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Intense immunosuppression and autologous hematopoietic stem-cell transplantation is a potential treatment option for severe autoimmune diseases.

Intense Immunosuppression and Stem-Cell Transplantation for Patients With Severe Rheumatic Autoimmune Disease: A Review

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Background: *Intense immunosuppression plus stem-cell transplantation (SCT) has emerged as a new treatment modality for patients with refractory, severe rheumatic autoimmune disease. Its rationale is based on eliminating autoaggressive lymphocytes by lympho- or myeloablative conditioning followed by stem-cell rescue. Preclinical studies in animal models of autoimmune disease and observations in patients with rheumatoid arthritis (RA) who were cured after allogeneic bone marrow transplantation for concomitant hematologic malignancy have provided support for the concept.*

Methods: *The authors reviewed the results of recent phase I/II studies and data from the EBMT/EULAR Registry on more than 400 patients with autoimmune diseases including RA, systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and juvenile idiopathic arthritis (JIA).*

Results: *Toxicity resulting from stem-cell grafting depended on underlying disease and the intensity of the conditioning regimen. Treatment-related mortality was low in RA (1.4%) but relatively high (>10%) in patients with JIA, SLE, and SSc, possibly related to visceral involvement in these patients. With the application of uniform and strict criteria, safety has improved. Long-term remissions up to 4 years have been observed in SSc and JIA, while relatively more relapses have occurred in patients with SLE and RA. Sensitivity to anti-rheumatic drugs was restored in RA and SLE patients, however, resulting in improved disease control.*

Conclusions: *Intense immunosuppression and SCT may be an effective therapy for selected patients with severe rheumatic autoimmune disease. Its merits need to be proven via multicenter phase III studies by comparing efficacy and safety with conventional therapy.*

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Introduction

Systemic rheumatic autoimmune diseases include rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), and systemic sclerosis (SSc). Although the etiology of each of these diseases remains unclear, significant progress has been made in identifying genetic and environmental components of the pathogenesis of these diseases that determine severity and outcome. Genetic components encompass functional polymorphisms of genes active in apoptosis, antigen recognition, adhesion, and cytokine production that may play a role in the immune dysregulation characteristic of these disorders.¹ Most of the immune abnormalities pertain to B and T lymphocytes and myeloid cells, all derived from hematopoietic stem cells, and stromal cells. In addition to genetic factors, environmental or stochastic factors must also play an important role, as illustrated by the observations that transfer of stem cells from a patient with RA and one with SLE did not result in disease in the recipient and that concordance rates of HLA-identical siblings in RA and SLE are relatively low (10% to 30%).^{2,4} Environmental factors include external triggers such as smoking and infection, as well as internal triggers such as changes in the levels of estrogens during and after pregnancy, which may explain the female preponderance of these disorders.¹

Major clinical hallmarks of these diseases are chronic inflammation of musculoskeletal structures (eg, joints, skin, and bone) and the endothelium, which underlies the protean manifestations of vasculopathy. The complexity of these diseases is mirrored by the striking heterogeneity of clinicopathologic features even within each disease category. While most patients have relapsing, remitting, or smoldering disease, others experience progressive disease that results in tissue destruction, severe disability, or even death. Although these diseases cannot be categorized as malignant, considering them as benign conditions underestimates their potential impact on morbidity, quality of life, and survival.⁵ Severity of the disease is determined not only by musculoskeletal symptoms, but also by systemic and extra-articular or visceral manifestations. Outcomes in SLE, RA, and JIA improved substantially after the introduction of effective conventional treatments, such as tumor necrosis factor (TNF) blocking medication for RA and JIA. However, disease control remains unsatisfactory in a significant number of patients, and these diseases are incurable in the majority of patients despite the new therapies. In patients with SSc, outcome has improved for the subset of patients developing renal crisis but not for those with diffuse SSc and lung involvement. For these patients, the 5-year mortality rate ranges from 30% to 70%.⁶

