Clinical and immunological outcome after paediatric stem cell transplantation in inborn errors of immunity

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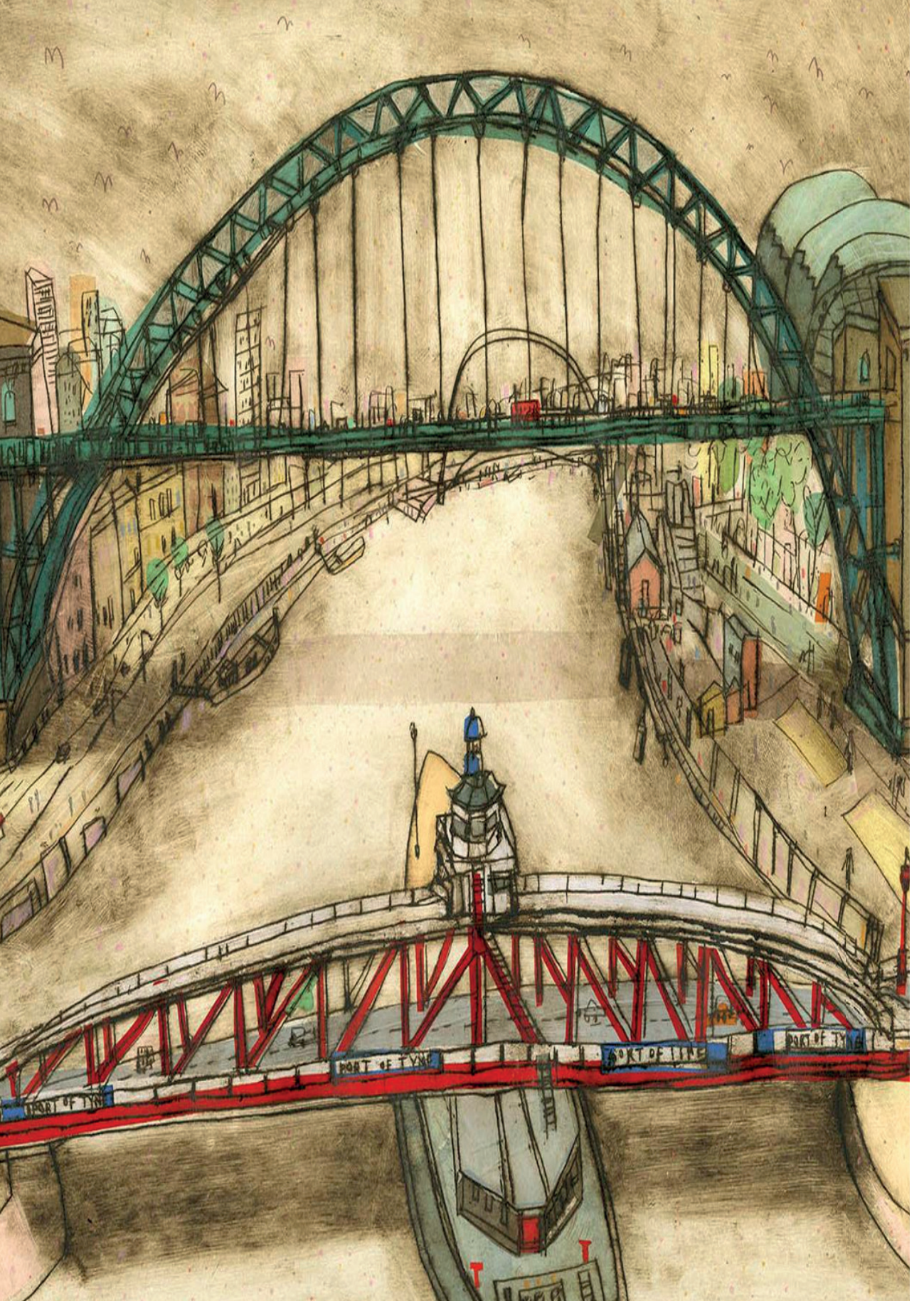
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Chapter 4

Haematopoietic cell transplantation in monogenic autoimmune diseases

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Abstract

Inborn errors of immunity (IEI) represent a broad and heterogenous spectrum of monogenic diseases that may present with a large variety of clinical manifestations which include the inability to properly respond to infectious pathogens, inflammatory disease, cancer susceptibility, and autoimmunity. Although autoimmunity may occur in any subgroup of IEI, it represents a hallmark of the category "diseases with immune dysregulation" as defined by the international Union of Immunological Societies. In this chapter we will focus on this particular category of IEI, describe the main disease characteristics, and review the reported experience with allogeneic haematopoietic cell transplantation (HCT).

