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Stem cell transplantation for immunodeficiency

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Introduction

Most primary immunodeficiencies (PID) consist in intrinsic defects of lymphocytic and/or phagocytic cell lineages. Therefore, replacement of genetically impaired hematopoïetic stem cells by normal hematopoietic stem cells is a logical therapeutic approach. First reports of successful bone marrow transplantation (BMT) for PID were published in 1968: Gatti et al. [32] described correction of a severe combined immunodeficiency (SCID) case and Bach et al. [6] partial correction of a Wiskott Aldrich syndrome (WAS) case. Since this time, it is estimated that over 1500 patients with PID have undergone allogeneic BMT. About 26 different inherited immune deficiencies have been cured by BMT (Table 1) including the different forms of SCID, of other T cell immunodeficiencies, WAS, various phagocytic cell diseases and more recently hyper IgM and XL-proliferative syndromes. BMT has also been used as a source of mature T cells to correct, at least for some time, the severe T cell lymphocytopenia observed in Di George's syndrome. Based on a better understanding of major histocompatibility complex (HLA) molecular biology and identification of T cell-associated antigens, alternatives to BMT from HLA genetically identical donors have been proposed, i.e., use of related, partially matched donors as well as matched unrelated donors.

Stem cell transplantation for severe combined immune deficiencies

SCID represent a group of diseases characterized by an inherited defect in T, with or without B, cell differentiation, resulting in the absence of mature T, with or without B, cells. The overall frequency is estimated at 1 in 75 000 live births. The four main SCID syndromes are reticular dysgenesis characterized by both defective myelopoiesis and lymphopoiesis; alymphocytosis where T and B lymphocytes are absent, while natural killer cells (NK) are present (as in the murine SCID model); selective blockade of T cell and NK cell differentiation which can be inherited either as an autosomal recessive, or more frequently, as an X-linked recessive disorder; and, finally adenosine

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Table 1 Immune deficiencies that have been cured by allogeneic bone marrow transplantation

Severe combined immunodeficiencies
Reticular dysgenesis
Alymphocytosis
Absence of T lymphocytes (autosomal recessive and X-linked inheritance)
Adenosine deaminase deficiency
T cell deficiencies
Omenn's syndrome
Defective T cell activation (combined immunodeficiencies)
ZAP 70 deficiency
Purine nucleoside phosphorylase deficiency
Major histocompatibility complex class II deficiency
Immune deficiency with cartilage-hair hypoplasia
Hyper IgM syndrome (HIGM-CD40L deficiency)
X-linked proliferative syndrome (XLP-Purtilo's syndrome)
Wiskott-Aldrich syndrome
Phagocytic cell diseases
Agranulocytosis
Leukocyte adhesion deficiency
Chronic granulomatous diseases
Chediak-Higashi syndrome
Familial hemophagocytic lymphohistiocytosis
Immune deficiency with partial albinism (Griscelli's disease)
Fas deficiency (lymphoproliferative syndrome with autoimmunity)

deaminase deficiency. The molecular basis of several SCID have been unravelled, including γc deficiency in X-linked SCID, JAK3 deficiency in A.R.B (+) SCID and RAG ½ deficiencies in A.R.B (–) SCID. In the absence of BMT, SCID syndromes are fatal, usually within the 1st year of life.

Gatti et al. [32] first reported the successful correction of SCID by allogeneic BMT. Since then, worldwide at least 200 children with SCID have received an HLA-identical BMT. Results have gradually improved because of earlier diagnosis, prevention of life-threatening complications such as transfusion-induced graft-versus-host disease (GVHD), and the availability of more effective antibiotics. In Europe, the cure rate has been greater than 90% since 1983 [27].