Because of the sensitivity of these diseases to immunosuppressive and cytostatic agents, the dismal outlook for a subset of patients, and the recognition that immune mechanisms play a notable role in the pathogenesis of the disease, intense immunosuppression with autologous stem-cell transplantation (SCT) has been developed as an approach to control these conditions. The conditioning regimen may delete the pathogenetically relevant autoreactive lymphocyte populations or “reset” the dysbalanced immune system.⁷ This may allow regeneration of a nonautoaggressive immune repertoire in the absence of the environmental triggers that originally perturbed the immune system of a genetically predisposed host. The subsequent transfusion of hematopoietic stem cells avoids prolonged cytopenias and associated infectious or bleeding complications and allows timely hematopoietic reconstitution.

Background

The concept of intensive immunosuppression is based on findings in animal models of autoimmune disease, as well as results obtained in patients who underwent SCT for hematologic or oncologic diseases while coincidentally also having an autoimmune disease. Hematopoietic SCT as a treatment option in autoimmune diseases was first evaluated in lupus models in rodents after studies showed that transplantation of bone marrow from the hereditary or spontaneous lupus-like mouse strain New Zealand Black induced antinuclear antibodies and glomerulonephritis in lethally irradiated DBA/2 mice.^{8,9} It was subsequently shown that infusion of bone marrow derived from nonsusceptible donors could prevent autoimmune disease after immunoblation of the host predisposed to develop autoimmune disease.^{10,11} Following these observations, animals with induced forms of autoimmune diseases were treated with allogeneic or syngeneic bone marrow transplantation (ie, bone marrow from a healthy donor from the same strain) and pseudoautologous bone marrow transplantation (ie, bone marrow from affected animals of the same strain).¹² These models differ from the spontaneous forms as immunization with specific antigens is required.

In the case of adjuvant arthritis, heat-killed *Mycobacterium tuberculosis* is used for induction of disease. Adjuvant arthritis is T-cell mediated since adoptive transfer of T cells from affected animals causes disease in healthy animals. Adjuvant arthritis in Buffalo rats is a chronic, progressive type of polyarthritis with proliferating synovitis and pannus formation reminiscent of histopathologic findings in synovium of RA patients. In adjuvant arthritis in rats, a myeloablative

regimen followed by allogeneic and also, unexpectedly, by autologous and syngeneic SCT not only prevented the disease but also induced remission.¹³ Spontaneous relapses after syngeneic bone marrow transplantation were rare in adjuvant arthritis but did occur more frequently in experimental allergic encephalomyelitis, a model for multiple sclerosis (30% after syngeneic vs 5% after allogeneic transplantation).¹⁴ Subsequent studies employing major histocompatibility complex (MHC)-matched allogeneic and pseudoautologous bone marrow transplantation strongly suggested that relapses in encephalomyelitis were due to residual host activated T lymphocytes and lymphocytes in the graft, respectively.^{15,16} This was supported by studies in adjuvant arthritis demonstrating superiority of more intense conditioning.¹⁷

In summary, valuable lessons have been learned from the animal studies that may be relevant in the application of SCT in rheumatic autoimmune disease: (1) myeloablative therapy, followed by bone marrow transplantation, has curative potential, (2) allogeneic SCT may be more effective than autologous SCT if a graft-vs-autoimmunity effect exists and if intrinsic stem-cell defects play a role in the disease pathogenesis, and (3) *in vivo* T-cell depletion may be a prerequisite for a sustained response.