Introduction

Inborn errors of immunity (IEI) encompass a group of more than 400 inherited disorders. (1) The defects of underlying IEI have impact on at least three important functions of the immune system: 1) inability to remove dangerous exogenous pathogens, leading to increased infection rate and severity; 2) defects in immune surveillance, DNA damage repair, leukocyte maturation and function, resulting in increased susceptibility to autoinflammation and malignancies; 3) abnormal regulation of immune responses, induction and maintenance of self-tolerance, contributing to autoimmunity, chronic inflammation, rheumatological features, granuloma formation, lymphoproliferation, focal or diffuse lymphocytic organ infiltration or haemaphagocytosis. As a consequence, it has become increasingly clear that IEI represent a broad and heterogenous spectrum of diseases that may present with a large variety of clinical manifestations which include the inability to properly respond to a multitude of infectious pathogens, inflammatory disease, cancer susceptibility, and autoimmunity. Although autoimmunity may occur in any subgroup of IEI, it represents a hallmark of the category "diseases with immune dysregulation" in the International Union of Immunological Societies (IUIS, 2019 version). (1, 2)

In this chapter we will focus on IEI in which autoimmunity is the dominant feature of the disease and for which experience with allogeneic haematopoietic stem cell transplantation (HCT) has been reported. We summarize the indications and transplant outcomes for regulatory T lymphocyte defects (immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX), cluster of differentiation 25 (CD25) deficiency, cytotoxic T-lymphocyte-associated protein 4 (CTLA4) deficiency, lipopolysaccharide (LPS)-responsive and beige-like anchor protein (LRBA) deficiency, Signal transducer and activator of transcription 3 (STAT3) gain-of-function (GOF), broad complex-tramtrack-bric a brac and Cap'n'collar homology 2 (BACH2) deficiency, CD122 deficiency, Differentially expressed in FDCP 6 homolog (DEF6) deficiency), autoimmune diseases with/without lymphoproliferation (autoimmune

polyendocrinopathy candidiasis ectodermal dystrophy (APECED), itchy (mouse) E3 ubiquitin protein ligase homolog (ITCH) deficiency, Tripeptidyl-peptidase II deficiency, Janus kinase 1 (JAK1) GOF, Prolidase deficiency), autoimmune lymphoproliferative syndrome and other IEI with prominent autoimmunity (recombination activating gene 1/2 (RAG1/2) deficiency, Zeta-chain-associated protein kinase 70 (ZAP-70) deficiency, STAT1 GOF, complement component 1 q (C1q) deficiency, and stromal interaction molecule 1 (STIM1) deficiency, and ORAI1 deficiency. The ORAI were named after the keepers of heaven's gate in the Greek mythological poem, the Iliad, and are proteins that are components of the calcium-selective, calcium-release, active calcium channels (CRAC)) (3). Diseases with reported HCT experience will be elaborated in the text while diseases without reported HCT cases will only be listed in Table 1.

General principles and mechanisms of autoimmunity in inborn errors of immunity

Whilst common autoimmune disorders such as systemic lupus erythematous (SLE) and rheumatoid arthritis (RA) are characterized by complex polygenic phenotypes, monogenic diseases may result in defects in a specific immune process or several pathways simultaneously. Fisher et al reported 26.2% of 2183 consecutive cases of primary immunodeficiencies (PIDs) in the Centre de Référence Déficits Immunitaires Héréditaires registry, had one or more autoimmune and inflammatory manifestations. Compared to the general population, the risk was 120 times for autoimmune cytopenia, 80 times for inflammatory bowel disease and 90 times for other autoimmune manifestations. (4) Autoimmune phenomena in IEI can develop at any age and at any stage in the course of IEI. They can affect single or multiple organ systems resulting in cytopenia, endocrinopathies, enteropathy, arthritis, hepatitis and lupus-like systemic manifestations. Among patients with IEI and autoimmunity, there tend to be IEI-typical patterns of organ manifestations. A younger age of onset of autoimmunity is observed with combined immunodeficiencies compared to those with B lymphocyte deficiencies (4).

