophosphamide (generally 4 g/m² or approximately 100 mg/kg) and G-CSF or granulocyte-macrophage (GM)-CSF, and only a single MS flare has been noted [66]. Reports from the 1980s of high-dose cyclophosphamide to treat MS (up to 100 mg/kg total dose over 10–14 days) showed a modest benefit at best [92,93], and there have been no MS patients enrolled on the currently active Johns Hopkins autoimmune disease protocol of high-dose cyclophosphamide (200 mg/kg per day total dose over 4 days) without H SCT [70]. However, there is a report of a patient on an HSCT protocol from the Czech Republic who improved 1.5 EDSS points following mobilization with cyclophosphamide (4 g/m²) and G-CSF and who, therefore, did not proceed with the transplantation [66]. Furthermore, in the Italian transplantation protocol that required MRI gadolinium enhancement for enrollment, there was a decrease in the number of enhancing lesions 30 days after treatment with cyclophosphamide and G-CSF for mobilization (but before high-dose immunosuppression) in all patients, but 7 of 10 still had some gadolinium-enhancing lesions [75]. Figure 4 shows an example of the clearing of MRI gadolinium enhancement after cyclophosphamide and etoposide were administered with G-CSF for stem cell mobilization [34].

It is difficult to evaluate efficacy in the presently available published clinical reports, abstracts, and registry reports. Follow-up in most studies is still short, and MS is a disease that is notoriously variable and hard to predict. There is an unambiguous effect on CNS inflammation as seen in MRIs. In the Italian study discussed above in which MRI gadolinium enhancement was required for enrollment, only 2 of 10 patients had gadolinium enhancement on monthly posttransplantation MRIs: 1 patient just in the first month and the other patient in each of the first 3 months posttransplantation. It was also noted that the second patient had new lesions on T2-weighted scans in the first 3 months, but no new T2 lesions were seen in the other 9 patients. The range of follow-up scans in this study was 4 to 30 months [73]. Other trials with less frequent scans reported a similar rare frequency of gadolinium enhancement: 2 in 24, 1 in 10, and 1 in 20 [65,68,94]. The durability of this anti-inflammatory response is unknown. There has been limited neuropathological study of patients who died after transplantation [34,95,96], but it is of interest that no active demyelination and no T-cells in MS plaques have been seen in these cases, including a patient who was neurologically stable when she died of pneumococcal sepsis 19 months after transplantation. In contrast, there is generally still evidence of CNS in situ Ig formation as shown by oligoclonal bands in the cerebrospinal fluid and an elevated CNS IgG synthesis rate after transplantation [34,75,90].

MS symptoms characteristically are worse with temperature elevation [11], and transient worsening associated with fever has been frequently reported in the early posttransplantation course [68]. The engraftment syndrome—fever, skin rash, pulmonary infiltrates, and capillary leak [97,98]—has been suspected in an unusually high number of MS patients in the first 3 weeks after transplantation. One of 12 patients with suspected engraftment syndrome had an EDSS progression of 1.0 point, which became permanent during the follow-up period [65]. Another patient whose condition worsened when G-CSF was reintroduced on day 25 improved promptly on methylprednisolone [34]. Because of this experience, the Seattle protocol was amended to include a prednisone course after transplantation.

