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Stem cell transplantation for severe autoimmune diseases: progress and problems

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ABSTRACT

Since Morton and Siegel's epochal experiments 30 years ago animal models have been successfully utilized both for transfer and resolution of autoimmune diseases (AID). More recently human lymphocyte xenografts have reproduced clinical AID in SCID mice. Allogeneic stem cell transplantation demonstrated therapeutic potential in fully developed autoimmune disease. Mixed allogeneic chimerism induced by a sublethal approach has also been shown to prevent and even reverse autoimmune insulitis in nonobese diabetic (NOD) mice. More unexpectedly it was found that experimental adjuvant arthritis (AA) and experimental allergic encephalomyelitis (EAE) could be cured by means of total body irradiation (TBI) followed by autologous hemolymphopoietic stem cell (HSC) transplantation. It was postulated that the newly developing T cells might be tolerant to self antigens.

The transfer of AID from affected donors to recipients of allogeneic HSC transplants has been reported for many organ-specific AID, including diabetes (IDDM), thyroiditis, myasthenia gravis and thrombocytopenic purpura (AITP); rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) were not transferred. Conversely patients with the combination of AID and a severe blood disease (leukemia, aplasia) were cured of both diseases following allogeneic BMT, with the notable exception of a relapse in a patient with RA despite full donor engraftment.

Allogeneic transplants are certainly more promising as far as concerns a resolution of AID, because they may also exert a graft-versus-autoimmunity effect by gradually eradicating the recipient's lymphopoiesis, but transplant related mortality (TRM) is considered still too high to employ this procedure consistently. New non-myeloablative conditioning regimens, designed to allow the donor's immune system to take over, are already utilized for malignant and non-malignant hematologic diseases, and may become an attractive option for severe, refractory AID. For the time being, however, autologous procedures are still safer, and are being utilized in many projects worldwide. The EBMT/EULAR Registry has collected over 70 patient reports. The more numerous and favorable results have been obtained up to now in multiple sclerosis and in systemic lupus erythematosus; the worst in refractory autoimmune thrombocytopenic purpura. No definite conclusions as to the efficacy of autologous HSC transplantation, from marrow or from blood, with or without T-cell depletion, may be drawn at this time, but the feeling is that real cures will be very difficult to obtain by this approach, and that corticosteroid-free remissions and a general lowering of the autoimmune potential will be more realistic goals. Accurate comparisons with already existing aggressive immunosuppressive protocols will become necessary, if possible by means of prospective randomized clinical studies.

Key words: stem cell transplantation, autoimmune diseases

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The successful treatment of experimental autoimmune diseases (AID) by means of immune ablation followed by allogeneic, histocompatible hemolymphopoietic stem cells (HSC) was generated by the epochal experiments performed in the '70s,[1,2] and has by now been confirmed and reviewed extensively. Since this is essentially a clinical overview, no effort will be made to review in detail the experimental literature.[3,4] An extensive overview has been recently published by Ikehara.[5] However, some aspects relevant to the understanding and further clinical applications will be briefly mentioned.

The utilization of transgenic and/or knock-out mice has been highly contributive.[7] A number of clinical AID have been transferred into SCID mice by means of xenogeneic human lymphocytes. They include autoimmune thyroiditis (both Hashimoto's and Graves' type[8]), primary biliary cirrhosis,[9] pemphigus vulgaris[10] and rheumatoid arthritis[11] (RA). However, there is still some uncertainty as to the identity of the cellular elements carrying the autoimmune information, or effecting the lesions of autoimmunity. In the original experiments unmanipulated marrow was utilized,[1,2] but it was shown subsequently that murine SLE of (NZBxNZW) F_1 mice could be transferred (perhaps more appropriately transplanted) utilizing T-cell depleted (TCD) marrow.[12] This was subsequently confirmed by other 3 log TCD experiments with the murine SLE subtype elicited by means of immunization with the monoclonal anti 16/6 idiotype antibody.[13] B lymphoid precursors from (NZB/NZW) F1 marrow cultures reproduced the disease in SCID mice.[14] However, the experimental antiphospholipid syndrome could be transferred only utilizing HSC in conjunction with T cells.[15] It has been stated recently that all the information required to cause the histologic change associated with SLE