The most remarkable features of HLA-identical BMT for SCID are the lack of an absolute requirement for conditioning, the rarity of acute and chronic GVHD and the rapid development of T and B cell function post-transplant. In most cases, only lymphocytes of donor origin develop. In pure T cell deficiency, donor-derived T lymphocytes coexist effectively with host-derived B lymphocytes [15, 17, 26, 31, 51]. It is unknown whether engraftment of stem cells occurs in the marrow with selective lineage differentiation, whether stem cells differentiate in the thymus, or whether only mature donor T cells expand (as observed after transfer of mature T cells in athymic nude mice). The latter hypothesis may account for the rapid (within a few weeks) development of full immune function and the success of BMT as a cure of Di George's syn-

drome [34]. The low incidence of GVHD may be related to the absence of a marrow ablative regimen pretransplant, thus possibly sparing natural suppressor cells. In some patients, a partial B cell immunodeficiency does persist, including IgA and sometimes IgG2 and IgG4 production impairment. It is not presently clear whether in these cases B cell immunodeficiency results from intrinsic host B cell deficiency, as observed in X-linked SCID in which B cells are unresponsive to IL-2 and IL-15 but responsive in part to IL-4 and to IL-13, or whether another mechanism caused residual B cell immunodeficiency. A minority (< 10%) of SCID patients who underwent HLA-identical BMT are supplemented with long-term intravenous immunoglobulin.

Only approximately 20% of SCID patients (as other potential bone marrow recipients) have an HLA-identical sibling. HLA phenotypically identical BMT from related donors has also been used successfully, although the success rate is significantly lower compared to HLA genotypically identical transplants [65% ($n = 23$) versus 85% ($n = 60$), $P < 0.50$ in Europe, F. Porta, personal communication].

Fetal liver cell transplantation

In the 1970s, the use of HLA-mismatched fetal liver cells as a source of hemopoietic stem cells to cure SCID patients without an HLA-identical donor was proposed. This was based on the knowledge that major histocompatibility complex (MHC) disparate stem cells could engraft and then generate T lymphocytes which differentiated in the host thymus to become tolerant to the recipient's tissues. In a low proportion of cases (11%), fetal liver transplantation was successful, leading to T (and sometimes B) cell differentiation without causing GVHD, provided that the fetal liver originated from a fetus not older than 12 weeks [49]. Some patients are alive and well with normal immune function 10–18 years after this procedure. However, the procedure often failed, and it required a very long time (1–2 years) before patients could safely leave the protected environment. In long-term surviving patients, interesting observations have been made concerning chimerism and tolerance. In a context where T cells are of donor origin, while B cells and monocytes are host and NK cells either donor or host [3, 5], it was found that donor anti-host reactive CD4 and CD8 T cell clones could be derived, while no GVHD occurred. This discrepancy is likely accounted for by the high level of immunosuppressive IL-10 production by anti-host T cells as well as by host non-T cells [4], while these T cells produce low levels of IL-2. These surprising findings show that tolerance in this setting is mainly the consequence of a peripheral control mechanism.

Partially matched marrow transplantation

As soon as T cell-depletion methods became available, HLA partially compatible BMT was proposed as an alternative to fetal liver transplantation. It was expected, from animal models, that T cell-depleted marrow transplantation would give rise to normal lymphoid differentiation in the absence of GVHD. Reisner et al. [55] successfully used a physical method (combination of soybean agglutination and sheep erythrocyte rosetting) to remove mature T cells from the marrow. Results were reproduced in other centers using other T cell-depletion methods, such as anti-T cell antibodies or sheep erythrocyte rosetting alone. From the literature, it appears that at least 600 patients with SCID syndromes received a T cell-depleted marrow from a related