Fassas has updated his clinical trial of 24 patients who were followed for a median of 40 months (range, 21–51 months) [68]. Patients with primary progressive MS (ie, whose clinical disease was progressive from onset) had limited evidence of benefit in that 4 of 8 progressed on the EDSS after transplantation. The remaining 16 patients had secondary progressive MS (ie, whose disease becomes progressive only after a remitting and relapsing course). These patients fared considerably better; only 1 has had an EDSS progression from pretransplantation level, and the remaining have remained stable or improved. It should be noted that of 18 patients considered to have improved, half worsened on follow-up, although not beyond the pretransplantation EDSS score [68]. Primary progressive patients on the Seattle protocol were accrued [65] but not on other single protocol studies [34,66,74,75,90], so data are insufficient to determine the value of HSCT in primary progressive disease. A report from the Northwestern group in 2000, when their first 10 patients had been followed 1 to 3 years, noted no EDSS progression and 4 patients with improved NRS scores [74]. However, an abstract a year later noted progression by more than 0.5 EDSS points in 6 of the Northwestern patients [99]. An abstract from 2000 summarizing the
experience on the Seattle protocol reported 2 of 13 patients followed >3 months had progressed at least 0.5 points on the EDSS [100], and a year later 5 of 22 patients followed >6 months had progressed at least 1.0 EDSS point [65]. With busulfan and cyclophosphamide conditioning, 1 of 4 patients in 1 study progressed at 13 months [34] and 1 of 5 in another study progressed during BCNU conditioning [90]. European single-protocol studies with BEAM conditioning showed stability or slight improvement in 10 Italian patients in 1 study (median follow-up, 15 months; range, 4-30 months) [75] and a 1.0-EDSS point worsening at 10 months in 1 of 9 Czech patients (median follow-up, 8.5 months; range, 1-16 months) [66]. There is additional information in EBMT registry reports [6], and Fassas et al. have recently summarized the MS cases reported to the registry [101]. However, for the purpose of this review, MS outcome results from the EBMT registry will not be presented because of the likelihood of dual reporting of cases.

There are intrinsic difficulties with the EDSS that are particularly problematic in uncontrolled trials. The EDSS is an ordinal rather than an arithmetical scale [53]. The mean time intervals for advancement of 1 point depend on where the patient is on the scale. Although natural history data are limited, particularly at the higher EDSS range, the mean time to advance from EDSS 6.0 to 7.0 has been reported to be almost 3.5 years [102] or just greater than 4 years [7], and it may take even longer to advance from EDSS 7.0 to 8.0. In contrast the mean times to advance from 4.0 to 5.0 and 5.0 to 6.0 are considerably less: 1.22 and 1.25 years, respectively [103]. Furthermore, natural history studies indicate that selection of patients at an EDSS of 6.0 or 6.5 points who have had recent rapidly progressive disease, as has been done in most HSCT feasibility studies, does not assure a continual high rate of progression [102]. This is why long-term follow-up is particularly critical in evaluating HSCT. EDSS stabilization at 1 to 2 years of follow-up may reflect the natural history of the disease rather than a therapeutic effect of the transplantation.

In October 2000, the FDA approved mitoxantrone for secondary progressive MS. Approval was on the basis of a

---

**Figure 4.** Magnetic resonance image of an MS patient receiving the immunosuppressive drugs cyclophosphamide and etoposide with G-CSF for peripheral blood stem cell mobilization [34]. Upper panels (premobilization) show gadolinium enhancement and lower panels (after mobilization) show lack of gadolinium enhancement. Both sets demonstrate “black holes” as evidence of axonal loss.
European phase III trial of 194 patients accrued between 1993 and 1997 [104]. Details of this study at 2 and 3 years of follow-up are on the FDA Web site (www.FDA.gov). Entrance requirement was an EDSS score of 3 to 6 points, lower than that for most patients who have undergone HSCT, but within the range of what is being proposed for future controlled trials of HSCT. Patients with primary progressive disease were excluded, whereas patients with secondary progressive disease and remitting relapsing disease with accumulative neurological disability were included. Treatment was given every 3 months for 2 years. At the end of 2 years, there was 1.0 point or greater sustained EDSS progression in 8% of patients receiving the higher mitoxantrone dose (12 mg/m2) compared to progression in 22% of the placebo group. This difference was sustained at 3 years of follow-up: 17% progression in the mitoxantrone group and 44% progression in the control group (reviewed in [105]). Moreover, mitoxantrone has been found to be safe in MS; no mortality and no serious cardiotoxicity was encountered even at higher doses, up to 140 mg/m2 as a total lifetime dose to avoid cardiotoxicity [106]. Whether HSCT can do as well and whether there will be differences in durability of the response are questions that will require a large randomized trial.

