Estimates of the prevalence of autoimmune diseases (ADs) in Western countries range from 3% to 6-7% of the population. The list of ADs is increasing mainly because of better insight into the pathogenesis of several diseases long considered to be of unknown origin. Establishing the autoimmune basis of human disease may occasionally be arduous, but satisfactory criteria have been repeatedly proposed and are generally utilized. Although autoimmunity has been thought of as the persistent failure of an integrated fabric of components rather than the consequence of specific forbidden clones, in practice diseases may be confidently classified as autoimmune when they exhibit defined reactions against self-antigens as a major component of their pathogenesis. The intricacies of distinguishing between intrinsic and extrinsic etiologic and pathogenic mechanisms are compounded by the diversities inherent in each AD and even within the subsets of specific diseases. It is not known whether the antibody response in systemic ADs is antigen-driven, such that the immune system is responding to self-proteins that have become autoantigenic, or if ADs represent a primary dysfunction of the immune system. The two hypotheses are not mutually exclusive and the prevailing conception is that of a combination of genetic factors responding to environmental triggers, these last including both exogenous and endogenous factors.

The majority of ADs are controlled, more or less satisfactorily, by conventional therapeutic manipulation of the immune system, but there is a hard core of refractory/relapsing, treatment-resistant ADs for which the term malignant autoimmunity has appropriately been proposed. As recently remarked by Mackay & Rose, the holy grail of therapy is a targeted treatment that would specifically destroy the pathogenic clones responsible for ADs. That ideal remains unrealized.

Intense immunosuppression (immunoablation), followed by autologous or allogeneic hematopoietic stem cell (HSC) transplantation, is a relatively new therapeutic approach, which was proposed for the first time in the clinic for the treatment of severe, refractory systemic lupus erythematosus (SLE). Immunoablation has produced encouraging results in patients with ADs who have undergone allogeneic bone marrow transplantation because of coincidental hematologic malignancies. A great deal of prior research had already produced impressive results using transplant-based procedures in experimental animals (see later). Suggestions to carry these encouraging results into the clinic soon followed. Phase I/II and II clinical studies have followed through the efforts of the European Group for Blood and Marrow Transplantation (EBMT) and the European League Against Rheumatism (EULAR), and the National Collaborative Study of Stem Cell Transplantation for Autoimmune Diseases. A number of exhaustive reviews of the experimental and clinical aspects of these approaches have been published.

Results in animal models

The preclinical area is very extensive, and cannot be discussed in depth here. There is a general agreement that there are basically two types of experimental AD: in one type the disease is antigen-induced, whereas it develops spontaneously in the other. This may influence the therapeutic strategy. Following the first demonstration of transfer/cure of murine SLE in 1974, the most important results of these experimental studies concern 1) the identity of the cellular elements responsible for the transfer of autoimmunity, 2) a possible graft-vs-autoimmunity effect following allo-BMT and 3) the therapeutic potential of autologous SCT. The first point is still controversial. It has been proposed that ADs, or at least experimental ADs, are polyclonal stem cell diseases.

An important therapeutic effect of allo-BMT in leukemia and in other malignant diseases is the well-known graft-versus-leukemia (GVL) effect. A putative graft-versus-autoimmunity effect is supported by experiments showing that allogeneic chimerism achieved using a sublethal radiation conditioning regimen followed by allogeneic transplantation can prevent the onset of diabetes and even reverse preexisting insulitis in nonobese diabetic (NOD) mice, whereas the same radiation protocol without allogeneic HSC is insufficient. A similar effect has been shown using sublethal conditioning and an anti-CD154 monoclonal antibody. These experimental findings support low-conditioning preparative regimens for allogeneic transplants also in human ADs. A graft-versus-plasma cell, meaning normal isohemagglutinin-synthesizing cells, has been demonstrated recently.

An unexpected but provocative finding was that autologous (and pseudoautologous) HSC transplantation is also effective in curing murine adjuvant arthritis and experimental autoimmune encephalomyelitis, although allogeneic transplants proved superior in curing the latter disease.
Clinical results

Post-transplant autoimmunity. The term adoptive autoimmunity was proposed in 1992 to indicate the transfer of an autoimmune disorder from a HSC donor to a recipient. If direct transmission of either pathogenetic lymphocytes or HSC that generate autoreactive clones from the donor can be demonstrated, the pathogenesis is clear. However, in many other instances, ADs can be attributed to the immunologic chaos or imbalance characterizing the post-transplant setting.