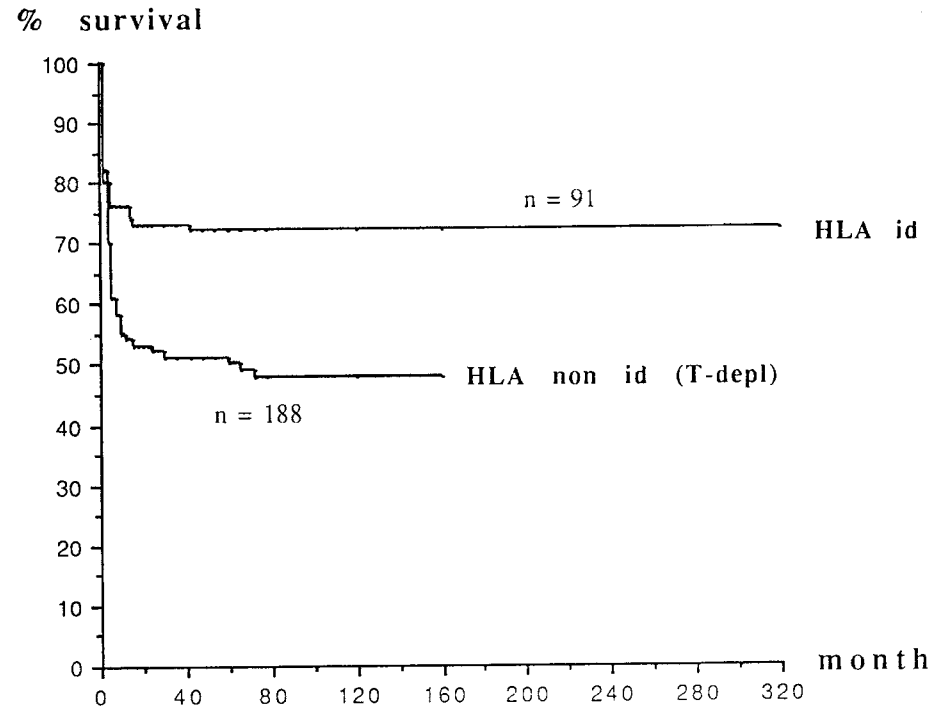

Fig. 1 Event-free survival of SCID patients transplanted in Europe from 1968 to March 1995 EBMT/ESID Registry (*id* identical, *T-depl* T cell depleted)

donor, usually a parent. About 60% are alive with development of immune function (Fig. 1). Some centers reported success rates above 70% [15–17, 31, 51, 61]. Overall, 2-year survival in Europe is now 60%. Analyses have been performed to delineate prognostic factors of these transplants. It appeared that the T cell-depletion method used had no influence on outcome. Major factors were the age at BMT or the presence of a lung infection prior to BMT (the two variables were not independent), use of a protective environment and a conditioning regimen (considering patients transplanted since 1986). A recent European survey has shown that the outcome of T cell-depleted HLA-nonidentical BMT in B(–) SCID is poorer than in B(+) SCID. This is in part related to a lower rate of engraftment, possibly caused by patients NK cell ability to reject donor marrows (Y. Bertrand et al., in preparation).

Altogether, results of HLA-nonidentical T cell-depleted transplants for SCID syndromes in Europe differ significantly from those of HLA-identical transplants ($P < 0.01$). It was recognized at that time that a combination of favorable factors (protective environment, optimal donor and use of a conditioning regimen) gave a 76% survival rate compared to 42% for all other patients.

In the absence of a conditioning regimen, failure of engraftment occurs in 40–50% of patients, while the use of busulphan (8 mg/kg) and cyclophosphamide (20 mg/kg) led to a 95% engraftment rate. It is possible that a conditioning regimen promotes the rate of development of immune function, and that both T and B cell function recover more easily. In the absence of a conditioning regimen, engraftment of donor B cell (and myeloid cell)

lineage occurs in 30% or less, while it is present in 75% of conditioned patients. Moreover, donor B cell chimerism is strongly associated with the development of B cell function (antibody production), although host B cells were shown to be functional in some cases [67]. A high-dose conditioning regimen, however, may be detrimental in profoundly immunedeficient patients. Thus, busulphan 16 mg/kg with cyclophosphamide is associated with significantly poorer survival compared to busulphan 8 mg/kg with cyclophosphamide (54.5% versus 69.5% 2-year cumulative survival rate, $P < 0.05$). Some SCID patients infected at the time of transplant cannot, however, tolerate a conditioning prior to BMT.

Graft failure and GVHD. Several factors have been proposed to account for the surprisingly high graft failure rate of HLA-nonidentical T cell-depleted marrow transplants in SCID patients. In the murine SCID model, it has been demonstrated that NK cells contributed to failure of marrow engraftment. This could be prevented by a 4-Gy total body irradiation (TBI). NK cells may also prevent engraftment in SCID patients [51, 54]. Other studies have shown disparate results [16]. NK cell activity is absent in some SCID syndromes in which a better engraftment rate is observed. Other mechanism(s) could be also involved. Engraftment of maternal T cells is frequent (30–50%) in SCID patients. They could contribute to graft rejection as suggested in a recent survey of results from one center (W. Friedrich, personal communication). It has, therefore, been suggested that the mother be the marrow donor if a conditioning regimen cannot be used pretransplant. Maternal T cells, however, are frequently oligoclonal and likely have a poor capacity to induce graft rejection, in the same way as they seldom induce GVHD in SCID recipients [58]. Persistence of maternal T cells after HLA-nonidentical BMT may lead to chronic GVHD-like features.