Systemic Sclerosis

Among the rheumatologic disorders, more patients with SSc have undergone HSCT than have patients with other diseases, despite SSc being less common than RA or SLE. This fact reflects the adverse prognosis of SSc, the lack of effective alternative therapies, and the ability to define candidates at risk of substantially shortened survival. To date, the mortality risk after autologous HSCT for SSc has been higher than that among the other autoimmune diseases. This higher risk appears to be related to the poor underlying prognosis of SSc combined with underlying organ damage that contributes to a greater susceptibility to the toxic effects of high-dose conditioning therapy. Initial case reports documented responses of SSc to high-dose cyclophosphamide and HSCT [4,107], and although there have been concerns about the toxicity, the later reports continue to show promising results regarding disease outcomes. In a report of 41 patients from the EBMT registry, the mortality rate in SSc patients after transplantation was 27% (11 of 41 patients with a median follow-up of 12 months) [56]. Four of these deaths were attributed to disease progression, and 7 were related to treatment (interstitial pneumonia 2, pulmonary hemorrhage 2, cardiac death 2, CNS bleed 1), including 3 patients who died as a result of mobilization chemotherapy. Autopsy findings of an additional cardiac death in an SSc patient 2 days after transplantation suggested cardiac involvement from SSc and not cyclophosphamide-induced cardiomyopathy as the cause of death [108]. The number of cardiac deaths has lead to stricter cardiac exclusion criteria for SSc [6]. Two patients died from regimen-related pneumonia superimposed on SSc pulmonary disease after receiving TBI-containing regimens, but further instances of this toxicity were avoided with lung shielding [64]. One patient died from EBV-associated lymphoproliferative disease that occurred in a recipient of rabbit ATG [64], similar to a death that occurred in a patient with MS [100]. Both patients received rabbit ATG because of hypersensitivity to horse ATG. Following this experience, the Seattle group discontinued the use of rabbit ATG in patients with positive skin test results to horse serum.

In the registry report of 41 patients, median follow-up was 12 months (range, 3-55 months) [56]. Although measurements were not standardized, a beneficial effect on skin disease was reported in 69% of evaluable patients based on their having an improvement of ≥25% in the baseline skin score, whereas 7% had progression of their skin disease. Lung function and pulmonary hypertension did not change significantly after transplantation. Survival was 73% at 1 year (95% confidence interval, 58%-88%). Disease progression was noted in 19% of patients and occurred a median of 67 days (range, 49-255 days) after treatment. The improvements in skin scores and the trend toward stabilization of lung disease were considered promising findings that warranted further studies of this modality [56].

In the North American collaborative study, 16 patients who received cyclophosphamide, TBI, ATG conditioning, and CD34-selected G-CSF–mobilized autografts were reported [64]. Three patients died of treatment complications and 1 of disease progression, indicating a survival rate of 75%. For 6 patients with >1 year of follow-up at 1-year posttransplantation, the mean mRSS improved from 38.2 ± 10 pretransplantation to 21.2 ± 6 (P = .002), and the mean mHAQ-DI improved from 1.8 ± 0.9 to 0.24 ± 0.3 (P = .005); whereas FVC and carbon monoxide diffusing capacity (DLCO) remained stable (mean FVC [%]: 73.5 ± 6 to 74.2 ± 6, P = .85; mean DLCO [%]: 56.5 ± 11.5 to 50.1 ± 13.5, P = .38) In 3 patients with >2 years of follow-up, mRSS improved from 28, 18, and 16 at 1 year to 22, 15, and 10 at 2 years, respectively, after high-dose immunosuppressive therapy, indicating that skin responses may continue to occur for extended times after HSCT.