The development of autoimmune disease (AD) depends on an imbalance between pathogenic factors generated by autoreactive T and B lymphocytes and the regulatory factors that normally control the immune response. The possible mechanisms include defects in central T lymphocyte tolerance, defects in B lymphocyte function and tolerance, defects in peripheral tolerance, defects in variable, diversity, joining (VDJ) gene recombination, defects in apoptosis, hyperactivation of lymphocytes, increased activation of type 1 interferon pathways, defects in early complement components and defective removal of lymphocyte defects (Figure 1). (4-6)

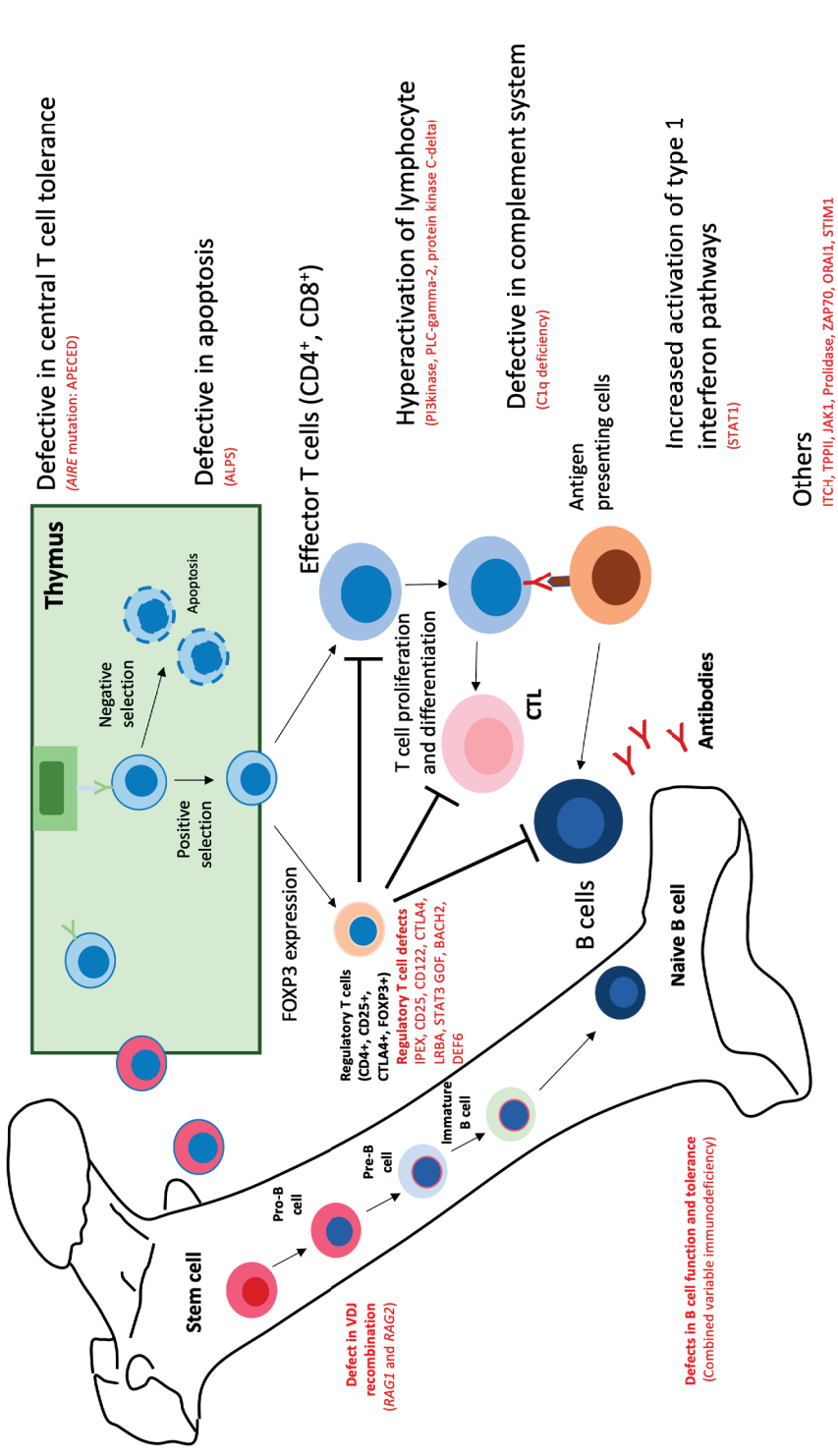

Figure 1: Mechanism of autoimmunity in inborn error of immunity

Haematopoietic Stem Cell Transplantation in Regulatory T lymph- ocyte defects

IPEX

Following its identification as disease causing gene defects in scurfy mice (7), mutations in Forkhead-Box-Protein 3 (FOXP3) have been first described two decades ago in patients with Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome. (8, 9) FOXP3 is a member of the forkhead/winged-helix family of transcriptional regulators and expressed in thymic CD4 T lymphocytes where it plays a pivotal role in the generation of thymus-derived regulatory T lymphocytes (Tregs) and thereby immune tolerance. Studies in scurfy mice have provided evidence for the curative potential of allogeneic stem cell transplantation (HCT) (10).

Since the first reports, many IPEX patients have been diagnosed and reported with mutations that impair either Foxp3 expression or function. With the increasing number of patients identified it has become clear that the clinical spectrum is highly variable. Whereas the classical triad includes neonatal enteropathy, type 