Provided that T cell depletion of marrow inoculum is sufficiently profound leading to infusion of less than 1×10^5 T cells/kg, the risk of severe GVHD is limited. Indeed, recipients of marrow treated by soybean agglutination and sheep erythrocyte rosetting rarely developed GVHD.

Recovery of immune function. The kinetics of development of T and B lymphocyte function are slower in recipients of T cell-depleted, HLA-incompatible marrow than in recipients of HLA-identical marrow [16, 22, 51, 56, 71]. Indeed, we found that full T and B lymphocyte-mediated responses were present at day 186 in recipients of HLA-identical transplants but at day 505 in recipients of HLA-nonidentical transplants [71].

Factors associated with slower development of T cell function are non-utilization of a conditioning regimen and GVHD. B cell function fails to develop in approximately 40% of transplanted patients. This is apparently strongly correlated with an absence of donor B cells and thus with lack of a conditioning regimen. Van Leeuwen et al. [67], however, found in a recent survey of the Leiden group experience that in nine long-term survivors of haploidentical BMT for SCID, IgG isotype antibody responses were detectable whether donor B cells were present or not. Three patients only had IgA deficiency. It is difficult at this time to understand the observed discrepancy.

An intrinsic B cell defect may be involved, although in some cases host B cells were shown to produce antibodies following HLA-identical and -nonidentical [26, 50, 67] BMT. Ineffective T cell stimulation (because of donor-derived MHC class II restriction) is excluded since (1) donor and recipient always share at least one HLA haplotype, and (2) engrafted MHC class II responsive (helper) T cells can recognize antigen in the context of host HLA class II antigens, as previously found in murine models of BMT.

It has been found that patients with selective engraftment of donor T cells exhibit T cell 'autoreactivity' specific for donor MHC class II molecules [21]. These results might be accounted for by the absence of donor-derived MHC class II-expressing cells of the monocyte lineage in host thymus, resulting in a lack of negative selection. The latter cells have been previously shown to be required for negative selection of autoreactive T cells [45, 63]. As in FLT recipients, it was demonstrated that in HLA-haploidentical T cell-depleted marrow recipients, anti-host T cell clones could be derived [33, 59]. Lack of reactivity in vivo appears to be associated with inability to produce high levels of cytokines including IL-2, IL-4, IL-5, IL-10, interferon-γ and granulocyte colony-stimulating factor (G-CSF) [4].

Bone marrow transplantation for other immune deficiencies

In 1968, Bach et al. [6] were successful in achieving HLA-identical lymphoid engraftment in a patient with WAS. Since then, allogeneic BMT has been found effective in at least 16 distinct non-SCID immune deficiencies (Tables 1, 2).

The conditioning regimen

The main difference compared to SCID patients is the usual requirement of a conditioning regimen to achieve engraftment [50, 53]. A few exceptions have been noted

Table 2 Survival in non-SCID congenital immune deficiency syndromes

Syndrome	Proportion (%) surviving to adulthood		
	No BMT	HLA-identical BMT	HLA-non-identical BMT
T cell immune deficiencies			
Omenn syndrome	0	80	50
Purine nucleoside phosphorylase deficiency	0	50	–
MHC class II deficiency	0	50	35
Others	0	60	50
Wiskott-Aldrich	50	> 90	40
XIGM	20	> 90	
XLP	25	> 90	
Phagocytic cell disorders			
Agranulocytosis	90–100	> 90 (see text)	–
Leukocyte adhesion deficiency			
severe phenotype	0	> 70	75
moderate phenotype	50		
Chronic granulomatous disease	80–90	70–90 (see text)	–
Chediak-Higashi syndrome	5	90	20 → 50
Familial hemophagocytic lymphohistiocytosis	0	70	