Resolution of preexisting autoimmune disease following allogeneic bone marrow transplantation. In most such instances, patients with preexisting ADs have developed a malignant disease of the blood requiring transplantation. If acquired aplastic anemia were classified as a bona fide autoimmune disease, then of course it would represent the most common autoimmune disorder to be treated by allogeneic transplantation. However, this is a special condition that will be not discussed here.

Nine patients with rheumatoid arthritis (RA) received allo-BMT from HLA-identical sibling donors for severe aplastic anemia (SAA) occurring after gold salt therapy. They have been reviewed extensively elsewhere. All patients entered remission, although 3 died of transplant-related mortality (TRM). Of the remaining 5 patients, 3 are in complete remission from their arthritis [one has been in complete remission for 20 years]; one developed a positive rheumatoid factor, and one relapsed 2 years after transplant even though the patient's immune system was 98.5% of donor origin. Relapse was also observed in a patient with psoriasis and arthropathy following allogeneic transplantation.

The occurrence of relapse despite complete donor hemolymphopoietic reconstitution may be related to intrinsic susceptibility of the transplanted immune system (HLA-identical to the patient's) to powerful autoregulatory stimuli. A patient with severe RA went into complete remission following a syngeneic transplant from a nonconcordant identical twin.

Between 1982 and 1992, 6 patients with Crohn's disease and leukemia underwent allogeneic marrow transplantation in Seattle. One patient died of septicemia 97 days after transplant; the remaining 5 were observed for several years post-transplant (4.5, 5.8, 8.4, 9.9 and 15.3 years, respectively). Four of these 5 evaluable patients had no signs or symptoms of Crohn's disease post-transplant. Only one patient with mixed donor-host hematopoietic chimerism had a relapse of both Crohn's disease and chronic myeloid leukemia 1.5 years after transplantation.

Three patients with Evans syndrome (ES), a combination of autoimmune hemolytic anemia (AIHA) and immune thrombocytopenic purpura, have received allogeneic transplants. A 5-year-old boy affected from immune thrombocytopenic purpura, have received allo-BMT from an unrelated volunteer donor. This might be the first clinical demonstration of the superior curing potential of allograft SCT. A third patient has received an allo-SCT from his HLA-identical sister following reduced intensity conditioning in Genoa, and is currently in hematologic remission but persistence of autoantibodies. He is being treated with donor lymphocyte infusions (DLI).

Autologous transplants for the treatment of autoimmune disease

Autologous HSC transplants (ASCT), from marrow or now almost exclusively from peripheral blood, are much more commonly used to treat ADs than are allogeneic transplants for two reasons: the encouraging experimental results from Rotterdam and Jerusalem, and the greater safety of the autologous procedures. TRM at 2 years post-transplant for ADs was 8.6%, which is comparable to the procedure-related mortality following transplantation for non-Hodgkin's lymphoma (NHL).

Contributing factors to higher than expected TRM may have been a learning curve for utilizing ASCT in new diseases, hitherto unrecognized hazard associated with profound immunodeficiency, especially following intense T-cell depletion, and unique organ dysfunction, as heart and lung failure in systemic sclerosis. A brief recapitulation of published reports follows.