The results from experimental animal studies were paralleled by clinical observations in patients with autoimmune diseases who were treated with bone marrow transplantation because of a concomitant severe hematologic disorder. These involved RA patients who received allogeneic bone marrow transplantation because of aplastic anemia due to gold and/or D-penicillamine therapy.¹⁸⁻²⁰ Of the 8 reported RA cases, 3 patients who underwent bone marrow transplantation in the early days of this therapy died due to transplant-related complications after achieving a remission immediately following transplantation. The other patients were free of symptoms (1 patient reportedly relapsed) with a follow-up ranging from 2 to 8 years. However, 1 patient who received an allogeneic bone marrow transplantation for aplastic anemia RA relapsed after 2 years despite full donor engraftment.²¹ Similar long-term remissions were observed in RA and SLE patients after autografting for a hematologic malignancy.^{22,23} In contrast, 2 RA patients treated with autologous unmanipulated SCT for non-Hodgkin's lymphoma fared worse, with relapse of RA occurring 5 weeks and 20 months after autologous SCT.²⁴ This was ascribed to the presence of potentially autoreactive lymphocytes in the grafts.

These experimental studies and clinical observations paved the way for collaborative efforts to further

explore the clinical potential of stem-cell grafting in human autoimmune disease. The lack of alternative treatment options for severe, uncontrolled autoimmune diseases prompted development of this treatment strategy. Until recently, mortality and morbidity of blood or marrow SCT were considered too high to justify the risk of such a procedure in patients with chronic autoimmune diseases where prevention of morbidity instead of mortality has long been the major goal. This pertains to allogeneic SCT in particular, with its attending transplant-related morbidity and mortality rates of 15% to 30% in hemato-oncologic diseases. Autologous SCT, however, carries a transplant-related mortality rate of less than 5% in malignancies such as myeloma, lymphoma, and breast cancer.²⁵⁻²⁷ Therefore, for safety reasons, priority was given to autologous SCT. An international collaborative committee was established in 1995 under the auspices of the European Group for Blood and Marrow Transplantation (EBMT) and the European League Against Rheumatism (EULAR), which later included active groups in North America, that developed guidelines on entry criteria and transplant protocols for severe autoimmune diseases.²⁸ Furthermore, a database was created to collect clinical data that would enable monitoring of feasibility, toxicity, and efficacy of the different treatment protocols. Since its inception, the database has collected data from more than 400 transplants. Analysis of these pooled data has yielded relevant information on trends with regard to mortality, type of protocols used, and diseases targeted. These data are thus complementary to the primary data from the various phase I/II studies. Most transplants involved multiple sclerosis,²⁹ followed by the rheumatologic conditions of RA, JIA, SSc, and SLE.

Rheumatoid Arthritis

The most common systemic autoimmune disease is RA, affecting 1% of the population. A minority of patients have severe disease and fail to be controlled by conventional treatments. In the short term, uncontrolled RA results in pain and stiffness, but long-term consequences are irreversible joint destruction, disability, reduced quality of life, and a shortened life expectancy. Following early case reports on patients with refractory RA who were successfully treated with cyclophosphamide 200 mg/kg and an unmanipulated stem-cell graft or with busulfan/cyclophosphamide and a T-cell-depleted autologous graft, several pilot studies were initiated to assess feasibility, toxicity, and efficacy in small groups of patients.³⁰⁻³⁵ In a multicenter study in the Netherlands on 14 patients, significant improvement in disease activity was recorded at more than half of the visits within the first year of follow-up in 8 of 12 patients who completed all treatment

steps.³⁶ The 4 nonresponders did not differ from responders with respect to disease or patient-related variables such as age, disease activity and duration, previous therapy, presence of rheumatoid factor, and HLA haplotype, although the numbers of patients may have been too low to detect such predictive factors. With longer follow-up, all patients relapsed, requiring reinstatement of disease-modifying anti-rheumatic drugs within 24 months after transplant.³⁷ Interestingly, serial immunohistochemical studies on synovial tissue biopsies in these patients demonstrated that the clinical effect of SCT correlates with T-cell debulking in synovial tissue. Relapses of disease activity in this and another study were preceded by the re-emergence of T cells in the synovium.^{38,39}

