Session: Yin and Yang of Autoimmunity and Immunodeficiencies in Hematology

Title: Allogeneic Hematopoietic Stem Cell Transplantation in Adults with Primary Immunodeficiency
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Abstract
With recent advances in genetic sequencing and its widespread adoption for clinical diagnostics, the identification of a primary immunodeficiency (PID) as the underlying cause of diseases presenting to hematologists including refractory autoimmunity, cytopenias, immune dysregulation and hematological malignancy, is increasing, particularly in the adult population. Where the pathogeneic genetic variants are restricted to the hematopoietic system, selected patients may benefit from allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Although generally accepted that *early* allo-HSCT (ie. in infancy or childhood) for PID is preferable, this is not always possible. The clinical phenotype of 'non-severe combined immune deficiency (SCID)' forms of PID can be very heterogeneous, due in part to the high number of genetic and functional defects affecting T-, B-, NK-cells, neutrophils and/or antigen presentation. As a result, some patients have less severe disease manifestations in childhood and/or a later 'de novo' presentation. For others, a delayed diagnosis, lack of a genetic diagnosis or a previous lack of a suitable donor has precluded prior allo-HSCT.

Specific issues, which make transplanting adult PID patients particularly challenging will be discussed below, including: understanding the natural history of rare diseases and predicting outcome with conservative management alone; indications for and optimal timing of transplant; donor selection; conditioning regimens; and PID-specific transplant management. The role of gene therapy approaches as an alternative to allo-HSCT in high risk, monogenic PID will also be discussed.

Key Words
Allogeneic hematopoietic stem cell transplant (Allo-HSCT); primary immunodeficiency (PID); inborn error of immunity (IEI); gene therapy (GT); algorithm.

Learning Objectives
1. Understand and evaluate the role of allo-HSCT in adults with PID. Although allo-HSCT can be curative, patient selection and optimal timing of transplant is complex.
2. Understand the importance of always taking a careful family history in younger adults presenting with refractory autoimmunity, HLH or lymphoproliferation/lymphoma to help identify an underlying PID.
3. Understand the need to integrate genetic, laboratory, clinical and family history data to predict prognosis.
4. Understand that alternative therapies instead of, or as a bridge to, transplant are increasingly available.

Clinical Cases
Figure 1 illustrates the clinical course of 2 adult PID patients with (i) autoimmune lymphoproliferative syndrome (ALPS) and (ii) hypomorphic Rag2 deficiency (combined immune deficiency)[1]. Both patients presented in childhood or adolescence with anemia (AIHA in patient 1 and red cell aplasia in patient 2). Both subsequently underwent allo-HSCT in adulthood.

Patient 1 presented with AIHA at the age of 12 weeks, which was successfully treated with steroids and ivIg. However, refractory ITP and splenomegaly developed soon after requiring splenectomy at the age of 2 years. There was a known family history of ALPS affecting her mother and 2 brothers. Genetic diagnosis was made in early childhood. Childhood and adolescence were complicated by inflammatory arthropathy, colitis secondary to lymphocytic infiltration of the gut mucosa, extensive genital HSV infection and recurrent, widespread reactive lymphadenopathy. Classical HL was diagnosed aged 18 years on inguinal lymph node biopsy. The decision to proceed to allo-HSCT was made after relapse of HL 2 years later at the age of 20 years.

Patient 2 initially presented at 14 years of age to dermatology with a non-traumatic leg ulcer and localized granulomatous skin lesions. There was no response to hyperbaric oxygen or topical steroids. Other therapies were declined. There was no family history of immunodeficiency. At 16 years he was noted to have hypogammaglobinemia and T cell lymphopenia. He was started on immunoglobulin replacement therapy but soon after developed severe, refractory red cell aplasia. Two years later he developed a clonal NK cell proliferation (no T cell clone detected) and genetic diagnosis was confirmed. He was then referred for allo-HSCT, which was performed at the age of 20 for NK cell clonal proliferation and associated bone marrow failure.

Introduction

For the last 30 years, allo-HSCT has been considered 'standard of care' and the major therapeutic option for children with serious inborn errors of immunity or primary immunodeficiency (PID)[2]. Early transplant is particularly important for infants or children presenting with serious or life-threatening infections, as without definitive treatment, patients with severe PID, such as severe combined immune deficiency (SCID), rarely survive beyond 1 year of age. Until recently, the vast majority of transplant procedures for PID were performed in childhood, with clinical expertise in these rare diseases residing almost exclusively in pediatric specialist centers.