BMT, Bone marrow transplantation

particularly in the treatment of profound T cell immune deficiency such as Omenn's syndrome. Initially, TBI was used to prepare immune deficiency patients for BMT. It was later recognized that TBI could be safely replaced by busulphan at dosages (16–20 mg/kg) that did not produce comparable adverse late effects. It was also found that such doses were sufficient for young patients (below the age of 2–4 years), despite the reduced bioavailability of busulphan in this age group [11]. There is now a general consensus on the use of 16–20-mg/kg busulphan together with 200 mg/kg cyclophosphomide as a conditioning regimen for patients with non-SCID immune deficiency treated by HLA-identical BMT [11]. One should, however, notice that recent studies have demonstrated high busulphan disposition variability among young children (by a factor of 6) [68]. These results favor a precise individual adjustment of busulphan. This regimen may, however, be insufficient in young patients with phagocytic cell disorders (see below). Alternatively, other myeloablative drugs could be utilized such as thiotepa.

Wiskott-Aldrich syndrome

After the partial correction obtained in WAS in 1968, full correction was achieved in 1978 [53] following the use of an appropriate conditioning regimen. HLA-identical BMT has been found efficient in 90% of patients who had an HLA-identical sibling [13, 47, 52]. All aspects of WAS are corrected by marrow transplantation, including the eczema, autoimmunity and the risk of lymphomas. This indicates that disease complications are related to the immune deficiency. Similarly, thrombocytopenia and bleeding tendency disappear after BMT. HLA-identical BMT is recommended for patients with WAS and should be performed as early as possible.

T cell immune deficiencies

Extension of BMT treatment to T cell immune deficiencies has not been as successful, although cure of a number of them has been achieved. Overall, HLA-identical BMT for various T cell immune deficiency syndromes, including Omenn's syndrome [35, 46], MHC class II deficiency [42], ZAP 70 deficiency, purine nucleoside phosphorylase deficiency [14, 18] and others [7, 8], cures approximately half the patients (a figure significantly inferior to that obtained for other immune deficiencies).

It appears that failure is often related to viral infection or organ failure. These complications are directly related to the pretransplant clinical status. Since the immune deficiencies are less pronounced than in SCID, they are compatible with life for several years, although infections caused by intracellular microorganisms develop and are exacerbated following marrow ablative and immune-suppressive conditioning. These immune deficiencies should be treated by BMT as early as possible to offer maximal likelihood of cure. Indeed, in a European survey, transplants performed before the age of 2 years showed a 79% success rate versus 48% for children over 4 years of age (including all non-SCID immunodeficiency diseases) [29].

Hyper IgM syndrome (CD40 ligand deficiency). X-linked hyper IgM syndrome is caused by mutations of the CD40L gene [48]. This syndrome is severe because it induces opportunistic infections that are often fatal during childhood. BMT is the sole curative treatment and has indeed been found to be successful [23, 64].

XL proliferation syndrome (XLP-Purtilo's syndrome). XLP is a fatal condition [62]. It is caused by poor control of Epstein-Barr virus (EBV) infection, although the disease mechanism is still unknown; BMT or cord blood transplantation can cure the disease and is, therefore, indicated provided a matched donor is available [28, 36, 69, 72].

Phagocytic cell disorders

Some inherited phagocytic cell disorders remain lethal, either because of the severity of infections in the absence of alternative therapy, or because of the onset of specific complications such as the 'acute phase' of the Chediak-Higashi syndrome.

Leukocyte adhesion deficiency (LAD) type 1 is a rare disease characterized by defective expression of the β2 integrin subunit shared by the leukocyte adhesion proteins. Its complete absence leads to the severe phenotype of LAD, which predisposes to severe bacterial infections, often causing death within the first years of life. HLA-identical BMT is the treatment of choice for this condition. Aggressive conditioning including the use of etoposide or TBI may be required for appropriate marrow ablation [26, 60, 65]. As shown in Table 2, results of allogeneic BMT have been satisfactory. Similarly, HLA-identical BMT can cure the hematological manifestations of the Chediak-Higashi syndrome [37], of familial hemophagocytic lymphohistiocytosis [10] and of immunodeficiency with partial albinism. In these instances, BMT prevents relapse of lymphohistiocytic activity. It is worth noting that mixed chimerism is sufficient to achieve disease control. This indicates that an abnormal regulatory process, rather than a malignant process, underlies these conditions. Use of TBI is not necessary; a combination of etoposide, busulphan and cyclophosphamide appears to be both a safe and efficient conditioning regimen for these diseases.