These results corroborate experimental animal studies showing the importance of in vivo T-cell depletion. They also may explain in part why a recently completed randomized trial of 31 patients comparing T-cell depleted vs unmanipulated SCT after high-dose chemotherapy (cyclophosphamide 200 mg/kg) without additional in vivo T-cell depleting agents (eg, antithymocyte globulin [ATG]) failed to demonstrate major differences with respect to number and duration remissions between the two groups.⁴⁰ One case report of a patient with refractory, active RA treated with cyclophosphamide (200 mg/kg), ATG (90 mg/kg), and CD34+ enriched SCT from his unaffected identical twin brother deserves mentioning: 4 years following transplantation, the patient remains free of disease symptoms without anti-rheumatic medication⁴¹ (Ian Wicks, MD, personal communication, 2001).

A recent retrospective analysis of registry data included 76 patients (including the aforementioned cohorts) from 15 centers and several single and multi-center transplant protocols.⁴² The eligibility criteria and treatment schedules varied among individual protocols. Of the 76 patients, 73 had received autologous HSCT and 3 were mobilized but had not undergone transplantation (1 due to good response, 1 due to coincident pulmonary embolism, and 1 due to transplant refusal). The median age of the transplanted patients was 42 years, 74% were women, and 86% were rheumatoid factor positive. They had been previously treated with an average of 5 (range 2–9) disease-modifying anti-rheumatic drugs. Anti-TNF blocking agents, which are now considered the most effective anti-rheumatic therapy, failed in 4 patients. Significant functional impairment was present at baseline, with a median Health Assessment Questionnaire (HAQ) score of 1.4 (range 1.1–2.0; normal range 0–3). Sixty-seven out of 68 patients were reported as having destructive arthritis. The conditioning regimen was cyclophosphamide alone in the majority of patients, mostly 200 mg/kg

(n = 62). Seven patients additionally received ATG, 2 received busulfan, and 1 underwent total body irradiation and ATG. One patient received fludarabine with ATG. Following treatment, 1 patient received bone marrow, but the rest received chemotherapy and/or granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral-blood stem cells. The graft was unmanipulated in 28 patients, and the remaining received some form of lymphocyte depletion, mostly through CD34 selection. Median follow-up was 16 months (range 3–55). Forty-nine patients (67%) fulfilled the American College of Rheumatology criteria for 50% improvement at some point following transplant. The level of disability, as measured by the HAQ, was significantly reduced ($P \leq .005$). In most patients, disease-modifying anti-rheumatic drugs were reinstated within 6 months for persistent or recurrent disease activity, resulting in improved disease control in half of the patients. The only factor that was significantly related to response was the presence of rheumatoid factor with significantly better responses in seronegative RA patients ($P = .02$). Disease duration, previous therapies, HLA-haplotype, or T-cell depletion of the graft did not correlate with response to treatment. Five months after transplant, 1 patient who had been treated with myeloablative conditioning (busulfan and cyclophosphamide) and a highly purified autograft died of infection and an incidental non-small lung cancer, corresponding to a treatment-related mortality of 1.4%.

Of note, most of the patients were treated before the introduction of TNF blocking treatments in rheumatologic practice, with only 4 of the 73 patients having received anti-TNF agents before treatment. These drugs have shown major therapeutic benefits in refractory RA with relatively low toxicity. The success of this therapy has led to the development of other so-called biological agents targeted at cytokines and cytokine-receptors (eg, interleukin-1 receptor antagonists). The effectiveness of these therapies reduces the number of patients with severe, resistant disease in whom immunoablation and autologous SCT could be considered.