However, as an increasing number of non-transplanted PID (almost all non-SCID) patients are now surviving, or only being diagnosed, beyond childhood, the majority of patients with PID are now found within the adult population[3]. The role of allo-HSCT for adults is therefore being carefully evaluated.

Uncorrected PID can lead to recurrent, progressive or life-threatening infections, autoimmunity, autoinflammatory manifestations and malignant disease (typically lymphoma or epithelial neoplasia). This places a significant burden on healthcare resources with frequent hospital admissions, the need for ongoing antimicrobial therapy and expensive therapy biological modifying drugs (e.g.monoclonal antibodies, mAbs) and immunoglobulin replacement therapy. The result can be poor quality of life and early death.

Within the last 3 years, evidence has been published that demonstrates selected adults with PID can be transplanted safely using reduced intensity conditioning regimens, achieving outcomes equivalent to that achieved in pediatric transplant practice[4,5]. However, questions remain regarding the indications for and optimal timing of transplant in adults.

Basic principles of allo-HSCT for non-malignant disease

Allo-HSCT allows the replacement of defective or dysregulated recipient immune and hematopoietic cells with long-term repopulating cells from a healthy donor. Apart from gene therapy, in the case of selected monogenic forms of PID, it is the only potentially curative therapy. PID patients undergoing allo-HSCT for non-malignant diseases do <u>not</u> benefit from the graft-versus-malignancy effect, unless they have a prior history of blood cancer (most commonly lymphoma). The prevention of graft-versus-host disease (GVHD) and successful long term immune-hematopoietic engraftment are therefore of paramount importance. Long-term stable donor chimerism in the previously affected cell lineage/s and correction of the clinical phenotype is the ultimate goal of transplant.

Major factors influencing outcome following allo-HSCT are broadly independent of the underlying disease and include preceding comorbidity, active infection at the time of transplant, end organ function, type of donor and age of the patient[6,7]. For PID patients, the shorter the time from onset of clinical symptoms to transplant, the lower the risk of developing resistant or refractory infections (bacterial, viral or fungal) and end organ damage due to uncontrolled inflammation or autoimmunity.

Who and when?

One of the biggest challenges for hematologists and immunologists looking after adults with PID is knowing 'which patient' and 'when' to refer for consideration of allo-HSCT. The clinical decision is straightforward if the underlying condition is known to be life-threatening or life-limiting and the patient has a predicted poor prognosis with conservative management alone. For rarer forms of PID the natural history with conservative management alone is often not known, which necessitates careful, shared decision making with a wider team of specialist healthcare

professionals, the patient and their family. This is essential for the patient to be fully informed of the risks and uncertainties. However, as with all potential allo-HSCT recipients, for maximal benefit, transplant must occur before serious end organ damage has occurred, which could make the risk of transplant unacceptably high. With respect to comorbidities, the HCT-CI score (a validated co-morbidity index predicting high risk patients for HSCT in the setting of hematological malignancies) has recently been validated as having predictive value for patients with non-malignant diseases including PID[8], with the caveat that most patients included in the analysis were children.

Background on natural history of PID in adults and data in allo-HSCT

Every year an international expert committee provides a genotypic and phenotypic classification of all human inborn errors of immunity. There are now 406 distinct clinical disorders with 430 different gene defects[1], and although individually rare, these disorders are enriched in patients with hematological malignancies and autoimmune cytopenias. In the more recent classifications, the concept of "pure" immunodeficiencies with predisposition to infections has been replaced with newly described autoimmune, auto-inflammatory conditions or syndromal disorders associated with immunodeficiency. Many of these disorders can be cured by allo-HSCT, while in syndromal disorders only the hematopoietic portion of the disease can be corrected, which may nevertheless be indicated with improved survival and quality of life in selected patients.

PID patients who survive to adulthood without having undergone an allo-HSCT in infancy or early childhood, will almost all have some residual immune function, even if grossly abnormal. Therefore, the majority of non-transplanted adult PID patients have 'non-SCID' PID, such as combined immune deficiency (CID, affecting both cellular and humoral immunity), CID with syndromic features, predominantly antibody deficiencies, diseases of immune dysregulation, phagocytic/innate immunity disorders, and auto-inflammatory disorders[1]. In many of these, the predominant clinical features include immune dysregulation, such as refractory autoimmunity, lymphoproliferation or autoinflammation; the presentation may be much later and the role and timing of allo-HSCT is currently less clear.