1 diabetes, and eczema, the clinical spectrum is much broader and variable in both onset and severity, and encompasses failure to thrive, food allergy, nephropathy, hemolytic anemia and cytopenias, thyroiditis, hepatitis, arthritis, alopecia and neurological abnormalities. Gambineri et al reported on a large cohort of 173 patients with an IPEX phenotype. In 88 patients FOXP3 mutations were identified. In the remaining 85 IPEX-like patients, disease-associated variants in immune regulatory genes were identified in a subgroup of patients (25%) including interleukin 2 receptor subunit alpha (IL2RA), CTLA4, LRBA, STAT1 (GOF), STAT3 (GOF), STAT5B, and dedicator of cytokines 8 (DOCK8) pointing to the overlap in clinical phenotype between these monogenic inherited immune disorders. In 163 evaluable patients, overall survival (OS; 30 years) was 47.5%. Within the IPEX group OS was influenced by the type of foxp3 mutation, and 10 year OS was better in the IPEX-like group compared to the IPEX group. However, it was mainly the burden of the chronic autoimmune manifestations, treatment with immune modulatory agents and concomitant infectious complications, that determined individual outcome. Both in the IPEX and the IPEX-like group a more favorable overall survival was reported in the patients treated with allogeneic cell transplantation (HCT). Nademi et al reported a single centre experience on five IPEX patients, diagnosed at a median age of one week with typical enteritis and transplanted at a median age of 10 months. Enteropathy resolved in all patients. (11) A French study reported 30 IPEX patients with a 10-year survival rate of 43%; seven patients underwent HCT at a mean age of 5.5 years and four died because of transplant-related complications. (12)