Multiple Sclerosis. Multiple sclerosis (MS) is characterized by demyelination, immunohistologic lesions around axons, and ultimately axon loss. Pathogenesis is widely held as autoimmune, with T-cell activity in the forefront. It has become the most common disease treated by ASCT, mostly because of extensive pioneering work by Fassas et al. Following an initial report, 24 patients with MS in progressive phase were conditioned with the BEAM regimen (carmustine, etoposide, cytosine arabinoside and melphalan). They then received autologous CD 34+ progenitors that had been previously mobilized by cyclophosphamide (CY) and granulocyte-colony stimulating factor (G-CSF). They were also conditioned with antithymocyte globulin in order to deplete lymphocytes in vivo. One patient died of aspergillosis in the post-transplant period; the other 23 sustained no severe transplant-related morbidity. Improvement in disability, as measured with the Kurtzke Extended Status Disability Scale (EDSS), was seen in 10 patients and stabilization of MS occurred in 10 patients (43%). Following mobilization there was a significant decrease of Gadolinium (Gd)-enhancing lesions on MRI imaging, and after ASCT out of 132 scans only 3 active lesions were found in 2 patients. In another clinical study, 6 MS patients were treated with a conditioning regimen of CY (20 mg/kg) and total body irradiation (TBI) (12.6 Gy fractionated over 4 days). Peripheral blood CD34+ cells were mobilized with G-CSF. All patients experienced subjective and objective neurologic improvement. There were no new Gd-enhancing
lesions detected after transplantation. Other 11 patients were mobilized with CY (4 g/mg) and G-CSF, and 8 of them were autografted following the usual BEAM protocol. There were significant improvements by the EDSS scale, and no fatalities. In addition to 2 autologous transplants, one patient with AML plus MS received an allogeneic transplant, with stabilization of MS at 48 months, and another had a syngeneic transplant, with stabilization of disease but no evidence of the oligolonal bands in the CSF which were present before transplantation.

In a cooperative ongoing study 10 cases of secondary progressive MS with EDSS initially between 5 and 6, a documented rapid progression over the last year unresponsive to conventional therapies and the presence of Gd-enhancing areas on brain MRI using a triple dose of GD60 underwent CD34+ mobilization and then ASCT following conditioning with BEAM. Ten cases have undergone ASCT with a median follow-up of 9 months (range 2-30 months). No major serious adverse events were observed during and after treatment. Mobilization was successful in all cases, with a median number of 9.06x10^6/kg of CD34+ collected. During the 3-months pre-treatment period 346 Gd-enhancing areas/month/patient in the same period was 10.5 (range 1-38). The number of Gd-positive areas decreased dramatically already after mobilization with CY and dropped into 0 during the 3 months pre-treatment period. The median Scripps scale increased to 70. In the first case MRI enhancing was still completely abrogated 30 months after transplantation. Although clinical amelioration/stabilization were observed, it was concluded that the final impact of this procedure on the natural history of the disease remains to be established in larger, possibly prospective randomized trials. Guidelines in a consensus report have been published.

Rheumatoid arthritis. Following a dramatic amelioration in a single case, 10 patients with rheumatoid arthritis (RA) have had autografts at St. Vincent's Hospital in Sydney, Australia, with no transplant-related mortality or serious toxicity. Two cohorts of 4 patients each, with severe, active RA, received autologous unmanipulated HSC following conditioning with 100 and 200 mg/kg CY, respectively. The subablative doses produced only transient responses, and superior results were obtained with the highest dose of CY. However in a prolonged study of 4 autologous transplant recipients with ADs (3 psoriasis, 1 RA) complicated by malignancies. ADs remitted in all of them but recurred at 8-24 months. It was suggested that a single autograft with non-T-cell-depleted HSC is unlikely to cure ADs. In 4 patients with severe RA mobilization with CY (4 g/mg) was sufficient to confer significant improvement. Other 4 patients were treated with CY 200 mg/mg, ATG 90 mg/kg, and in 1 patient TBI 46 y, and autotransplanted with T-cell depleted CD34+ cells, but there was a relapse even in the irradiated patient. As already mentioned a 39 years old patient is in CR following a syngeneic transplant, and his T-cell repertoire became almost identical with the donor's. Exhaustive reviews have been published.

Juvenile chronic arthritis. Although the overall prognosis for children with JCA is good, the disease is refractory and severely progressive in a small proportion of patients. Four such cases autotransplanted with marrow HSC have been reported, but others have followed. The grafts were purged with 2 cycles of TCD. The conditioning regimen include 4 days of ATG, CY 200 mg/kg and low grade (4 Gy) single dose fraction TBI. This intense conditioning regimen was well tolerated, and there was a substantial resolution of signs and symptoms of active disease, but there was also limited recurrence. One death was caused by post-transplant disseminated toxoplasmosis, but others have also occurred. A so-called macrophage-activation syndrome (MAS) has been described in these patients, but there is no reason to distinguish it from the well-known hemophagocytic lymphohistiocytosis.