Studies that address the long-term prognosis of PID patients are very difficult to perform, but natural disease outcome data are desperately needed to be able to determine the optimal role of allo-HSCT[9] particularly with PID that are newly described or have wide phenotypic heterogeneity in disease severity. For example, the majority of patients with common variable immunodeficiency (CVID), the commonest form of PID in adults, have an excellent prognosis and few complications if receiving adequate immunoglobulin replacement therapy, whilst others with additional features of immune dysregulation develop severe complications of the lung and liver and have a very poor prognosis[10]. Published retrospective data for HSCT in adult patients with complex CVID have indicated worse outcomes than for other PID following transplant[11] underlining the need for better information to select patients and timing for HSCT in CVID. For other PID subtypes there is accumulating evidence of continued disease progression throughout adulthood, including CGD, XLP and CD40L Deficiency[12-15] resulting in serious morbidity and mortality in these studies. Importantly, for other PID, such as DOCK8 Deficiency recent studies have indicated that a plateau in OS may be reached in adulthood, but nevertheless there is a progressive fall in EFS with conservative management alone[16].

There is a growing body of publications detailing outcome data on approximately 200 allo-HSCT for PID in adults[4,5,11,17-25]. Additional data on a similar number of adults has been published in abstract form. In the majority of published series, the overall survival was equivalent to that achieved in children and infants being in excess of 80% at a median follow-up of between 14 months and 5 years. The majority of data relates to patients with CGD, HLH and GATA2 deficiency, for whom the data is therefore most robust. The published data is summarised in Table 1.

As published adult transplant outcome data is limited for most PID subtypes a large retrospective study is underway co-ordinated by the Inborn Errors Working Party (IEWP) of the EBMT to address this issue. Ideally, decisions about allo-HSCT would be based on prospective randomised studies. However, these are not feasible in rare and ultra-rare diseases. In an attempt to utilise retrospective data, a large Franco-British retrospective case-controlled study is comparing outcomes of transplanted and matched non-transplanted adults with various subtypes of severe PID with the aim of identifying whether allo-HSCT in adulthood confers genuine benefit in terms of overall survival (OS), disease free survival (EFS) and cumulative incidence of PID-associated events. Provisional, unpublished data suggests that allo-HSCT in adult PID patients may prevent the progressive morbidity associated with PID in adults and outweigh the negative impact of TRM (Cheminant M, Fox T, et al., unpublished).

Optimal timing of allo-HSCT in adults with PID

In pediatric practice, 'well' infants/children with a diagnosis of severe PID are typically offered a pre-emptive allo-HSCT prior to the development of significant infections, autoimmunity and/or autoinflammation in order to reduce the risk of peri-transplant complications. Where the transplant-related mortality (TRM) risk is small and the severity/prognosis of the underlying disease is well understood *and* predictable, the 'pre-emptive' use of allo-HSCT is justifiable; examples of specific PID in this category include SCID, chronic granulomatous disease (CGD), Wiskott-Aldrich Syndrome (WAS) and primary HLH. For specific PID with well described high risks of developing lymphoma or other malignancies, there may be a role for pre-emptive allo-HSCT after careful discussion with the patient. However, for adults with known PID who remain *clinically well* beyond early adulthood, the risk-benefit balance of transplant is less clear, particularly for PID subtypes with less well studied allo-HSCT outcomes. In these circumstances proceeding to transplant without a clear 'trigger' or indication is *not* currently recommended.

The majority of adult PID patients referred for transplant are not at immediate risk of death but are at risk of ongoing recurrent, progressive or life-threatening infection, autoimmunity, autoinflammation and malignant disease, typically lymphoma or epithelial neoplasias. For other younger adults, there may have been gradual disease progression through adolescence and therapeutic options at the time of referral include a trial of biologics and/or immunomodulatory therapies (where appropriate) or allo-HSCT. In rarer or more recently described PID the long-term efficacy and toxicity of non-transplant treatment modalities (examples include PI3Kd inhibitors, jak/stat inhibitors or abatacept) is also unknown. Whether to use such agents (singly or sequentially) as a 'bridge to transplant' by reducing PID-associated complications pre-transplant with the aim of reducing TRM or using them longer-term, which may eventually lead to refractoriness is open to discussion. However, some universal truths of transplantation can guide us – outcomes are generally better when disease is in remission, the recipient is younger and has less co-morbidities at the time of transplant. Such uncertainty requires haematologists and immunologists to work together effectively to build consensus and where possible recruit patients to international studies.