The results of initial studies have encouraged the design of phase III studies. The European (Autologous Stem Cell Transplantation International Scleroderma [ASTIS]) study is a randomized study comparing conventional-dose cyclophosphamide with high-dose cyclophosphamide (50 mg/kg × 4). Cyclophosphamide–mobilized (2 g/m2 × 2 + G-CSF) CD34-selected autografts are given after high-dose cyclophosphamide. A similar study planned for North America will compare cyclophosphamide, TBI, ATG conditioning, and G-CSF–mobilized CD34-selected autografts with conventional-dose cyclophosphamide (750 mg/m2 × 12). By design, the entry criteria and control arms for the European and North American studies are virtually identical. This design will allow some comparison of the respective regimens for efficacy and toxicity.

Systemic Lupus Erythematosus

In the EBMT registry, mortality was 13% for 23 patients undergoing transplantation for SLE [6]. None of 7 patients who underwent transplantation performed by the Northwestern group died, but 2 patients who underwent mobilization for transplantation developed serious infections that ultimately proved fatal in 1 patient and prevented both patients from undergoing the transplantation [84]. Many of these patients, very ill to begin with, had stormy transplantation courses with fluid overload and pulmonary edema a particular problem, requiring intubation and dialysis in
almost half of the Northwestern patients. However, once through the acute transplantation course, there was only mild expected morbidity with varicella zoster or herpes simplex virus infection in 3 of the 7 patients and Pneumocystis carinii pneumonia in 1 of the patients.

Of the registry patients, 19 of 23 improved, although 5 of these patients subsequently relapsed. Three patients who underwent transplantation in Europe whose cases were reported individually [109-111] had been in clinical remission or with improving laboratory abnormalities for up to 3 years at the time of this report. These 3 cases may be included in the EBMT registry and are already counted in the 19 improved SLE registry patients, referred to above. All of the Northwestern patients have been followed for more than 1 year, and 2 patients have been followed for more than 3 years. All 7 patients have had improvement in SLEDAI scores, from 12 to 37 (median, 28) prior to mobilization to 0 to 5 after transplantation. There were also decreased antinuclear and anti-dsDNA antibody titers, decreased proteinuria, increased FVC, normalization of representative T-helper type 2 and T-helper type 1 cytokines, and a normalization of T-cell repertoire after transplantation [84].

Most SLE patients in the EBMT registry received cyclophosphamide and ATG in the preparatory regimen (Figure 3). The Northwestern patients received cyclophosphamide (200 mg/kg total over 4 days, days –6 to –3) without TBI or myeloablative chemotherapy, ATG on days –5 to –3 (but not at the time of stem cell reinfusion), and CD34+ cell selection. Stem cell reinfusion on day 0 was intended to minimize the duration of neutropenia [57]. White cell engraftment occurred on day +9 of transplantation [84], 16 days after administration of the initial cyclophosphamide dose. Brodsky and coworkers have used a similar regimen in SLE but without HSCT, thus avoiding the risk of reinfusion of autoreactive T-cells and the neutropenia associated with cyclophosphamide/G-CSF mobilization. This regimen used cyclophosphamide 200 mg/kg given over 4 days, without ATG [70]. The median time to neutrophil recovery (>500 neutrophils/µL) was 17 days after the initial cyclophosphamide dose. Brodsky et al. have shown that the neutrophil count generally does not fall below 500/µL until 7 to 8 days after administration of the initial cyclophosphamide dose; so, severe neutropenia on their protocol was only 9 to 12 days [69], a duration comparable to treatment on most HSCT protocols. The first SLE patients treated using this protocol had marked improvement: complete remission in 4 and partial remission in 3 [112]. Comparison trials—cyclophosphamide with or without HSCT—will be necessary to evaluate whether HSCT affects safety or efficacy.