Systemic lupus erythematosus. As originally suggested in 1993, SLE is rapidly becoming another major target for autologous transplants. Four cases of concomitant SLE and malignancy have been published. They include chronic myeloid leukemia and SLE, NHL and SLE, and Hodgkin's disease and SLE. In one case, the NHL did not relapse, but autoimmune thrombocytopenic purpura (ATIP) supervened in association with an anti-centromere antibody; the autoimmune disease thus appeared more refractory than the neoplasia.

A number of concomitant SLE patients have undergone ASCT. Most of them have been reported in abstract form, and will not be discussed here. The first two cases were published in 1997. As of this writing, there are 4 fully published cases of severe, relapsing/refractory SLE that have undergone intense immunosuppression followed by ASCT. The first case, with a 50-month follow-up, was transplanted with positively selected CD34+ marrow cells after conditioning with Thio-Tepa and CY, 50 mg/kg. This patient is still in clinical remission 4 years after transplant, but there is a slow gradual reappearance of antinuclear antibodies (ANA), with a shift from a speckled to a homogeneous pattern. Also antibodies to double stranded DNA antibodies have reappeared. In all the other cases PBSC were utilized following mobilization with CY-6-CSF; the CY dosage varied from 2 to 4 g/mg. In the Palermo case the patient had a refractory Evans syndrome secondary to SLE that resolved after transplant.

The Paris case was conditioned with the BEAM regimen and had a continuous clinical remission, with a gradual reappearance of ANA. Although the overall prognosis for children with JCA is good, the disease is refractory and severely progressive in a small proportion of patients. Four such cases autotransplanted with marrow HSC have been reported, but others have followed. The grafts were purged with 2 cycles of TCD. The conditioning regimen include 4 days of ATG, CY 200 mg/kg and low grade (4 Gy) single dose fraction TBI. This intense conditioning regimen was well tolerated, and there was a substantial resolution of signs and symptoms of active disease, but there was also limited recurrence. One death was caused by post-transplant disseminated toxoplasmosis, but others have also occurred. A so-called macrophage-activation syndrome (MAS) has been described in these patients, but there is no reason to distinguish it from the well-known hemophagocytic lymphohistiocytosis.

Systemic lupus erythematosus. As originally suggested in 1993, SLE is rapidly becoming another major target for autologous transplants. Four cases of concomitant SLE and malignancy have been published. They include chronic myeloid leukemia and SLE, NHL and SLE, and Hodgkin's disease and SLE. In one case, the NHL did not relapse, but autoimmune thrombocytopenic purpura (ATIP) supervened in association with an anti-centromere antibody; the autoimmune disease thus appeared more refractory than the neoplasia.

A number of concomitant SLE patients have undergone ASCT. Most of them have been reported in abstract form, and will not be discussed here. The first two cases were published in 1997. As of this writing, there are 4 fully published cases of severe, relapsing/refractory SLE that have undergone intense immunosuppression followed by ASCT. The first case, with a 50-month follow-up, was transplanted with positively selected CD34+ marrow cells after conditioning with Thio-Tepa and CY, 50 mg/kg. This patient is still in clinical remission 4 years after transplant, but there is a slow gradual reappearance of antinuclear antibodies (ANA), with a shift from a speckled to a homogeneous pattern. Also antibodies to double stranded DNA antibodies have reappeared. In all the other cases PBSC were utilized following mobilization with CY-6-CSF; the CY dosage varied from 2 to 4 g/mg. In the Palermo case the patient had a refractory Evans syndrome secondary to SLE that resolved after transplant.
patients after transplant. ANA became negative, and spontaneous T-cell activation marker CD69 declined or normalised after transplantation.

A retrospective, multicenter EBM/UEULAR study has assembled 22 cases, which are in the course of being submitted for publication.

Systemic sclerosis. Systemic sclerosis (SSc) of the diffuse type is a devastating disease in which pulmonary interstitial fibrosis is in the most frequent cause of death.77 Two transplants have been performed in Basel using CY 200 mg/kg and CD34+ cell rescue, with moderate benefit.82,83 Five patients in Seattle received treatment with CY 120 mg/kg, TBI 8 Gy and ATG 90 mg/kg followed by CD34+ cell-selected autografts. The first 3 patients, followed for 13, 7 and 4 months, respectively, showed no evidence of disease progression. Their skin scores, mobility, skin ulcers and arthalgias improved with a trend toward improvement in pulmonary function, although in one patient renal function deteriorated. One patient developed grade III noninfectious pulmonary toxicity.84 An extensive clinical report of a multicenter experience is being published,83 and a prospective randomized trial (ASTIS) is running.