Juvenile Idiopathic Arthritis

Patients with JIA, a heterogeneous disease, experience different outcomes, depending on the subtype. Systemic and polyarticular forms carry the burden of morbidity and mortality, which explains why these subsets in particular have been targeted with SCT.⁴³ At present, data are available on 15 patients from a single-regimen study in the Netherlands, as part of the 43 patients from the International Registry. In a preliminary report on the first 4 patients,⁴⁴ conditioning with cyclophosphamide (200 mg/kg), ATG (20 mg/kg) and

low-dose total body irradiation (4 Gy), followed by reinfusion of T-cell-depleted bone marrow SCT resulted in eight full remissions and two partial remissions. Unfortunately, following transplant, 2 patients died of infection-associated hemophagocytic syndrome known as macrophage activation syndrome. The same fatal complication was also noted in another study,⁴³ and a possible role of in vivo T-cell depletion has been suggested. This led to modifications of protocols, and no mortality has occurred since.

Systemic Sclerosis

This rare heterogeneous condition is characterized by abnormal collagen deposition in skin and internal organs and by vasculopathy. Two main clinical subsets of SSc — limited cutaneous and diffuse cutaneous forms — are distinguishable by the extent of skin involvement, the autoantibody profile, the pattern of organ involvement, and the specific cutaneous manifestations of limited disease.⁴⁵ Both subsets are associated with vascular abnormalities clinically manifest as Raynaud's phenomenon. Many aspects of the complex interactions among autoimmune responses, vasculopathy, and fibrosis remain unresolved. The perceived failure of immunosuppressive treatments in the reversal of established fibrosis suggests that once initiated, the fibrotic process becomes independent of the immune drive and may continue autonomously.

Progressive diffuse SSc is associated with significant morbidity due to skin thickening and excess mortality (estimated to be 40% to 50% in 5 years) due to pulmonary, cardiac, and renal involvement.⁶ In clinical trials performed to date, no therapy has been proven effective to prevent disease progression or reverse fibrosis. This can partly be attributed to (1) the heterogeneity of patients included, (2) the low incidence and prevalence of SSc, and (3) the lack of well-defined and validated criteria for disease activity, response, and remission. Skin thickening has been proposed as a surrogate measure of disease severity and has prognostic value, particularly in patients with diffuse cutaneous SSc.⁴⁶

In view of the poor prognosis of SSc, the presumed autoimmune origin, and the lack of effective therapies, this disease was considered suitable for initial investigation of the tolerability and efficacy of autologous SCT.⁴⁷ Also, more so than with other autoimmune diseases, it was possible in SSc to identify poor-prognosis patients with much shortened expected survival based on established prognostic criteria. Most groups followed a core protocol based on conditioning with high-dose cyclophosphamide as cyclophosphamide-based therapies have been shown to improve skin thickening, sta-

bilize pulmonary function, and increase survival in non-randomized studies.⁴⁸ The results of treatment in the first 41 patients from the EMBT/EULAR registry, with a median follow-up of 12 months (range 3–55), showed a significant positive impact on skin score and a trend towards stabilization of lung function.⁴⁹ Although assessments were not standardized, an improvement of 25% or more in skin score was documented in 69% of the patients. In this cohort, cumulative 1-year survival was 73%, with 17% of mortality attributed to transplant-related causes and 10% to progressive disease.

In the largest single protocol study conducted in a number of US institutions, 19 patients were treated with total body irradiation (8 Gy in 4 fractions), cyclophosphamide (60 mg/kg × 2), and equine ATG (15 mg/kg × 6).⁵⁰ Peripheral-blood stem cells were collected with G-CSF mobilization and were CD34 selected. Some minor disease reactivations were noted in 4 patients during the mobilizations. In the early phase of the trial, 2 died of pulmonary failure due to presumed regimen-induced pulmonary damage. With 11 subsequent patients, lung shielding was used to reduce the lung dosage to approximately 2 Gy, and no further severe pulmonary toxicity was seen. One patient died of Epstein-Barr virus-related lymphoma after receiving high doses of rabbit ATG (6 × 2.5 mg) as a substitute for horse ATG. One other patient died of disease progression.