Rheumatoid Arthritis

Mortality associated with HSCT for RA has been low compared to that for SSc and SLE. Seventy patients with RA have been reported to the EBMT registry, and there are adequate follow-up data for 43 patients [6]. Of these 43, 1 patient (2%) died of HSCT-related complications. This low mortality rate may have been because of the less intensive immunosuppressive regimen in RA compared to that in MS or SSc as well as the relative sparing of vital internal organs in RA compared to that in SSc or SLE. Fourteen patients were described as stable (1 patient) or better (13 patients). Although most patients responded to treatment, relapses occurred in at least 50%. The criteria for assessing improvement were not defined by the report.

More details are provided in individual published reports of pilot studies than in current summaries of registry data. Mobilization was safe and efficacious with G-CSF alone [113]. Transient flares of RA were seen in 3 patients. Flares may be prevented with the preadministration of corticosteroids, but this combination has been investigated in only a small number of patients [114]. Other studies have included cyclophosphamide with G-CSF for mobilization to prevent flares and to enhance the collection of stem cells [60,115]. If corticosteroids are effective in preventing flares, their use would be preferable to avoid the risk of chemotherapy-induced neutropenia at mobilization.

A total of 25 RA patients treated with autologous HSCT have been described in 4 reports [58-60,115]. The high-dose immunosuppressive therapy before SCT consisted of cyclophosphamide (200 mg/kg) in 20 patients, cyclophosphamide (100 mg/kg) in 4 patients, and the combination of busulfan/cyclophosphamide in 1 patient. ATG was administered to 4 patients. High-dose chemotherapy was well tolerated with no mortality in these published reports. The median period of neutropenia was 10 and 11 days in the 2 studies in which it was reported. Significant responses were observed in 10 of 20 of the evaluable patients receiving cyclophosphamide (200 mg/kg), and these responses were sustained from 6 to 20 months after HSCT. Many of the 10 patients with significant responses after HSCT remained on lower doses of disease-modifying antirheumatoid drugs (DMARDs) or were considered to be more responsive to DMARDs when symptoms required them to be restarted. In a follow-up of the Dutch study with 11 patients followed for a minimum of 1 year, there was a significant reduction in the mean disease activity score [115]. In one study, 4 patients who received cyclophosphamide (100 mg/kg) had only transient responses lasting 3 to 4 months [59]. A complete remission at 10 months was described in a single patient who was treated with high-dose busulfan and cyclophosphamide in combination [58].

HSCT with high-dose cyclophosphamide was not associated with significant early toxicities. Patients will need to be followed longer to assess the significance of late complications. The studies to date would suggest that most patients have early responses, and a subset of patients may continue to have a clinical benefit longer than 1 year after HSCT. When the disease relapses, patients appear to be more responsive to DMARDs. Future studies of RA patients refractory to conventional therapy appears to be warranted and will need to focus on the prevention of relapse or other post-SCT strategies for the control of the inflammatory process.

Juvenile Idiopathic Arthritis

JIA is a relatively new diagnostic term replacing juvenile RA and juvenile chronic arthiritis [116], N. Wulfraat and colleagues published a report of the first small series of HSCT in JIA and updated the series to 12 patients in 2000 [76,117]. A summary of EBMT registry data prior to the 2000 Basel meeting indicated 32 patients total were treated with almost half the transplantations performed in the Netherlands [6]; there has been only 1 patient treated in the United States, and
environmental agents, which originally set the stage for on autoimmunity as a T-cell rather than a B-cell disease. HSCT protocols in use were designed with a greater focus in disrupting T-cell than B-cell function, and the pathology and pathogenesis has suggested a heterogeneity of antibody and immune cell mediated [9]. Recent work in MS has identified tissue injury in these diseases as an acute illness and a decrease in white blood count, platelet count, and erythrocyte sedimentation rate. The syndrome typically involves persistent fever, hepatosplenomegaly, lymphadenopathy, and liver abnormalities with jaundice and abnormal coagulation test results. A bone marrow showing hemophagocytosis is diagnostic. The pathogenesis is thought to involve a dysregulation of macrophage-lymphocyte interaction with proliferation of activated macrophages and a release of proinflammatory cytokines. Treatment is with high-dose corticosteroids and cyclosporine. The anti-TNF agent, etanercept, has also been shown to be effective [119]. The high frequency of MAS after HSCT was unanticipated, and certainly the presenting abnormalities of MAS can easily be mistaken for other systemic complications following transplantation. All instances of MAS after HSCT were fatal, with death occurring as early as 18 days and as late as 5 months after HSCT [117,120]. JIA patients who died with MAS after HSCT had systemic infections: EBV reactivation in 1 patient and toxoplasmosis in the other 2 [62,120]. To decrease the risk of MAS, JIA protocols were amended to provide a slow steroid taper after HSCT. Also to improve safety, there has been more emphasis on control of the systemic rheumatological disease prior to HSCT, and there has been a reduction in the degree of T-cell depletion of the graft.