It is well understood that patients proceeding to transplant incur an immediate risk associated with transplant conditioning and immunosuppression. If the TRM is high due to comorbidities at the time of transplant, the potential benefit from transplant can be lost for a given individual. Because many patients with PID have several comorbidities at the time of transplant, early differences in survival between transplanted and non-transplanted patients can be small or non-existent because of the negative impact of a high TRM.

There are clear data demonstrating that within pediatric cohorts transplanting earlier in the disease course improves outcomes[26-29]. However, in adolescent and young adult cohorts, the impact of age appears less significant[4,5]. There are very few older adults (> 50 years) included in published series detailing outcome following allo-HSCT for PID patients [(4,5, 11, 18-25)], and until further data is available, patients should only be transplanted with a very clear indication.

Similarly, for patients with very rare PID diagnoses or with PID for which the number of transplants performed to date are very small (eg., <10 reported cases) the data to support allo-HSCT over trials of biologics/targeted therapies is likely to be scarce.

Unfortunately, in real-world clinical practice, many adult PID patients are referred for consideration of allo-HSCT too late. Typically, referrals for transplant are triggered by a severe PID-related event (for example, a life-threatening infection, malignancy or major organ dysfunction), which act as a declaration of the severity of the clinical phenotype and predictor of future complications. If these complications do not respond promptly to treatment, the 'window of opportunity' for transplant may be missed.

Indications for allo-HSCT in adults with PID

Figures 2 and 3 suggest algorithms for identifying adult PID patients who may benefit from allo-HSCT and for whom referral to a specialist transplant unit is appropriate. The process requires close multi-disciplinary patient-specific discussion between the immunology and transplant teams. Additional input from pediatric immunologists who have previously cared for the patient and/or other family members may be beneficial. Decisions are made with consensus based on the experience of the group also taking account paediatric transplant data, any reported adult transplant outcomes, known natural history of the specific condition and international advice for very rare cases.

In the UK we have established a national virtual multi-disciplinary team (MDT) expert panel to discuss all adults with PID being considered for allo-HSCT. The MDT serves to share expertise, discuss diagnosis, further investigations where indicated, appropriateness of transplant, conditioning regimens and donor selection. Discussion of non-transplant treatment options is also included.

In summary, for patients who have either known pathogenic variants in PID genes (Figure 2) and/or a family history of serious PID, or clinical and laboratory findings consistent with PID (Figure 3) the currently accepted indications for transplant include:

(a) Recurrent, persistent or life-threatening infections (bacterial, fungal and/or viral, including chronic active EBV, CAEBV1);
(b) Refractory autoimmune cytopenias;
(c) Bone marrow failure;
(d) Hemophagocytic lymphohistocytosis (HLH);
(e) PID associated hematological malignancy; and/or
(f) Refractory autoinflammation (eg. severe colitis).

Evolution of clinical cases
Patient 1 was referred for allo-HSCT at the age of 20 years following relapse of HL, fulfilling the indication criteria of PID associated hematological malignancy/lymphoma. Patient 2 was referred for allo-HSCT after the development of a clonal NK cell proliferation and associated bone marrow failure, fulfilling two of the accepted transplant indications.

The role of genetic diagnosis and family history
It is our practice to perform genetic sequencing for all PID patients being considered for HSCT, if this has not already been done. Although it is sometimes necessary to proceed to HSCT for adults with PID, based on clinical disease progression alone, it is our preference to know the precise genetic diagnosis, which permits maximal prior consideration of natural history, published transplant experience and specific extra-hematopoietic features of the disease.

For many patients, their underlying PID is well characterized – genetically, functionally and clinically, but treatment decisions can still be challenging. As with other rare or ultra-rare diseases predicting outcome with conservative management alone is difficult due to very small numbers of affected individuals and limited published data. Similarly, if the genetic variant has only recently been described as potentially pathogenic or is a variant of uncertain significance (VUS), therapeutic decisions need to be based on the clinical picture alone, including the cumulative rate of serious PID-related complications, family history and quality of life.