To date, the most successful case of autologous transplantation for SSc is that of a 13-year-old girl with severe, progressive lung involvement who underwent peripheral HSC transplantation after mobilization with CY and G-CSF, CD34+ selection, conditioning with CY (200 mg/kg), and the infusion of the monoclonal antibody CAMPATH-6. Two years after transplantation, progressive and marked improvement had occurred; the pulmonary ground-glass opacities disappeared, the body CAMPATH-G. Two years after transplantation, protooncogenes were normalized after transplantation. ANA became negative, and evidence of disease progression. Their skin scores, mobilization of progenitors could on the other hand significantly change.

Evans’ syndrome and autoimmune thrombocytopenic purpura. Refractory ES and refractory AITP that relapse after splenectomy and do not respond to corticosteroids are associated with substantial morbidity and mortality because of the combined effects of disease and treatment.87 In a case report of a patient treated with ASCT, a 25-year-old woman with ES received peripheral-blood stem cell mobilization with routine doses of 4g/m2 CY and G-CSF; this was followed by exacerbation of hemolysis and thrombocytopenia, and the patient died of an intracranial hemorrhage.88

Four cases of refractory post-splenectomy relapsed AITP have been treated with intensive immunosuppression followed by ASCT. The first 2 cases responded dramatically89 but then relapsed (S Lim, personal communication). The other 2 cases did not respond at all.90,91

Special issues

Conditioning. The main conditioning regimens are well known, and include CY 200 mg/kg over 4 days, the variant with Thiotepa utilized in Genoa, and the equally well-known BEAM protocol, which has been found attractive for MS because of its intense lympholytic effect and the capability of BCNU and ARA-C metabolites to cross the (already disrupted) blood- brain barrier. Although the combination of CT with TBI has been shown to be significant risk factor for developing therapy-related AM/MDS,92 van Bekkum is of the opinion that the combination with moderate-dose TBI is superior to CT alone.93 AS already mentioned, this combination has been utilized for JCA.66

Intense immunosuppression without HSC rescue for treatment of autoimmune disease. Treatment with high-dose CY alone (200 mg/kg) has been used to treat severe aplastic anemia (SAA),90 and has subsequently been extended to a spectrum of severe ADs95 including Felty’s syndrome (2 cases), AITP and ES (1 case each) and SLE. One patient with AITP experienced disease progression and died following high-dose CY. A patient with refractory demyelinating polyneuropathy that had been refractory to plasmapheresis had a complete remission. Hematologic reconstitution was similar to that generally found after autologous HSC rescue. This has been attributed to the fact that primitive HSC express high levels aldehyde dehydrogenase, an enzyme responsible for cellular resistance to CY.94

Six patients with severe, relapsing SLE have also been treated with this regimen and published,99 but there are many more. Two are in complete, steroid-independent remission, one is in a partial remission, and three are showing dramatic improvement (although follow-up is currently less than 6 months). In one case of SLE,95 the inadvertent administration of a single high dose of CY (5 g) resulted in a sustained remission, further confirming the efficacy of CY alone. However the ex vivo expansion of progenitors could on the other hand significantly shorten the duration of neutropenia.96,97 as has been impressively shown in patients autotransplanted for multiple myeloma.100

Use of T-cell depletion (TCD) prior to HSC infusion in patients with autoimmune disease. Depletion of T lymphocytes has been widely utilized in allotransplantation to reduce the incidence and severity of GVHD following allogeneic HSC transplants. Unfortunately, TCD is accompanied by many disadvantages, including rising in graft rejection, leukemic relapse, and delayed immunologic reconstitution. New approaches that are being studied include the use of a higher proportion of donor HSC, selective T-cell subset depletion, and post-transplantation donor lymphocyte infusions (DLI). Because patients with active ADs are not in complete remission at the time of transplantation, van Bekkum et al.62 considers it mandatory to deplete the autograft of autoreactive lymphocytes. Most ADs are T-cell mediated and B-cell-mediated ADs often display prominent T-cell dependency. Thus, TCD may be useful in the treatment of ADs. Theoretically, both activated and memory T (and B) lymphocytes should be eradicated, or at least maximally depleted. This can be achieved either by positive CD34+ selection or by immunologic TCD. In addition TCD has been performed in vivo by administering ATG to the recipients. There is no indication of a potential threshold dose of T cells acceptable for reinfusion. A 3-log depletion has been customary, but further depletion has
been performed recently. However marked TCD may be accompanied by late fungal and viral infections and lymphoproliferative disease. There seems little point in curing ADs at the cost of profound and permanent immunosuppression.