resides in the peripheral blood lymphocytes.[16] The complexity of the differentiation from HSC to T or B lines, which has been reproduced *ex vivo* quite recently,[17,18] renders distinctions somewhat uncertain. However on the basis of his extensive experimental research Ikehara has defined AID as *abnormal polyclonal proliferations of HSC*,[5] and has also found that HSC deriving from autoimmune animals are more *resilient* than those coming from healthy ones, inasmuch as they can proliferate under major histocompatibility complex (MHC)-incompatible microenvironments, and do so at a faster rate than normal HSC.[19] In addition, it has become recently apparent that there is a direct relationship between HSC and diabetes of NOD mice, which is the primary model for human type I diabetes.[20] T-cell depleted and even isolated HSC are sufficient to transfer the disease.[4,5] Still more recently it has been shown that in mixed allogeneic chimerism induced by sublethal irradiation both prevention and reversal of pre-existing insulitis could be obtained.[21] In addition, insulitis and diabetes (61%) developed in NOD recipients who were sublethally irradiated but did not receive bone marrow. The mechanism does suggest a graft-versus-autoimmunity effect. In other experiments the development of self-reacting cells from the circulating B repertoire was excluded if a source for non-autoreactive B cells was present.[22]

Two other significant findings are first, the demonstration by van Bekkum and his group that autologous (and pseudoautologous) HSC transplantation is equally (or almost equally) effective in curing adjuvant arthritis[23] and experimental allergic encephalomyelitis[24] (EAE), although allogeneic transplants were proved to be superior in the latter condition.[25] A second stimulating finding is the demonstration that human cord HSC are capable of controlling the MLR-lpr subtype of murine lupus.[26]

In humans more than 40 diseases are recognized as having an autoimmune pathogenesis by the revised Witebsky's postulates.[27] Among these treatment resistant autoimmune rheumatic diseases,[28] multiple sclerosis (MS) and many others are urgently in need of more efficient therapeutic measures.[29] However, an oversimplified extrapolation from the dramatic experimental results to the clinic must be resisted. Human AID are considerably more multifactorial than those in experimental models, where the influence of genetic factors is overwhelming.[16] They do occur on a multiple susceptibility background,[30] but they are also strongly modulated by environmental factors.[31,32]

Initial insights were obtained by integrating occasional cases of adoptive, post-allogeneic bone marrow transplantation (allo-BMT) with other equally occasional cases of resolution of AID in patients having been transplanted for a coincident hematologic disease.[29,33-35] Following these results further attempts have been and are being performed utilising autologous procedures, especially in the framework of the *EBMT/EULAR Autoimmune Disease Stem Cell Project*.[36] An attempt will be made here to review the most relevant clinical data up to now and to discuss further developments. It must be acknowledged that although this will be more a narrative than a systematic review,[37] the collection of data and the discussion of concepts and strategies is of great importance at the present time. Besides the already existing reviews,[5] recent ones dealing mainly with experimental investigations[38] and two other clinical ones[6,39] are particularly informative.

Allogeneic experience

Adoptive autoimmunity

The transfer of an autoimmune disorder from a donor to a recipient is clearly one of the best criteria for establishing autoimmunity.[40] There is a group of patients who have received transplants from their HLA-identical siblings who were harbouring an AID, and who were cured of their hematologic disease, but developed the sibling's AID. The AID include thyroid disease (five patients have been reported so far), myasthenia gravis, diabetes (IDDM), autoimmune thrombocytopenic purpura (AITP) and, quite recently, celiac disease.[41] These cases have been reviewed and discussed extensively elsewhere.[6,29,34,35] The simultaneous transfer of autoimmune thyroiditis and resolution of palmoplantar pustular psoriasis following allo-BMT in a patient with acute myeloid leukemia (AML) has also been reported recently.[42] Two recent reports are of special interest. The transfer of autoimmune thyroiditis after allotransplantation of positively selected $CD34^+$ cells has shown that a 3 log T-cell depletion (TCD) may not be sufficient to prevent transfer of AID.[43] In two cases observed in Genoa the synthesis (not the passive transfer) of two different thyroid autoantibodies (anti-TSH from a donor with Graves's disease, anti-thyroglobulin from a donor with Hashimoto's disease) was transferred from donor to recipient.[44] Both recipients have not (yet?) shown signs of AID, thus demonstrating as in an experiment the temporal interval between autoantibody production and the development of target tissue lesions.