Although allogeneic BMT has been demonstrated to cure agranulocytosis and chronic granulomatous disease (CGD), alternative therapies currently offer good quality long-term survival (G-CSF in agranulocytosis, and cotrimoxazole and possibly interferon-γ in CGD). BMT should thus not usually be recommended for these conditions. However, some CGD patients still develop life-threatening fungal infections and/or granulomas. It has, therefore, been advocated that BMT from an HLA-identical donor could be proposed in this setting. It has recently been shown that 9 out of 11 BMT performed in CGD patients were successful despite ongoing aspergillus infections in 3 cases (R. Seger, personal communication).

The long-term (≥ 10-year) outcome of HLA-identical BMT for most immune deficiency syndromes appears reasonably satisfactory. Correction of the underlying deficiency is sustained, despite frequent mixed chimerism in the absence of TBI usage. Sequelae are generally limited to consequences of the primary disease. Chronic GVHD is of limited frequency in these young patients [26]. Over the last decade, increasing numbers of allogeneic transplants have been performed for immune deficiency syndromes.

Younger age at the time of BMT is associated with excellent outcome (79% below 2 years of age versus 48% over 4 years age) [29], and progress has been made in recent years, particularly in infection prevention (intravenous immunoglobulin, antiviral drugs) and GVHD prophylaxis (combination of 'short' methotrexate and cyclosporin). For instance, in Europe, the success rate for BMT performed since October 1985 (up to March 1991) was 81.5% versus 52% before October 1985.

Alternative donors

Following the improvement in the results of HLA-nonidentical BMT for the treatment of SCID syndromes, a similar approach has been taken for the treatment of the other lethal immune deficiencies. Unfortunately, results have been disappointing because of a high incidence of graft rejection (up to 75%) [25, 26, 28] and of infectious complications. More recently, successes have been obtained using matched unrelated donors (MUD) [1, 24, 41]. In a survey of matched unrelated donor BMT, Kernan et al. [41] indicated that the success rate of BMT for patients with inborn errors was 50%. Filipovich et al. [24] have reported the success of MUD-BMT in 6/8 SCID recipients, 2/2 patients with WAS and 2/2 patients with Chediak-Higashi syndrome. Some success using HLA partially incompatible unrelated donor marrow has also been reported, especially when the degree of incompatibility was restricted to one HLA antigen and the marrow was T cell depleted [1].

Anti-LFA 1 antibody pretreatment for graft rejection

In the mid-1980s, we were surprised by the success of three HLA-nonidentical BMT for patients with the severe phenotype of LAD [44]. This has since been confirmed in 7 out of 9 patients with the severe phenotype of LAD who received an HLA-nonidentical BMT: engraftment occurred in all 7, who are alive with partial or full correction of the LAD [65]. This is in sharp contrast to the engraftment rate of marrow transplanted under the same conditions to other immune deficiency patients (excluding SCID), where the engraftment rate was 26% [25].

It was, therefore, postulated that the defective expression of the LFA-1 molecule on graft rejection effector cells (cytotoxic T cells and NK cells) impaired cell contact with donor marrow cells and thereby permitted engraftment [66]. This led to the infusion in vivo of a monoclonal anti-LFA-1 (CD11a) antibody to inhibit LFA-1/ligand interactions.

In a multicenter trial, we showed that a 10-day course of 0.2 mg/kg antibody per day reduced the graft failure rate from 74% to 28% following transplantation of T cell-depleted marrow in patients with immune deficiencies and osteopetrosis [25, 66]. No late rejection occurred. Acute GVHD was observed in 35.5% of cases, and chronic GVHD in 12.9%. The survival rate with a functioning graft was 47% in 42 patients (median follow-up 50 months), instead of 20% in similar patients who did not receive the anti-LFA-1 antibody. Updating of these data show a 74% engraftment rate with 45% long-term survival in 38 immunodeficient patients who were treated with anti LFA-1 antibody, while engraftment occurred in only 37.5% and survival in 20.8% of 24 patients similarly treated except for anti LFA-1 antibody [28]. Addition of an injection of an anti-CD2 antibody might further improve engraftment [40].