For other adult patients, the genetic cause remains undefined despite sequencing or the urgency of transplant precludes obtaining genetic sequence results in advance. It should be remembered that serious monogenic PID are, in general, more likely to present at an early age, resulting in a lower rate of genetic diagnosis for PID presenting in adulthood.

For some PID disorders, members of the same family/kindred sharing the same genetic variants can have highly variable clinical presentations, such as NFkB1 Haploinsufficiency[30], LRBA Deficiency[31] and CTLA4 Deficiency[32] so that some have severe disease and others are asymptomatic. The reasons for this are poorly understood but may relate to environmental triggers, such as infection, other genetic background and epigenetic factors. Highly variable clinical phenotypes may also arise as a result of incomplete penetrance, variable expressivity as well as gain of function (GOF) or loss of function (LOF) variants in the same gene and finally, hypomorphic ('leaky') defects where residual gene expression and function may be preserved. Clinical case 2 illustrates exemplifies this. Rag gene mutations can cause SCID with life-threatening presentations in infancy if recombinase activity is lacking, whilst hypomorphic mutations in the same PID gene, which permit 5-30% recombinase activity, result in a combined immune deficiency (CID) clinical phenotype, often much later in onset[33].

Where possible, functional analyses of genetic diagnoses should be performed prior to transplant. Exceptions include rapidly deteriorating patients requiring urgent intervention and/or novel genetic variants for which no validated functional assay exists. Functional assay development for novel variants predicted to be pathogenic is also critical for the informed selection of HLA-matched family donors, who may be heterozygous carriers for the same genetic variant. This is complicated further in phenotypically variable and late onset PID. In such cases, although TRM risks are generally higher with unrelated donors, these may be preferable.

In all cases of adult PID being considered for allo-HSCT the final decision is a clinical one and the absence of genetic and functional data should not necessarily preclude transplant if the clinical evidence is compelling.

Evolution of clinical cases

Both patients described in Figure 1 have heterozygous pathogenic variants in PID associated genes. Patient 1 had a heterozygous pathogeneic variant in the death domain (DD) region of TNFRSF6 gene (also known as Fas and CD95), resulting in defective apoptosis in lymphoid cells (p.I246T). This patient also had other affected family members (mother and 2 brothers) with a milder clinical phenotype, illustrating the additional complexity resulting from varied clinical phenotypes within the same kindred and/or incomplete penetrance. Patient 2 was found to have compound heterozygouspredicted pathogenic variants in the RAG2 gene [c.104G>T (Gly35Val)/het and c.814G>A (Val72Ile)/ het and c.965T>C (Met 322Thr)/ Het]. This patient had no family history of PID.

Donor Selection

Preferred stem cell donors are 12/12 Human Leukocyte Antigen (HLA)-matched, CMV sero-matched, *unaffected* related donors in order to minimise TRM and the risk of GVHD. However, most series published to date include large numbers of matched or one antigen mismatched unrelated donor transplants (MUD, typically 10/10 or MMUD, typically 8/10 or 9/10), with good results. HLA-matched family members should be genetically screened if a known pathogenic variant has been identified in the recipient.

In pediatric practice, unmanipulated haploidentical transplants using PTCy (post-transplant cyclophosphamide) and αβTCR/CD19 depleted haploidentical (Haplo) transplants have achieved excellent results for infants and children with PID and other inborn errors, where no matched donors are available[34]. However, there are currently insufficient published data in older PID patients to definitively support the use of haploidentical donors in preference to MMUDs. In non-PID settings, a number of prospective RCTs are being planned to determine the safety and efficacy of MMUD vs Haplo in patients > 18 years at HSCT.

Conditioning regimens

PID patients surviving to adulthood typically have residual functional cellular immunity necessitating conditioning to permit engraftment of allogeneic stem cells and prevent graft rejection, as a consequence, unconditioned transplants are *not* indicated.

In order to limit TRM in older PID patients either reduced toxicity or reduced intensity conditioning is recommended in all cases. However, it is increasingly evident that achieving stable donor chimerism is important for PID transplants and this is not always reliably achieved with reduced intensity conditioning regimens. Typically, 10-20% of children undergoing allo-HSCT for PID require a second procedure or DLI, with HLA mismatch and the use of RI conditioning being significant risks[35].