On the other hand autoimmunity was not transferred into two other recipients with leukemia (CML and AML) who received unmanipulated marrow from HLA-identical donors affected with rheumatoid arthritis[45] (RA) and systemic lupus erythematosus[46] (SLE) respectively. It has been mooted that fundamental differences may account for the apparent transfer by BMT of organ-specific diseases and not (up to now) of systemic rheumatic AID. Anyway one must agree with Snowden *et al.*[45] in assuming that systemic AID should not necessarily be a deterrent for the donation of allogeneic HSC. At the time of writing this review, a patient with CML is being programmed in Genoa for allo-BMT from his HLA-identical sister who has long-standing SLE.

Resolution of pre-existing AID following allo-BMT

The number of such cases is small, since the patients must have had both an autoimmune condition and a severe blood disease requiring a transplant, must have had a histocompatible donor, and been in transplantable age. However, if one accepts the concept that aplastic anemia is a genuine acquired AID,[47-50] then of course this is the most important AID clearly benefiting from allo-BMT.[51] The same can be said of the very few cases of pure red cell aplasia (PRCA) having failed immunosuppressive treatments and having received allogeneic transplants.

The non-hematologic AID with the highest number of performed allogeneic transplants is rheumatoid arthritis (RA).[6,34,35] In almost all patients the reason for transplantation was iatrogenic, gold related SAA. All patients had an initial complete, clinical and immunologic, resolution of their RA. However 3 patients died of transplant-related toxicity (TRM) and one died of hepatitis 2 years after transplant. Of the remaining 5 one is still in complete remission after 20 years of follow-up,[52] another 2 are also in CR, 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.[53] This accurately investigated case with a 13 year follow-up illustrates that RA may recur and progress even after complete allogeneic myeloid and immune engraftment. The long-term outcome of 3 of the RA patients and of another one with psoriasis having received an allogeneic transplant because of the development of CML have been analyzed recently,[54] and it has been found that in one of the 3 with RA allogeneic reconstitution did not prevent recurrence of the autoimmune disease. The patients who had significant acute and chronic GVHD remained in remission, whereas 2 patients who had relapses showed no evidence of GVHD. It is suspected that re-exposure to an endogenous or exogenous antigenic trigger might result in the developmnent of autoreactivity in a susceptible transplanted immune system.[53,54] A case of severe eosinophilic fasciitis (Shulman's syndrome) complicated by severe aplastic anemia (SAA) was transplanted from an HLA-identical sister, and is reported to be in CR of both diseases 28 months post-BMT.[55]

Between 1982 and 1992, 6 patients with Crohn's disease and leukemia underwent allogeneic marrow transplantation in Seattle.[54] One patient died of septicemia on day 97 after transplant; 5 patients were observed for 4.5, 5.8, 8.4, 9.9 and 15.3 years post-transplant, 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 Crohn's disease 1.5 years after transplantation.

The results suggest to the authors that the patients' immune dysregulation plays a role in the perpetuation of Crohn's disease, and that it can be corrected by allogeneic HSC transplantation.

Other significant single case reports include a case of MS having developed CML who received an HLA-identical allo-BMT, with no further progression of the neurologic disease one year later,[57] a 5-year boy with refractory Evans syndrome who was successfully transplanted with HLA-identical sibling cord blood, but who died 9 months later of acute liver failure,[58] and a case of autoimmune hepatitis having resolved following allo-BMT.[59]

Autologous transplants

Autologous transplants, whether from marrow or blood (or the combination of both) have been and are being utilized more extensively because of two reasons: the encouraging experimental results from Rotterdam[23-25,60] and from Jerusalem,[61,62] and, most importantly up to now, the greater safety of the autologous procedure.[6,34-36] Cases are miscellaneous and mainly anecdotical, but they are increasingly being incorporated in the EULAR/EBMT Registry, which by now includes over 70 cases.[63]

In the beginning, similarly to allogeneic transplants, patients were transplanted because of the concomitance of blood disease and AID. Four cases were published recently (myasthenia gravis + ovarian carcinoma, NHL+SLE, atopic dermatitis + NHL, and a case of the CREST variant of scleroderma alone); early relapses or persistence of disease were reported.[64] TCD had not been performed, and it was accordingly recommended. Other combined cases of RA and NHL have been autotransplanted in our Institution, but the persisting remission of RA that occurred may be attributed to the fact that they relapsed with respect to their lymphoma and received additional chemotherapy. There is, however, a 62-year-old female patient who had seropositive erosive RA, developed AML, was autotransplanted and is still in CR from both diseases 3 years later. In addition, there are 2 cases of severe, erosive rheumatoid arthritis who received autotransplants with PBSC. The first was a 46-year-old man with seropositive (RF titre >250) polyarthritis who received his own mobilised (CY-GCSF) $CD34^+$ cells, 2.6×10^6/kg, following conditioning with 200 mg/kg of CY over 4 days combined with dexamethasone, 8 mg daily. He enjoyed a dramatic remission, although the RF titre after therapy was not specified.[65] The second case concerns a 22-year-old woman whose PBSC were mobilised with CY, etoposide and G-CSF, and whose $CD34^+$ cells were purified both positively and negatively. The pre-transplant conditioning regimen consisted of BUCY2. At 3 months the patient is free of joint symptoms.[66] In addition to these 2 cases two cohorts of 4 patients each with severe, active disease received unmanipulated autologous HSC following conditioning with, respectively, 100 and 200 mg/kg of CY. Subablative doses produced only transient responses, while superior results were obtained with the higher dosage.[67] However, in the most carefully prolonged study of 4 patients with autoimmune dis-