**CONCLUDING COMMENTS**

**Problems in Rationale of HSCT for Autoimmune Diseases**

As pointed out by Furst and other investigators [3,121], effective HSCT for autoimmunity rests on several assumptions, not the least of which concerns “overcoming” the autoimmune-prone genetics of the autologous stem cell. To be something more than transient anti-inflammatory therapy, the preparatory regimen must effectively ablate the immune effectors. Target-tissue injury in these diseases is thought not to be exclusively from T-cells but to be both antibody and immune cell mediated [9]. Recent work in MS has suggested a heterogeneity in the disease, with antibody playing the primary role in a subset of patients [122,123]. HSCT is more effective long term in disrupting T-cell than B-cell function, and the HSCT protocols in use were designed with a greater focus on autoimmunity as a T-cell rather than a B-cell disease.

Another assumption for effective therapy is that the environmental agents, which originally set the stage for autoimmunity, are absent or their effect is no longer reflected in the target-tissue microenvironment after transplantation. However, because the environmental agents involved have not been identified, any discussion on reexposure is highly speculative. Moreover, patients who have received HSCT for autoimmune diseases may be expected to have an array of exposed or altered autoantigens from target-tissue damage, not present earlier in individuals destined to develop clinical autoimmunity, and these autoantigens may replace environmental agents as disease triggers.

Finally, there is the assumption that target-tissue damage will abate once the pathogenic immune effectors are fully eliminated. However, this assumption has been called into question at least in MS, for which an axonal degenerative component is now recognized even in early disease [124], and this component probably becomes the major pathogenetic mechanism in patients who enter the progressive stage of the disease. The effect of immunosuppression on this degenerative component is uncertain.

**Problems in Morbidity and Mortality**

Overall transplantation-related mortality was reported as 9% in the EBMT registry and 11% in North American cases [6]. These rates are considerably higher than the 3.4% treatment-related mortality of autologous transplantations for hematological malignancies and solid tumors reported in community cancer centers [125]. Some of this higher mortality relates to a learning curve. Technologies used in treating cancer patients have been applied to a new group of patients with different underlying problems. In particular, a fundamental difference between SLE or SSc patients, in whom the mortality has been highest, and cancer patients is the underlying organ dysfunction affecting lungs, liver, and heart. These organ-specific abnormalities identify autoimmune patients who qualify for HSCT, but similar laboratory abnormalities in cancer patients may discourage enrollment of those patients in high-dose investigational protocols. Observations from HSCT pilot studies have prompted protocol and eligibility changes for future studies that should reduce treatment morbidity and mortality. This review has discussed some of these protocol modifications: shielding lungs during radiation therapy in SSc, avoiding high-dose rabbit ATG in patients with T-cell-depleted grafts, making multiple treatment modifications to decrease risk of MAS in JIA, using corticosteroids in MS patients at the time of G-CSF mobilization and as a prophylaxis against persistent fever in the engraftment syndrome, and other protocol modifications. Also of particular importance in patients receiving T-cell-depleted grafts is the appropriate timing and extent of reimmunization against infectious agents [126].