Other experimental strategies

Delay in the recovery of T and B cell function (6–40 months) causes significant infectious complications that remain a major concern in recipients of T cell-depleted HLA-nonidentical transplants. For example, 16 of 71 patients who underwent two or three HLA antigen-incompatible T cell-depleted BMT for primary immunodeficiencies (excluding SCID) had EBV-induced B lymphocyte proliferative syndromes; 10 of them died from this compli-

cation. This complication is particularly frequent in WAS patients who undergo HLA-nonidentical BMT. In a recent European survey, 39% of such patients (compared with 12% of patients with T cell deficiencies, and 3% of those with SCID) developed a lymphoproliferative disorder after HLA-nonidentical BMT (EBMT registry, unpublished data). This may have been caused by poor T cell control of EBV replication.

Rummelhart et al. [57] have described success in 3 of 4 WAS patients, while Brochstein et al. [13] reported success in only 1 out of 6 patients with the same condition. These contrasting results stress the need for careful evaluation of the suitability of HLA-haploidentical BMT for these patients who lack both HLA genetically identical and MUD-HLA. Indications depend on the patient's clinical status as well as the prognosis defined by the type of immunodeficiency, age (results are poorer above 2 years of age) and degree of HLA incompatibility. For instance, Mullen et al. [47] recently stressed that splenectomized WAS patients could survive at least until adulthood. Nevertheless, WAS patients who developed refractory thrombocytopenia and/or severe autoimmune manifestations could be considered for HLA-haploidentical BMT (Table 2). Similarly, patients with functional T cell immunodeficiencies (including HLA class II deficiency) have a poor prognosis (median survival 5–8 years) in the absence of BMT [42]. Apart from LAD (see above), the suitability of HLA-haploidentical BMT for patients with phagocytic cell disorders remains highly debatable given the high risk of failure (Table 2). It is possible though that the Chediak-Higashi syndrome, once an acute phase has occurred, or familial hemophagocytic lymphohistiocytosis could be good indications.

Transplantation of very high numbers of stem cells is a tempting approach to circumvent graft failure. Aversa et al. [2] have provided promising results in adults with malignancies. Other strategies aimed at selectively inhibiting graft rejection have been developed experimentally and could be of potential benefit: anti-CD4 and anti-CD8 antibody infusions promote engraftment of H-2-incompatible marrow in mice [20]. The major residual problem lies in the prolonged immunodeficiency that follows T-cell-depleted stem cell transplantation. This 3– to 6-month period is characterized by a profound T cell lymphocytopenia, which is responsible for lethal infections including EBV-induced B lymphocyte proliferative disorder. The latter complication can be, in some instances, efficiently treated by anti-B cell monoclonal antibody or infusion of EBV-specific cytotoxic T cells from the donor [28].

The ultimate goal would be to shorten the window during which T cells are virtually absent. Manipulation with cytokines, such as IL-7 [12], or infusion of low T cell numbers transduced with a suicide gene depleted of alloreactivity [19] toward the host might represent possible solutions.

Alternative therapies

Alternative treatments (to BMT) have been devised for some congenital immune deficiencies over the last decade. For instance, congenital agranulocytosis is efficiently treated by daily subcutaneous injections of G-CSF. The prognosis of chronic granulomatous disease has been profoundly modified by the prophylactic use of antibiotics (cotrimoxazole) and possibly of interferon-γ [39].

Adenosine-deaminase (ADA)-negative SCID can now be treated by a weekly intramuscular injection of bovine ADA covalently coupled to a carbohydrate, polyethyleneglycol (PEG-ADA), that stabilizes ADA and diminishes its immunogenicity. More

than 40 patients have currently been treated worldwide [38]. In most, a significant improvement occurred that allowed normal or close-to-normal lifestyle.

It is possible that gene transfer into mature T cells as shown for ADA deficiency [9] or into stem cells would be of benefit to immunodeficient patients. SCID, where a selective advantage conferred to transduced cells is expected, represent the best disease models (ADA deficiency, XL SCID, etc.), although gene integration into non-cycling stem cells remains an unresolved issue. Cord blood gene transfer might also be envisaged, as attempted at birth in three ADA-deficient patients [43].

In utero transplantation

Most primary immunodeficiencies can now be diagnosed in utero. If the family does not wish to terminate the pregnancy, stem cell transplantation in utero is an option as shown by the success of HLA-haploidentical $CD34^+$ transplantation into two SCID fetuses [30, 70].

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