eases (3 psoriasis, 1 RA) complicated with malignancies and autotransplanted, the autoimmune disease remitted in all of them, but it recurred at 8-24 months, so that the authors suggest that a single autograft with unpurged stem cells is unlikely to cure autoimmune diseases.[68]

Three patients with juvenile chronic arthritis (JCA) were treated with autologous, TCD marrow after conditioning with ATG, CY and low dose TBI. Tolerance was good, and the follow-up of the first two patients showed a marked decrease in disease severity.[69] Other cases with connective tissue diseases include one patient with systemic sclerosis,[70] who got some benefit, and one with severe pulmonary hypertension associated with an anticentromere antibody, in whom no advantage was obtained.[71]

As originally suggested five years ago[72] SLE is rapidly becoming a major target for autologous transplants. Two cases in which a transplant was performed because of a concomitant hematologic malignancy have been reported. One is still in second chronic phase of CML controlled by hydroxyurea and is also in complete clinical and serologic remission from SLE.[73] In the other case the NHL did not relapse, but AITP supervened in association with an anticentromere autoantibody[74] (ACA), thus showing a greater refractoriness of the autoimmune processes than of the lymphoid neoplasia. A similar occurrence has been reported very recently:[75] a patient with Sjögren's syndrome and dysglobulinemic vascular purpura developed an aggressive immunoblastic lymphoma of B-cell origin, which relapsed repeatedly after chemotherapy (VACOP-B, VIPE), and finally went into long-term remission following an autologous unmanipulated peripheral blood progenitor cell ($CD34^+$) graft. Conditioning was performed according to the BEAM regimen. However two months later thrombocytopenia and autoimmune vasculitis recurred, similarly to the early recurrences first reported in Euler's paper.[64]

There are now 6 published cases of SLE alone which have undergone TCD autologous transplants, one with marrow and 4 with PBSC. The first case and that with the longest follow-up was transplanted in Genoa.[76] This patient is in good clinical remission, has a borderline ANA positivity of the speckled type 2 years after transplant, and her corticosteroid requirement has decreased from 40 to 5-10 mg of prednisone daily. Four SLE patients have received PBSC transplants with 3 log TCD following 200 mg/kg CY conditioning in Chicago. The first patient was a 24-year-old woman with rapidly declining renal function, who went into complete clinical and immunologic remission,[77] and is still in remission 8 months after transplantation maintaining corticosteroid independence.[78] The second patient is a 15-year-old girl with recurrent pulmonary hemorrhage who is now well over 6 weeks after HSC infusion and tolerating a tapering of prednisone as her only immunosuppression.[78] A 35-year-old woman with severe SLE complicated with stage III focal proliferative glomerulopathy was transplanted with $CD34^+$ PBSC after conditioning with the BEAM regimen, and had no complications.[79] Finally, there are two patients with SLE who had severe blood complications (Evans syndrome in one case and pancytopenia in the second). Both received autologous $CD34^+$ cells; however, in the case from Palermo[80] with the Evans syndrome, conditioned with ALG/CY (100 mg/kg) there was a good remission which is still holding 8 months after transplant, while in the patient from Thessaloniki, who was conditioned with the BEAM regimen, hematologic autoimmunity appears to be relapsing.[81]