Most experience to date has been with Flu/Bu, Flu/Mel or Flu/Treo based reduced intensity conditioning (RIC) incorporating serotherapy (Alemtuzumab or ATG) for *in vivo* T cell depletion. Recent improvements in conditioning regimens for non-malignant diseases such as PID, have primarily come from pediatric centers and include the introduction of Treosulfan[36,37], the use of targeted bulsulfan[24,38] and personalised serotherapy dosing[34,35,39].

The use of PTCy or αβTCR depletion to remove alloreactive T cells has facilitated the use of haploidentical donors in older recipients with hematological malignancies, without prohibitive risks of GVHD and/or graft rejection[40]. Similarly, in pediatric series these approaches have been used with excellent results in non-malignant disease and PID[41-43].

However, as the cumulative experience transplanting older adults with PID using haploidentical donors remains very small, further studies are warranted.

Evolution of clinical cases

Patient 1 had an unaffected sibling who was HLA-matched and CMV-matched (+/+). Patient 2 had a fully matched unrelated donor, also CMV matched (-/-). Both patients received reduced intensity conditioning with fludarabine, melphalan and alemtuzumab was used, together with single agent ciclosporin as GVHD prophylaxis.

Adult PID specific transplant management

Additional pre-transplant investigations are indicated in many PID patients to document the presence or absence of specific pathogens, anti-microbial sensitivities and/or degree of organ specific inflammation. Examples include: colonoscopy and GI tract imaging for patients with inflammatory colitis or prior chronic norovirus or cryptosporidial diarrhea; high resolution CT chest imaging, bronchoscopy, lavage and/or biopsy in patients with granulomatous lymphocytic inflammatory lung disease (GLILD), previous aspergillosis or atypical mycobacterial infections; and liver biopsy, fibroscan and/or measurement of portal pressures in patients with abnormal liver function tests and a history of nodular regenerative hyperplasia or autoimmune hepatitis. Other pre transplant investigations occasionally indicated are lumbar puncture with CSF culture and biopsies of atypical granulomatous lesions, where relevant, in order to exclude or identify persistent pathogens requiring tailored anti-microbial prophylaxis throughout the transplant period.

Where possible control of autoimmunity or inflammation should be achieved prior to transplant. This reduces the inflammatory cytokine milieu at the time of transfer of allogeneic cells, thus reducing the risk of acute GVHD and ensures end organ function is optimised pre-transplant. Pre-existing PID-associated malignancies should be treated and in remission as per routine practice in HSCT for lymphoid malignancies. For patients with EBV handling disorders, the inclusion of rituximab in the conditioning regimen can bridge the gap until functional immune reconstitution is achieved post-transplant.

Specialist infectious disease advice should be sought for patients with a history of refractory or atypical infections preceding transplant. Regular post-transplant monitoring for recurrence of previous, persistent or latent opportunistic pathogens is indicated on a per-patient basis. We recommend the continued use of prophylactic antimicrobials until cessation of immune suppression as GVHD prophylaxis or treatment.

Splenomegaly in PID is not uncommon and has multiple causes. A number of studies have clearly demonstrated that poor graft function and hematological recovery following allo-HSCT is associated with splenomegaly[44,45]. Although prior splenectomy may improve hematological recovery post-transplant it is associated with peri-operative complications and life-long impaired immunity to encapsulated bacteria, it is therefore only rarely performed.

Recurrence or de novo autoimmunity post-transplant has also been reported in PID transplant cohorts, particularly in the context of mixed chimerism[6,46] discussed below. The exact pathophysiology underlying persistent or late onset autoimmunity is poorly understood.

Evolution of clinical cases

Patient 1 developed early EBV-associated PTLD at 2 months post-transplant. She responded to 4 cycles of rituximab and prompt withdrawal of immune suppression, without the development of GVHD. EBV viremia (without lymphadenopathy) resolved by 5 months post-transplant.

The importance of donor chimerism post-transplant

Conditioning regimens using reduced doses of cytoreductive agents are better tolerated in older recipients with higher co-morbidities, but they carry the risk of failing to eradicate host hemopoiesis. This can result in mixed chimerism in differentiated lineages including neutrophils, B cells, red cells and platelets, although the T cell compartment is most

commonly affected. Mixed T cell chimerism post-transplant can follow re-expansion of residual recipient T cells not effectively depleted by lymphodepleting conditioning +/- serotherapy (Alemtuzumab or ATG)[47,48].