Immune reconstitution following stem cell transplantation. Reconstitution of the immune system following either allogeneic or autologous transplantation has been studied extensively. Exhaustive reviews have been published.

The most common immunologic feature, also seen after intense chemotherapy, is a severe prolonged depression of CD4+ T cells, although in some cases CD3+ T cells have returned to pretransplantation levels after 10 months without disease relapse. Age, prior TCD, radiation and other factors may all modulate thymic or extrathymic pathways and influence the rate and extent of T-cell recovery after transplantation. The sites of lymphoid reconstitution, whether thymic or extrathymic, in young and older patients has been the subject of an abundant and frequently controversial literature. The thymic output in adults following ASCT has been studied very recently utilizing the numbers of TCR-rearrangement excision circles (TREC) in peripheral blood T-cells 100%. It was found that increases in concentrations of TREC post-transplant were associated with the development of broader CD4 T-cell TRC repertoires, and that patients with no increases in TREC had limited and highly skewed repertoires. The relative importance of thymus-dependent and thymus-independent pathways in adults is still controversial. The expanding CD4+ T-cell population may exhibit increased susceptibility to apoptosis. It appears that also the healthy immune cells could also be envisaged, as has been elegantly shown in the case of CD34+ CML progenitors.

Discussion

Prevailing concepts of autoimmunity dictate that a stable cure of ADs can only be expected if the patients' autoreactive immunocompetent cells are replaced by healthy, non-autoreactive cells. The healthy immune cells must also remain unsusceptible to whatever phenomenon provoked the initial breakdown in tolerance. Of the three approaches discussed here - allogeneic HSC transplantation, autologous HSC rescue following intense immunosuppression and intense immunosuppression alone - allogeneic HSC transplantation is theoretically the most promising. Allogeneic transplants have generally been followed by long term remissions and possible cures. However mortality and morbidity associated with allogeneic transplantation, although decreasing steadily in other disease contexts, is still unacceptable for most ADs. In addition, there are reports of patients with RA relapsing despite complete or nearly complete donor immunologic reconstitution following allogeneic transplantation. Leukemia relapse in donor cells is rare but established occurrence following transplantation. Transfection and/or chromosomal fusion have been considered as possible explanations, but they seems quite improbable in the autoimmune setting, where extrinsic events such as resensitization to autoantigens appear more probable. If relapses following allogeneic transplantation for ADs continue to be observed, the theoretical edge of an allogeneic procedure over an autologous transplant would be considerably weakened. However the case report of a severe autoimmune hemolytic anemia having relapsed after ASCT but having achieved long-term clinical and immunologic CR following a MUD allograft is encouraging.

The recent introduction of minimally myelosuppressive regimens which avoid the devastating cytokine storm associated with the classical dose-intense conditioning regimens and exploit donor lymphocyte immune effects, is a promising development in the treatment of malignant and nonmalignant diseases. If a graft-vs-autoimmunity effect were to occur clinically, it might also prevent recapitulation of disease. The simplest explanation for a similar effect consists in the progressive substitution of normal T and B cells in the place of autoreactive lymphocytes. However a selective elimination by cytotoxic lymphocytes of target autoimmune progenitor cells could also be envisaged, as has been elegantly shown in the case of CD34+ CML progenitors.

In the rare setting of an identical twin non-concordant for disease a syngeneic transplant may be considered. A dramatic result following a syngeneic transplant in a patient with severe RA has been published. In the case of SLE only 23% of 66 monozygotic twins were found to be concordant for disease, although a higher concordance has also been reported. Concordance of antibody production is higher than disease concordance. Also cord blood stem cells may become an attractive option for the treatment of ADs.