Four patients with post-splenectomy relapsed, refractory AITP have been treated with autologous HSC therapy. Two were transplanted with unmanipulated PBSC after conditioning with 200 mg/kg CY, and both had an excellent, steroid-independent remission.[82] However, both relapsed, one after 18 months and one after 12 months (*Lim, personal communication*). Two other similar cases failed to present a satisfactory response following similar conditioning and rescue with autologous $CD34^+$ positively selected cells with 3 log TCD.[83,84] A severe hemophiliac A patient who had developed a high level of anti-human VIII:C antibodies (αh VIII Ab) also developed a diffuse large cell NHL. He was treated with a high-dose sequential CT program with autologous PBPC rescue. At 36 months after autograft the patient is in CCR from NHL, with complete recalcification of the osteolytic lesions; in addition he has become a low responder in terms of αh VIII Ab, allowing him to receive rHVIII:C on demand.[85]

The single autoimmune disease which has received most autologous HSC transplants is MS, which is fast becoming one of the main clinical targets of this type of treatment, even if attempting it has been likened to opening Pandora's box, with uncertainty and danger, but also with hope.[86] The largest clinical material comes from Thessaloniki, Greece, where 15 patients with progressive MS were treated with the immunomyeloablative regimen BEAM, followed by autologous, CY-mobilized HSC plus antithymocyte globulin (ATG) administered to the patients as an *in vivo* TCD.[87] There was no TRM, 7 out of the 15 patients showed an improvement on the *Kurzke Expanded Disability Status Scale* (EDSS), and all 15 improved on the *Scripps Neurologic Rating Scale* (SNRS). In another clinical study 3 patients with decline of their EDSS by 1.5 points over the 12 months preceding enrollment and an EDSS of 8.0 at the time of enrollment were treated using a conditioning regimen consisting of CY (120 mg/kg), 6-methylprednisolone (4 g) and TBI 12Gy. Hematologic rescue was performed with peripheral, TCD $CD34^+$ enriched cells. Functional improvements occurred in all 3 patients, albeit no significant changes in EDSS or SNRS scales were apparent at the time of publication. Magnetic resonance imaging (MRI) showed stability with no new lesions and no

enhancement.[88]

In the first case of severe, progressive MS treated with peripheral autologous CD34+ cells following the BEAM conditioning regimen in Genoa all the over 40 gadolinium enhancing lesions dropped to 8 already after CY mobilization (4 g/mq), and disappeared completely after transplantation (Mancardi *et al., in preparation*).

Many other MS patients are being currently treated with different immunomyeloablative regimens followed by autologous HSC rescue worldwide. In addition, 2 Consensus Conferences recently took place in Milan and in Florence.

Discussion

On examining the limited clinical material available one gains the opinion[29,33-35,90] that allogeneic HSC transplants have generally been accompanied by long-term remissions (cures?). In the case of experimental SLE it has been shown that abnormalities in the B cell repertoire of autoimmune persons determines whether contact with foreign DNA-leads to a protective response, or to a deleterious one to the conserved conformational determinants on all, self included, DNA.[91,92] Switching normal in the place of autoimmune-prone DNA, even if coming from an HLA-identical sibling, may be advantageous. In RA, however, even after allogeneic transplants some relapses have been reported despite complete donor hemopoietic and immune reconstitution.[53,54] Leukemia relapse in donor cells is a rare but acknowledged event,[93,94] which is, however, being almost not reported any more with the utilization of more sophisticated techniques. However, events such as transfection and/or chromosomal fusions are *prima facie* quite improbable in the autoimmune setting, whereas extrinsic events such as resensitization to autoantigens would seem more probable. After all, much of the autoantibody response, such as the anti-DNA response in murine and human SLE, is thought to be an antigen-driven immune response.[31] If additional similar cases were to be observed, the whole allogeneic HSC transplant strategy would have to be revised, and the edge of the allogeneic versus the autologous procedure would be considerably weakened.[95] In view of a possible graft-versus-autoimmunity (GVA) effect which will be discussed later it is of interest to note that the 2 patients whose RA has effectively remained in remission for more than a decade after allo-SCT had significant acute and chronic GVHD, whereas 2 patients who had relapses showed no evidence of GVHD.[54]

The reasons for the profound difference between the experimental and the clinical results are intuitive. Whereas inbred strains of mice and rats have an overwhelming genetic predisposition, in human SLE (and AID) the relationship between environment and genes is much more finely balanced.[16,29] Another question is the identity of the disease-transferring cell, which is some experiments was shown to be the HSC,[4,5] but in others a B-cell precursor.[14] The transfer of peripheral blood lymphocytes from SLE patients into SCID mice, which are capable of reproducing the human disease, shows that much of the information resides in them.[16]