For very long-term functional immune reconstitution, multi-lineage stable donor chimerism is considered optimal, even though full donor chimerism in any given lineage is not *per se* required for correction of a functional deficit.However, mixed donor/recipient stem cell chimerism is expected to only partially correct the underlying immunogical disorder with a risk of late complications or disease recurrence.

During the first year following transplant chimerism may fluctuate. The use of DLI to promote/force conversion from mixed chimerism to full donor chimerism should be evaluated carefully as it carries with it a risk of GVHD. Previously the use of DLI was only considered where worsening mixed chimerism raised concerns of incipient graft rejection. However, recent data suggests that persistent mixed chimerism post-transplant is associated with poorer event free survival as long as 20 years post transplant (Morris, personal communications) and late complications such as autoimmunity[6,46]. Future studies should investigate the role of prophylactic or pre-emptive DLI early post-transplant in the setting of allo-HSCT for PID.

For patients with neutrophil defects achieving high level stable myeloid chimerism is essential. Studies in male patients and female carriers of the X-linked form of CGD, have demonstrated that symptoms arising from inflammation or autoimmunity may be present in carriers with extreme degrees of lyonisation (resulting in 20-30% normally functioning phagocytes), although the risk of serious infection is rarely present if >10% of circulating neutrophils are functional[49,50].

Where at all possible known carriers should not be used as stem cell donors in PID as even with full donor chimerism, full immunological correction may not be achieved.

For rarer non-SCID PID and immune dysregulatory syndromes such as APDS, CTLA4 Deficiecny, LRBA Deficiency and STAT1 GOF there is insufficient data regarding the optimal chimerism required for long term immunological correction and cure, although insight into the disease specific pathophysiology may predict which lineages are critical to correct[19,51, 52, 53].

How do we measure success following allo-HSCT in adult PID?

In malignant disease a successful transplant results in long-term survival, no recurrence of the original malignancy, normal hematopoietic reconstitution, no chronic graft versus host disease and no late complications. Recently the use of composite outcome measures such as GVHD-free, relapse-free survival (GFRS) or chronic GVHD-free, relapse-free survival (CFRS) has been included in studies of allo-HSCT[54]. In parallel the CIBMTR are developing the use of patient reported outcomes (PROs)[55]. In adult PID the indication for transplant is often the prevention of progressive decline in quality of life secondary to the accumulation of PID-related medical complications, PROs should be important in evaluating success. Other important endpoints for PID patients include the reconstitution of normal pathogen-specific immunity, resolution of autoimmunity and/or inflammation and reduction in future malignancy risk.

For some PID functional correction of the underlying immune deficit is easy to measure, for example, the correction of neutrophil function in CGD, as measured by NBT or DHR assays. In X-linked PID where carriers are asymptomatic, it is possible to achieve functional/clinical correction without full donor chimerism in the relevant lineage. In the context of gene therapy, it is relatively easy to track the gene-corrected immune cells and quantify functional correction. In allo-HSCT recipients, lineage specific donor chimerism is a surrogate marker for functional correction, but 'proof' of transplant efficacy relies on functional immunological assays (eg., response to vaccination, T cell proliferation, normalisation of lymphocyte subsets) and clinical responses. For patients going into transplant with pre-existing end-organ damage it is critical that the consent process involves a clear discussion regarding which disease-associated symptoms/complications can be improved by transplant and which cannot (eg, bronchiectasis/pulmonary fibrosis, gut strictures and extra-hematological complications).

Evolution of clinical cases

Patient 1 is now alive and well, off immune suppression and immunoglobulin replacement therapy, with no GVHD, no recurrence of lymphoma and in employment at 40 months post-transplant. Patient 2 is alive and well, off immune suppression and immunoglobulin replacement therapy, with no GVHD, normal peripheral blood counts and at University 5 years post-transplant.

The role of solid organ transplant in combination with allo-HSCT in adult PID patients with end organ failure

The incidence of end organ failure increases over time for untransplanted PID patients. As a result, a proportion of adult patients referred for transplant may already have or be a risk of imminent end organ failure. There is a small published literature on the role of solid organ transplant either before or after allo-HSCT and in selected cases this should be considered[56]. Most available data in PID is for combined liver transplant in combination with allo-HSCT. Physicians and patients should be aware that allocation of cadaveric organs for patients with uncorrected PID also requiring an allo-HSCT for which outcome data is scarce is not universally guaranteed. Due to limited availability of such organs, they are typically reserved for clinical scenarios for which the evidence of long-term benefit is strongest. Furthermore, in a subset of patients the severity of their liver disease may not yet meet criteria for liver transplant but preclude safe allo-HSCT. This very specialist area of clinical practice would benefit from ongoing international collaboration and prospective pilot studies.