Autologous transplantation has been hailed as a possible therapy for severe refractory ADs because of lower transplant-related mortality and greater feasibility. In the EBMT registry, the overall survival at 2 years was 89±7%, with a median follow-up of 10 months for surviving patients. The transplant-related mortality at 2 years was 8±6%, which is comparable to that associated with ASCT for malignant disease. Selection of...
patients with less severe disease could further reduce mortality, but on the other hand one must consider that the procedure is meant for refractory/relapsing patients who often have accumulated diffuse visceral damage. Peripheral HSC are generally preferred to marrow HSC in almost all clinical situations, but very high doses of CY for mobilization should be discouraged. A dose of 4 g/m² is generally utilized with adequate mobilization and minimal toxicity. These CY doses are immunosuppressive and may contribute to the efficacy of transplantation, as was clearly shown in MS15,56,58 and in RA46,65.

A hitherto unsolved but fundamental question is whether intense immune suppression followed by ASCT is indeed capable of eradicating autoimmunity and thus inducing tolerance, or if the immune system remains fundamentally unaltered, and the so-called transplant is nothing more than a hematopoietic rescue. The first goal appears to have been achieved experimentally,14,15,22 but in clinical settings what has been called reprogramming the immune system120 has not yet been demonstrated. In SLE it has been proposed that the conditioning, with concurrent use of ATG, might provide a window of time free of memory T cell influence, during which the maturation of new lymphocyte progenitors may occur without recruitment to anti-self reactivity.30 In order to elucidate whether, if relapses occur, disease is reinitiated by lymphocytes surviving the conditioning regimen, or from the SC compartment, sophisticated studies with gene-marked autologous SC are being performed.121 If Shoenfeld’s122 concept of an idiotypic induction of autoimmunity will be shown as part of the etiology of SLE and other ADs, the impact of all these treatments would need further evaluation. Empirically, however, long-term remissions and relapses may also depend on the single disease and patient, but in most cases there is a distinct lowering of therapy-dependence, in addition to the resolution of severe/autoimmune "crises". Whether this effect will prove to be superior to other immunosuppressive and/or immunomodulating treatments will have to be evaluated in prospective randomized trials, notwithstanding the problems inherent to recruit sufficient numbers of homogenous patients. This may well be feasible in not infrequent diseases such as MS, SSc and RA, but will present many difficulties in other diseases such as SLE and others.

Even if the problem of the up to now excessive TRM will be almost certainly solved, the problem of late onco- geneticity cannot be ignored, especially in younger patients with nonmalignant diseases. The risk of developing solid cancers was 3-4 times higher in patients treated with combined modality therapy during marrow transplantation than in controls.123 In one study, a higher risk of acute myeloid leukemia was found following ASCT when the conditioning regimens included TBI.124 In addition, some of these patients may have already been treated with prior chemotherapy, including large doses of alkylating agents, which has been shown to be the most important risk factor for developing MDS/AML. Preliminary cytogenetic screening could be useful to exclude patients already bearing chromosomal abnormalities.

Finally prospective randomized studies are being initiated for SSc (ASTIS trial) and rheumatoid arthritis. Also for MS a prospective trial comparing ASCT with mitoxantrone is being organized. In addition, post-transplant treatment with β-interferon, which has been validated recently,125 could prolong transplant-induced remissions. In JCA ASCT should be compared with the pulse CY program that has been utilized recently.126

Conclusions
The excellent experimental results obtained with allogenic and even autologous stem cell transplantation for ADs have given considerable impetus to similar treatments for refractory/relapsing patients with severe ADs. Encouraging results following allogeneic SC transplantation have been reported in small numbers of patients with coexisting ADs and malignancies. However some relapses have occurred despite donor immune cell engraftment. If a GVA effect will be confirmed, the non-myeloablative allogeneic procedures could become extremely useful. In the meantime autologous transplantation using peripheral blood SC is currently being performed world-wide to treat ADs. Results are encouraging, but remissions rather than cures have been obtained. In some diseases, especially MS, results are superior to those obtained with conventional therapies. Long term remissions have also been obtained by intense immunosuppression alone,127 demonstrating that autologous SC have mainly a rescue effect. Further clinical trials are clearly indicated.

References


104. Frassoni F, Labopin M, Gluckman E et al. Results of allogeneic bone marrow transplantation for acute leukaemia have improved over time in Europe. Bone Marrow Transplant 1997; 19: 17-38.