Following allo-BMT T-cell reconstitution does not follow the pattern of physiological T-cell differentiation.[96] It is unclear whether thymic or extrathymic pathways are more determinant. An extrathymic mechanism is capable of regenerating CD45RO+ cytotoxic/suppressor cells, but residual thymus has been considered as essential in order to reconstitute early primitive CD45RA+ thymocytes.[97] A recent study on the immune recovery patterns in patients following myeloablative chemotherapy and stem cell therapy, both allogeneic and autologous, besides confirming the significantly reduced absolute numbers of CD4+, CD45RA+ and CD45RO+ cells, provided indirect evidence for continued, albeit reduced, functional activity of the thymus.[98] In the case of T-depleted allotransplants the recovery of total and CD45RA+ CD4+ cells is delayed in adults when compared to that in children.[99]

The reconstruction of the immune system after marrow and blood HSC transplants has been studied,[100,101] and it has been shown that the recovery of T-lymphocyte counts, CD3+, CD4+ and CD8+ cells, is significantly faster after blood cell transplants than after marrow transplants.[102,103] One of the main features, also after chemotherapy, may consist in the deep and prolonged depression of the CD4 helper subset,[104, 105] which has been confirmed in the autoimmune transplant setting.[76,77,80] A recent study in 50 patients affected by hematologic malignancies and autotransplanted with blood HSC showed an important depression of the CD4+ helper/inducer subset in all patients (<500/uL) during the first 15 months, with a strong inversion of the CD4 /CD8+ ratio, and a probability of reaching a >200/uL threshold of 75% at the first month.[98] Also after dose-intense chemotherapy a greater than 90% loss of total CD4+ cells was found, and it was shown that thymic production was not the main route of CD4+ regeneration, with a severe impairment of CD45RA+ cells.[105] In addition an increased susceptibility to apoptosis within the expanding CD4+ population was also noted. These features might be of significance in all AID, and perhaps particularly so in MS, where, similarly to EAE, CD4 T_H1 cells mediate the disease.[106] The importance of CD4+ inactivation in order to obtain an active suppression of autoimmunity has been shown utilizing an anti-CD4+ monoclonal antibody.[107] This effect has been interpreted as a selective effect on the T_H1/T_H2 dichotomy, thus ensuring a therapeutic *reprogramming* of the immune system.[108] Notwithstanding a recent controversy,[109,110] the role of T_H1/T_H2 dichotomy in autoimmunity has been emphasized,[111] but further studies in this area are necessary.

The introduction of non-myeloablative, predominantly immunosuppressive conditioning regimens, devised to utilize essentially the immunologic effects of the donors' T cells rather that the brute chemoradio-

therapeutic component,[112] will probably deeply affect strategy and practice of HSC allotransplantation in the very near future.[113-115] Along the same line of strategy, a potentially efficient way to eradicate T and B memory cells following allogeneic HSC transplants could be derived from the encouraging experience with donor lymphocyte infusions (DLI) for leukemia relapse, most markedly in chronic myeloid leukemia.[116, 117] DLI are capable not only of eradicating recurrent leukemia cells, but also surviving host lymphocytes.[118] This switch to all donor T chimerism should also include autoreactive T cells, thus exercising a GVA effect.[119] Whether such an effect could be achieved in clinical settings is, of course, hypothetical, but it would seem to have been proven experimentally. Stable chimerism achieved in nonobese diabetic (NOD) mice using a sublethal conditioning approach was sufficient to prevent insulitis and even abrogate it, while NOD mice that were irradiated but did not received bone marrow developed acute diabetes by 12 months.[21] Thus the combination of immunosuppression, normal HSC and gradual eradication of autoimmune lymphoid clones could (it is to be hoped) be a successful strategy for the treatment of severe AID. However, a final hurdle could still consist in the sensitization of the new immune system to the persisting autoantigens. If, in a typical AID such as SLE, nucleosomes deriving from increased tendency towards apoptosis are indeed the driving autoantigens,[120] then the chance might still exist of a sort of recapitulation of disease. As already pointed out, some cases of relapsing RA following allogeneic transplants have been reported.[53,54]

Autologous transplants are, for the time being, safer,[6,26] and have accordingly been recommended.[33-36] However, two patients died during HSC mobilization.[51] Mobilization of HSC will be briefly discussed later, but the point should be made that high doses of CY are quite unnecessary, unless one wishes to perform a sort of pre-emptive immunosuppression under the disguise of a mobilizing procedure. It should be noted that patients in advanced stages of AID, similarly to end-stage malignancies, are no longer suitable for aggressive therapy. The utilization of T-cell depletion is also recommended, bearing in mind that a minimum of 2×10^6 $CD34^+$ cells/kg recipient body weight are required for hematological and immune reconstitution, and that T-cell depletion must reach $<1\times10^5$ CD3 lymphocytes.[36,121] It is doubtful, however, whether this is capable of eradicating minimal residual autoimmune disease, independently of an extrinsic pathogenetic mechanism.