Among the other patients, significant beneficial responses ($P < .05$) were observed as assessed by skin scores and HAQ scores. Among 12 patients with follow-up of more than 1 year, the median change in skin score was -13 (range -8 to -13; normal range 0–51). The HAQ score changed by a median of -1.675 (range 0 to -2.26). Pulmonary, renal, and cardiac functions were overall stable, although several patients had evidence of disease reactivation after treatment. These results suggest that intensive immunosuppression may reverse skin thickening, improve physical functions of debilitated patients, and arrest deterioration of organ functions.

The relatively high overall risks of these procedures have been partly attributed to patient selection and partly to compromised vital organ function in these patients. Risk factors for toxicity have not been fully determined due to the low numbers of patients treated and the confounding variables associated with treatment on many different protocols. High-dose cytotoxic therapy may be poorly tolerated by some patients, including those with pulmonary hypertension, advanced pulmonary interstitial lung disease, and active cardiac disease.

It is anticipated that the risks of the intervention will diminish with judicious patient selection, current

protocol modifications, and intensive monitoring during treatment. Since the analysis of the first cohort, the number of transplants reported to the European and American registries has increased to 72 patients at the time of this writing, and the transplant-related mortality has dropped to 12.3% at 1 year, or 7.7% with exclusion of patients who did not meet the consensus guidelines on patient selection. In the US collaborative group study, with accrual increased to 26 patients, the early treatment-related mortality has fallen from 25% in the initial cohort of 8 patients to 5.5% in the 18 subsequent patients who received total body irradiation with lung shielding. These recent data suggest that disease-specific problems using high-dose therapy have been identified and are now more effectively addressed. Furthermore, the beneficial effects on skin thickening and functional abilities suggest that this treatment will prove valuable if the treatment risks can be reduced to acceptable levels.

Systemic Lupus Erythematosus

With its wide array of serum autoantibodies, linkage to genes encoding complement activation and apoptosis, and responsiveness to immunosuppressive medication, SLE is the prototype multisystem autoimmune disease. The prognosis of lupus patients has improved with the introduction of corticosteroids and cyclophosphamide pulse-therapy for nephritis and central nervous system involvement. Nevertheless, some patients do not respond to this therapy and need renal replacement therapy in case of renal failure. Chronic immunosuppressive treatment and intrinsic immune abnormalities account for the high number of infectious complications observed in patients with severe lupus. At the time of this writing, 23 SLE patients treated with intensive immunosuppression and SCT have been reported so far, most as case reports or in small series.⁵¹⁻⁵⁴ The majority of patients received conditioning with cyclophosphamide (200 mg/kg) and ATG. Disease activity was significantly decreased in all patients after conditioning, but 8 patients needed immunosuppressive medication again after transplant. Six of 13 patients with renal involvement improved, and another 4 regained normal kidney function. One patient died after mobilization from disseminated mucormycosis. In the patient with the longest follow-up, reappearance of serum autoantibodies preceded renal relapse after a 3-year corticosteroid-free remission. High-dose cyclophosphamide (200 mg/kg) without stem-cell rescue has been successfully used in a small cohort of lupus patients.⁵⁵ This regimen was well tolerated and no serious adverse events were recorded, despite prolonged thrombocytopenia. A number of patients in this cohort had not previously been treated with standard pulse-therapy cyclophosphamide, howev-

er, and it remains to be established that similar responses can be attained in patients with refractory disease.

Of the 51 patients registered in the EBMT/EULAR database, disease manifestations at baseline involved kidneys (27 patients), central nervous system (21), skin (31), joints (23), hematologic abnormalities (24), vasculitis (9), serositis (6), lungs (9), peripheral nervous system (2), and other (10), reflecting its multisystem character. Investigators reported that 27 of the patients improved, 14 improved initially and then relapsed, and 7 died. Of the 7 deaths, 5 were considered transplant related (2 of septicemia, 1 of thrombotic thrombocytopenia, 1 of bleeding complication, and 1 of secondary leukemia), while 1 patient died of progressive disease (bronchiolitis obliterans) and another as a result of an accident. Thus, the treatment-related mortality in this cohort was 11% (95% confidence interval, 2%–20%).