**Future Direction of Clinical Trials**

As emphasized in this review, multiple centers, with both small and large differences in approach, have contributed to the early experience of HSCT in autoimmune diseases. This participation has been advantageous in establishing experienced centers for the second and more rigorous stage of this work: namely, controlled trials of HSCT versus best medical care. The diversified approach with multiple small feasibility studies has also allowed the assessment of safety of many treatment variations, includ-
ing different preparatory regimens and different degrees of T-cell depletion. Although registry data can be informative, analysis is often confounded by missing data points, the heterogeneity of the patient population, and variability of treatments for the enrolled patients. Despite the fairly large number of patients treated in pilot trials, there is no assurance that the optimum HSCT method has been found for any particular autoimmune disease. Also, various comparative mechanistic studies of HSCT patients that could possibly be helpful have not been done. Nevertheless, the consensus of investigators in the field is that carefully planned randomized studies are required to advance the field. For some diseases, randomized phase II studies now are being discussed, eg, comparison of high-dose non-
myeloablative therapy with and without HSCT in SLE and possibly RA. In other instances, the time may be right for phase III studies: eg, comparing HSCT to pulse cyclophosphamide treatment in SSc and HSCT to mitox-
ane treatment in MS. There is also agreement on the importance of having assessors “blinded” to the patient’s treatment group and appropriate early stopping rules for these randomized studies.

REFERENCES

1. Storb R. Hematopoietic stem cell transplantation in nonmalig-
2. van Bekkum DW. Stem cell transplantation in experimental mod-
3. Sullivan KM, Furst DE. The evolving role of blood and marrow transplantation for the treatment of autoimmune diseases. J Rheuma-
13. Good R, Ikehara S. Preclinical investigations that subserve efforts to employ bone marrow transplantation for rheumatoid or autoimmune diseases. J Rheumatol. 1997;48(suppl):5-12.
14. van Gelder M, van Bekkum DW. Treatment of relapsing experi-
mental autoimmune encephalomyelitis in rats with allogeneic bone marrow transplantation from a resistant strain. Bone Marrow Transplant. 1995;16:343-351.
15. Burt RK, Padilla J, Begolka WS, Canto MC, Miller SD. Effect of disease stage on clinical outcome after syngeneic bone marrow transplantation for relapsing experimental autoimmune encephalomye-
16. Wang B, Yamamoto Y, El-Badri NS, Good R. Effective treat-
17. Mizutani H, Engelman RW, Kinjoh K, Kurata Y, Ikehara S, Good RA. Prevention and induction of occlusive coronary vascular disease in autoimmune W/B F1 mice by haploidentical bone marrow transplantation: possible role for anti-cardiolipin autoanti-
18. Kirzner RP, Engleman RW, Mizutani H, Specter S, Good RA. Prevention of coronary vascular disease by transplantation of T cell depleted bone marrow and hematopoietic stem cell prepara-
19. Kushida T, Inaba M, Takeuchi K, Sugiu RA, Ogawa R, Ikehara S. Treatment of intractable autoimmune diseases in MRL/1pr mice using a new strategy for allogeneic bone marrow transplan-
betes in nonobese diabetic mice by allogeneic bone marrow transplan-
23. van Gelder M, Kinwel-Bohre EP, van Bekkum DW. Treatment of experimental allergic encephalomyelitis in rats with total body irra-
diation and syngeneic BMT. Bone Marrow Transplant. 1993;11: 233-241.
24. Guillaume T, Rubinstein DB, Symann M. Immune reconstitution and immunotherapy after autologous hematopoietic stem cell trans-
26. Mackall CL, Bare CV, Granger LA, Sharrow SO, Titus JA, Gress RE. Thymic-independent T cell regeneration occurs via antigen-
driven expansion of peripheral T cells resulting in a repertoire that is limited in diversity and prone to skewing. J Immunol. 1996; 156:4609-4616.
apy (HDIT) and autologous stem cell transplantation (SCT) [abstract]. Blood. 2001;98:687a.