The prevalence of AID is estimated to reach 6-7% of the population in Western countries,[122] and, although the distinction between organ-specific and systemic disease is still widely accepted,[29] there is extreme heterogeneity among the various entities, and the severity of single diseases. Only a minority may be considered as very severe, treatment-resistant[25] and life-threatening.[123] In addition, as already pointed out, AID are multifactorial disease processes, involving immune reactions against autoantigens, occurring on a polygenic susceptibility background, but being modulated by environmental factors,[29] such as estrogens in SLE.

These and additional considerations affect the whole concept and strategy of HSC for AID, but are obviously more cogent in the case of autologous procedures. Both in allogeneic and autologous HSC transplants, leaving aside the question of cellular immune therapy which has been discussed formerly, the predominant change in immune status is acute suppression. This is especially true in the autologous setting. A recapitulation of lymphocyte ontogeny, with the generation of self-tolerant lymphocytes, has indeed been found in experimental animals,[3,6,60] but in the Rotterdam investigations the destruction of both central and peripheral lymphoid tissue was necessary to achieve this.[3,23,60] In MRL/lpr mice the transfer of syngeneic marrow purged of T-cells was shown to be capable of preventing disease.[124] However, further investigations are needed to confirm or negate this in human patients. The studies on T lymphocyte subtypes, and more specifically on the generation of $CD45^+$ RA cells, have already been discussed; they certainly need further investigations in the autoimmune area. With the current conditioning regimens, including the widely utilized 200 mg/kg CY protocol, it seems improbable that radical changes of re-emerging immune system may be expected. This is one of the reasons why the combination of chemo- and radiotherapy (TBI) has been suggested[3] and utilized, both in low dosage for children with JRA[69] and in full dosage (12 Gy) for adults with MS.[86] Although no adverse events affecting the CNS were reported with the latter modality, the problem of late oncogenicity cannot be ignored, most especially dealing with non-neoplastic patients. The risk of developing solid cancers was 3 to 4 times that among the patients who did not undergo irradiation.[125] In addition, and leaving aside abundant information about increased leukemogenicity in patients treated with combined modalities for Hodgkin's disease (HD) and NHL,[126] strongly increased risks for AML/MDS have been reported following ABMT in patients with HD and NHL.[127] One study observed higher AML risk after a conditioning regimen incorporating TBI.[128] This whole area has been reviewed recently.[129] Anyway, it is essential that patients with severe AID be exposed to minimal oncogenic risk when undergoing autologous HSC therapy.

There is no doubt that PBSC have almost completely replaced the harvesting of marrow progenitors also in the autoimmune area. This is not the place to discuss the relative merits of the two procedures, even if it is well established that the cytopenic post-transplant period is somewhat shorter when utilizing peripheral cells. It has been shown recently that both cycling and non-cycling primitive progenitors continue to be mobilized into the circulation during the leukapheresis of patients pre-treated with chemotherapy and G-CSF.[130] Human PBSC grafts contain 10-fold more T cells and

19 to 25-fold more NK cells than marrow grafts.[131] This may translate into a more vigorous GVL effect in allogeneic settings,[132] but it is predictable that autoreactive, pathogenic cells may also reside in these T lymphocytes, so that when utilizing PB T-cell depletion appears even more mandatory than with marrow explants, even if the degree is still uncertain, and it is doubtful whether an authentic *purging of autoimmunity* will ever be attainable.

Coming now to the mobilizing procedures, it is well-known that the sequential combination of a myelosuppressive agent followed by G-CSF has the greatest mobilizing power; however G-CSF alone is currently utilized for allogeneic HSC donors.[133] Potential contraindications were considered to be persons with a history of autoimmune disorders, including RA and SLE; however even in long-standing RA it has been demonstrated recently that G-CSF alone can mobilise hematopoietic progenitor cells in numbers suitable for harvesting, without flares in disease activity referable to the cytokine.[134] In another similar study utilizing filgrastim at 10 mg/kg/day it was shown that the factor may administered safely to patients with severe active RA for effective HSC mobilization with only routine side effects and unfrequent flares.[135] This approach obviates the need of using CY for HSC mobilization, thus allowing the whole procedure to be conducted more safely; on the other hand one loses the *priming* immunosuppressive effect induced by the mobilizing chemotherapy regimen. In designing project protocols it will be appropriate to retain combined mobilization for patients previously untreated with alkylating agents, while G-CSF alone would be more suitable for patients already heavily pretreated with CY and/or other immunosuppressive drugs.