Discussion

In less than a decade, intense immunosuppression and autologous hematopoietic SCT has evolved from a hypothetical and experimental treatment to a potential treatment option for severe autoimmune diseases including refractory rheumatic conditions such as RA, SSc, SLE, and JIA. Although it is too early to assess the full merits of this new treatment modality, several important lessons have been learned from case reports, phase I/II studies, and data registry analyses as a result of intensive international collaboration.

First, it has been convincingly demonstrated that the treatment modality is feasible: autologous peripheral-blood stem-cell grafts can be procured containing sufficient numbers of progenitor cells to ensure rapid engraftment of all lineages. Flares have been observed with G-CSF-based mobilization, and the combination of cyclophosphamide and G-CSF was more likely to ameliorate disease activity than G-CSF alone.⁵⁶ Hematopoietic and immune reconstitution in these heavily pretreated patients was a matter of concern, especially with the use of T-cell-depleted grafts and/or in vivo T-cell depletion. In keeping with previous observations in hemato-oncologic diseases, numerical recovery of all peripheral-blood subsets has been rapid, returning to baseline levels within 6 months except for naive CD4+ T lymphocytes. Whether the prolonged lymphopenia has clinical sequelae remains to be determined. Also, levels of immunoglobulins returned to baseline quickly, although detailed functional studies have not been published yet.

Second, treatment-related morbidity and mortality have been shown to be significant in patients with

SLE, SSc, and JIA, but low in those with RA.⁵⁷ Some toxicities seemed disease specific (eg, macrophage-activation syndrome in JIA, and cyclophosphamide-related cardiotoxicity and total body irradiation-related pulmonary damage in SSc). The shared opinion in the field is that the extent and nature of organ involvement in SLE, SSc, JIA (vs the lack of it in RA) are probably important determinants. Consequently, patient selection has emerged as a critical component in this respect, with patients with advanced disease having a higher risk of complications and benefiting less than those with early-stage disease. In general, patients with a therapy-refractory, progressive, active disease who are at risk of further functional disability and early mortality are considered eligible for treatment with autologous SCT. The goal is long-term improvement of disease activity and quality of life. However, when offering SCT to patients with systemic rheumatic autoimmune diseases, these benefits should be balanced against toxicities and treatment-related mortality. Advances in identifying high-risk patients may allow for SCT at an earlier stage of the disease, before the development of severe end organ damage.

New tools based on genomics and proteomics will undoubtedly aid in outcome prediction and in the identification of patients with an adverse prognosis. More important is the willingness of physicians and patients to accept risk-taking treatment, at least for RA patients for whom alternative experimental therapies are available; a treatment-related mortality rate of more than 5% was considered unacceptable by the majority of rheumatologists and RA patients in a recent survey in the Netherlands.⁵⁸ This was in accordance with a decision analysis using Markov modeling that showed a treatment-related mortality rate of more than 3.3% would probably not be compensated by superior efficacy of intensive immunosuppression vs continued conventional treatment.⁵⁹ These results do not necessarily apply to potentially more aggressive diseases such as SLE, SSc, or JIA patients. Long-term safety is another important issue. The use of total lymphoid irradiation to treat refractory RA in the 1980s has only recently been identified as a source of excess late mortality in these patients.⁶⁰