The role of gene therapy as an alternative to allo-HSCT

For patients without a matched related donor or a fully matched unrelated donor, the decision between using multiple mismatched cord units, a mismatched unrelated donor, a haploidentical donor or to consider gene therapy (where available, eg for X-SCID, ADA-SCID, WAS, X-CGD, and in development for other diseases including AR-CGD and CD40L deficiency) remains difficult, in part due to the relatively limited experience of all these modalities in older patients with PID.

The use of alternative donors has a proven safety and efficacy record in younger children with PID and in adults with haematological malignancies. It is predicted that the use of PTCy and or αβTCR depletion in these older patients will also facilitate the safe use of allo-HSCT in a wider group of potential recipients lacking a 'perfect' donor.

Gene therapy has been successfully used in adults for Wiskott Aldrich Syndrome, WAS[57,58] and X-linked CGD[59] where appropriately matched allogeneic stem cell donors were not available. Gene therapy approaches currently rely on the *ex vivo* modification of autologous hematopoietic stem cells with viral vectors encoding the wild-type version of the absent or mutated gene. The early clinical trials of hematopoietic stem cell gene therapy using gammaretroviral (γ-RV) vectors resulted in clonal expansion of gene-corrected cells, mediated by potent enhancer elements in the γ-RV long-terminal repeats (LTRs) and led to the development of leukemia in some patients[60]. In addition, CpG dinucleotide promoter methylation led to silencing of transgene expression limiting durability of effective gene correction[61]. The most recent trials have demonstrated improved outcomes with the use of self-inactivating lentiviral vectors (developed to minimize the mutagenic risk) and enhanced promoter sequences.

The potential advantage of gene therapy is the requirement for less immunosuppressive conditioning and no risk of GVHD. Both of these potential benefits are important in adult PID patients, who typically have high co-morbidity scores when referred for a definitive procedure. Theoretically, gene therapy approaches in adults could be preferred to allo-HSCT if long-term correction and immune reconstitution is proven to be effective and durable.

The role of allo-HSCT in adults and adolescents who have failed gene therapy

As a reflection of the profound impact of gene therapy in monogenic PIDs including X-SCID, ADA-SCID, CGD and WAS some of the first ever patients who were treated with hematopoietic stem cell gene therapy have recently transitioned into adult care. The first gene therapy protocols for ADA-SCID and X-SCID used minimal or no chemotherapy conditioning as the objective was to secure T cell reconstitution, with the expectation that T cells arising from gene corrected stem cells would have a clear 'competitive advantage' securing successful engraftment gene corrected cells. However, a small number of recipients of unconditioned gene therapy have failed to reconstitute humoral immunity, requiring long-term immunoglobulin replacement therapy[62] and others remain lymphopenic despite persistence of

gene corrected cells. Some of these patients, now young adults, have undergone or are being considered for either repeat gene therapy or allo-HSCT as a rescue procedure.

Understanding of the durability of gene therapy efficacy is limited by its relatively recent introduction compared to allo-HSCT for PID. As more recent gene therapy protocols have adopted targeted conditioning with improved engraftment of gene-corrected stem cells and incorporated safer and more efficient vectors it is predicted that in the future results will continue to improve.

Conclusion

Recent data has established that allo-HSCT in adults PID is safe, that engraftment can be reliably achieved, and overall survival is excellent for well selected patients. Despite the availability of next generation gene sequencing for a large proportion of patients, the decision to proceed to transplant remains a complex clinical decision.

There is an urgent need to inform practice further with large international multicenter studies designed to assess outcome following allo-HSCT for PID in adults, together with equivalent studies describing the natural history of these rare diseases for un-transplanted patients. It is important that future prospective studies include detailed analysis of functional immune reconstitution, lineage-specific chimerism, quality of life, psychosocial impact and late effects.

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Legends to Figures

Figure 1. Clinical cases

Figure 2. Decision flowchart (algorithm) for Adult PID patients with *known genetic diagnosis* referred for allogeneic HSCT.

Figure 3. Decision flowchart (algorithm) for Adult PID patients *without a genetic diagnosis* referred for allogeneic HSCT.