In the rare case of identical twins non-concordant for disease syngeneic transplants could be envisaged. In the case of SLE several instances of monozygotic twins discordant for the disease have been reported, and only 23% of 66 monozygotic twins were found to be concordant for SLE in a comprehensive study.[136] This is partially in contrast with the recent statement that the majority of monozygotic twins described in the literature have been concordant for SLE.[137]

The utilization of cord HSC has been defined recently as a new frontier in transfusion medicine.[138] The possible combination with *ex vivo* expansion could also offer the benefits of an allogeneic approach combined with less GVHD and less toxicity in general. The brilliant results obtained utilizing human cord HSC to control murine SLE[26] are certainly encouraging.

The results from the EULAR/ABMT Project and from other clinical studies will tell whether the autologous procedure has indeed the potential to treating severe AID effectively. Recurrences have been reported up to now, so that repeated (tandem) autotransplants have been considered.[139] Since collections of great numbers of $CD34^+$ cells are now possible, multiple cycles of high dose immunosuppressive chemotherapy can also be programmed, thus enhancing the total dose of chemotherapy over and beyond what is achievable with a standard autologous transplant.[140] In addition it will be necessary for a proper comparison of the results of autologous HSC therapy with those of other aggressive immunosuppressive treatments. In the case of SLE a confrontation might be considered with the synchronized plasmapheresis-pulse CY program, with which ANA-negative, treatment-free remissions have been reported.[141] In the case of JRA the preliminary transplantation results[63] should be programmed for a confrontation with the prolonged CY pulse program which has been performed recently.[142] There is no doubt that, in future prospective trials, a randomisation between the two approaches should be considered. In both circumstances a downgrading of autoimmune potential, as suggested by Lim,[43] could be helpful, reducing the need of long-term corticotherapy. As has been stated recently, suppression of RA, and for that purpose also of other autoimmune rheumatic diseases, is feasible and effective, but a real cure is still some way off.[143]

The spectrum of AID is extremely heterogeneous, and initial good or bad results may also depend on the disease category. Predominantly T (such as MS) or B (such as AITP) diseases may have different sensitivities and responses. As already pointed out some long-term, corticosteroid-independent remissions in severe cases of SLE have been reported. On the other hand the results in refractory AITP are certainly not encouraging. Both Lim's cases, despite an excellent initial course,[82] eventually relapsed, and there was no response at all in the Basle[83] and Genoa[84] patients. It is known that refractory patients with AITP respond poorly to subsequent treatment, have a significant morbidity from the disease and its treatment, and have a mortality rate of about 16%.[144] Four levels of therapy have been suggested recently by McMillan,[145] including high-dose CY. If autologous transplants were to give better results in other cases, they would fit in between levels 3 and 4, but they do not seem to have attained better results than CY alone, especially by the pulse methodology.[146]

When I first proposed using HSC therapy (ideally allogeneic, autologous as a possible substitute) for the prototype of human AID – SLE – 5 years ago,[72] my hope was that clinical results could and would somehow duplicate the dramatically successful results achieved in experimental animal models. Although a better evaluation is to be expected from the cumulative EULAR/EBMT Registry and from the many clinical projects, reports up to now are sometimes encouraging, but other times deceiving. Few severe adverse events have occurred, however, and there are no serious ethical objections against the continuation of clinical studies. Transplant procedures may become an effective strategy for some categories of severe AID, but it cannot be stated that *BMT beats autoimmune disease*,[147] especially in the autologous setting. Resetting the immune thermostat, as recently proposed by

Hahn[148] would seem more probable. Although status-of-art procedures, autologous and, it is hoped, non-myeloablative allogeneic transplants, are now relatively safe, patients with severe organ failure and end-stage disease should not be treated out of desperation. Whether patients will ultimately emerge from the procedure with an intact but non-autoreactive[147] immune system has already been discussed.

All in all, one important result is being achieved. Bringing hematologists and transplanters, basic and clinical immunologists, rheumatologists, neurologists and other specialists to work together and to share their specific knowledge can only be beneficial to medical science and to the patients.

Disclosures

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