Third, the observation of long-term remissions in all diseases studied underscores the potential clinical benefit of SCT. Although expectation bias on the part of patients and physicians and the use of high-dose corticosteroids during conditioning may have contributed to some of the short-term effects reported, the long-lasting effects (2 to 3 years) in a number of patients suggest that fundamental alterations in the disease state were induced. It is too early to conclude which of the multiple components of any transplant

protocol is critical in achieving a sustained clinical response. Conversely, failures defined as relapse or persistence of disease activity also have been reported, notably in RA and SLE, and the reasons for these are unclear. Responses and failures have been reported with all regimens used. Sensitivity to conventional drugs was regained in a number of patients with relapsed or persistent disease. From a T-cell-centered perspective, it might be inferred from the present studies that not all pathogenic T lymphocytes were eradicated or that some had been reinfused with the graft. This would imply that remissions could be achieved only by further intensification (eg, by in vivo T-cell depletion). Clearly, this could add to the toxicity, but other pathogenetic explanations for failures also can be considered, such as persistent innate immune abnormalities, intrinsic stem-cell or stromal-cell defects, or reactivation of autoaggressive lymphocytes as a result of renewed exposure to autoantigens.

From the perspective of the patient and the treating physicians, responses were clinically meaningful in a majority of patients with resultant enhanced quality of life. It remains to be seen if any superior efficacy of a more rigorous approach will compensate for increased toxicity in terms of quality-adjusted life expectancy.

The principal conclusion is that safety and efficacy should now be investigated through phase III studies comparing intensive immunosuppression with conventional treatment and employing uniform eligibility criteria, treatment regimens, and study parameters. Adequate assessment of risk/benefit requires properly designed and conducted prospective randomized, controlled trials with a long duration of follow-up. The issue is whether intense immune suppression aimed at immunoablation is superior to continuous moderate immune suppression with respect to toxicity and efficacy in the long run. Two such studies are ongoing (the Autologous Stem Cell Transplantation International Scleroderma Trial [ASTIS]) or are planned for patients with RA (ASTIRA) under the auspices of EBMT/EULAR. The ASTIS trial⁶¹ compares intense immunosuppression and autologous SCT vs monthly pulse-therapy cyclophosphamide in patients with recent-onset diffuse SSc and major organ involvement (heart, kidney, lung) at risk of premature mortality. The ASTIRA study will compare intense immunosuppression and autologous SCT vs mobilization-dose cyclophosphamide in patients with refractory, destructive RA. Similar studies for SLE and JIA are being planned. The designs and transplant protocols for these studies differ, reflecting differences in drug sensitivity between diseases and perceived goals of the trials (eg, improving disease control in RA vs improving event-free survival in SSc).

Given the low number of eligible patients, multi-center international collaboration is essential to the success of these trials to accrue the required number of patients. Once safety and efficacy of the treatment modality have been established, future studies could focus on cost effectiveness and on the identification of the critical components of the treatment schedule. However, if intense immunosuppression proves too toxic or not sufficiently efficacious, alternative transplant strategies could be considered. More intensive (eg, myeloablative) conditioning regimens might be more efficacious, although this remains to be demonstrated in any of the autoimmune diseases described. Not unexpectedly, the more intensive conditioning protocols proved more toxic in a retrospective registry analysis.⁶² Allogeneic transplantation has not yet been evaluated in systemic rheumatic autoimmune diseases due to risks of transplant-related mortality and graft-vs-host disease. Allogeneic SCT may be more effective than autologous SCT if intrinsic stem-cell abnormalities exist in these diseases and if host hematopoiesis and abnormal immune-cell populations can be eradicated via a graft-vs-autoimmunity effect. Recent advances in allografting have improved safety, thereby allowing application in nonmalignant conditions. However, whether the potential benefit of allogeneic SCT justifies the risk of graft-vs-host disease and treatment-related mortality is yet to be determined. Furthermore, a well-documented case of relapse of RA despite full donor chimerism after allografting for concomitant malignancy cautions against unrealistic optimism.²¹

Other lessons may be learned regarding pathogenesis and particularly the role of the immune system. According to the current paradigms, reinstatement of self-tolerance should be the "immunologic" goal of immunoablation, in order to cure systemic rheumatic autoimmune diseases. Also, our understanding of the processes that underlie relapses or remissions of systemic rheumatic autoimmune diseases is fragmented. These issues need to be addressed in meticulous clinical studies, with a thorough understanding of the needs and expectations of the patients involved.

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