In a retrospective multicenter study, Barzaghi et al. reported the impact of various treatment strategies in a cohort of 96 genetically confirmed IPEX patients with a median age at disease onset of 2 months and a median time to diagnosis of 14 months. Of the 34 patients treated with various immunosuppressive agents (median follow-up 4 years) only 10 achieved complete disease remission whereas the remainder had residual disease activity resulting in an overall survival of 65.1%. Among the various immunosuppressive agents, rapamycin appeared to result in the best disease response. (13) In a recent study, evidence was provided that rapamycin has the potential to restore regulatory T lymphocyte function in an FOXP3-independent manner. (14) In the group of 58 patients treated with HCT (median follow-up 2.7 years) median age at disease onset was 1 month and median age at HCT 1.4 years. In half of the HCT patients, clinical disease manifestations improved due to immunosuppressive treatment prior to HSCT. The majority of patients (37/58) received reduced intensity conditioning and anti-thymocyte globulin (ATG) or alemtuzumab serotherapy was administered in 49/58 patients. In the HCT group the estimated OS at 15 years was 73.2% with a more favorable outcome in the subgroup of patients with limited disease burden as reflected by a low organ involvement score at HCT. Donor type, graft source and conditioning regimen did not impact on OS. Transplant related mortality was 26% and mainly clustered in the first year after HCT. Acute graft versus host disease (GvHD) occurred in 19 (all grades) and 9 patients (grade III-IV), respectively. (13) In line with what was previously shown in the scurfy mouse model (10), disease control and remission after HCT was not correlated with the presence of full or mixed chimerism which may be explained by sufficient levels of selectively expanded donor-derived regulatory T lymphocytes in the latter setting. (15-17) Although a subset of IPEX patients seem to benefit from immunosuppressive therapy, disease recurrence or new disease manifestations frequently occur. The persistence or de novo occurrence of autoimmune manifestations was significantly lower in the HCT group compared to the non-HCT group treated with immunosuppressive agents. Whereas OS in the HSCT group shows a plateau from several years post-transplant onwards, it drops steadily in the non-HCT group reflecting ongoing and increasing disease burden. In a recent systematic review, Jamee et al. reported a cohort of 459 IPEX and IPEX-like patients. The cohort included 312 patients with a disease-causing foxp3 mutation and 98 patients without such mutation (IPEX-like). In the IPEX-like group disease-causing mutations could be identified in 58 patients with STAT1 and LRBA mutations in half of them. The first autoimmune manifestation was at a median age of 0.2 year and 2 years in IPEX and IPEX-like patients, respectively. In the IPEX group, the patients receiving HCT had a significantly lower mortality (24%) compared to the non-HCT group (43%).(18)

Despite its proven curative potential, one of the major limitations of HCT remains the inevitable risk of GvHD particularly in those patients that enter HCT with insufficiently

controlled disease. Supported by the observations that mixed chimerism may be sufficient to control and prevent disease, and that functional regulatory T lymphocytes may selectively expand in vivo, autologous gene therapy is being developed as an alternative curative therapeutic option. Recent studies using either somatic cells or hematopoietic progenitor cells have provided preclinical evidence for the potential of both gene addition and gene editing approaches. (14, 17, 19)

Taking the limitations of retrospective studies into consideration, the available data indicate that IPEX patients represent a heterogeneous group with variable disease onset, disease manifestations, and response to immunosuppressive agents. Given the unfavorable natural course of the disease in the majority of patients, timely consideration of allogeneic HCT as the so far only available curative therapy is recommended prior to clinical deterioration and high disease burden which will negatively impact on HCT-related morbidity and mortality. (20)

CD25 deficiency

IL-2 receptor consists of a heterotrimeric receptor complex comprised of a low-affinity α-chain (CD25), a β-chain (CD122) and a γ-chain (CD132). CD25 deficiency is caused by mutations in the gene encoding CD25 or interleukin2 receptor alpha causing aberrant or lack of expression of the high-affinity IL2 receptor on T lymphocytes including regulatory CD4 T lymphocytes which results in a clinical phenotype that resembles IPEX syndrome (21). CD25 deficient mice have normal T and B cell development but develop enlargement of peripheral lymphoid organs due to T and B cell expansion, followed by the manifestation of autoimmune disorders, including hemolytic anemia and inflammatory bowel disease. (22) In humans, it is a very rare autosomal recessive disorder first reported by Sharfe et al. that shows a clinical phenotype highly overlapping with IPEX syndrome. Contrasting FOXP3 deficiency, mutations in *IL2RA* and *ILRRB* (vide infra) increase susceptibility to severe herpesvirus disease, highlighting the requirement for intact signalling through the IL-2/IL-5 receptor for effective immunity to complex viral infections. Moreover, and distinct from IPEX, endocrinopathies are not consistently observed in these patients. (23)

To date, Vignoli et al reported the first and only HCT experience in CD25 deficiency. It was a successful correction of this defect with HCT in a two-month old boy who presented with early onset of IPEX-like features, including intractable diarrhoea and severe dermatitis. Although the patient required a second matched unrelated donor transplant following graft failure from first T cell receptor (TCR) αβ/CD19 depleted haploidentical graft, his diarrhoea and dermatitis completed resolved at 4 months after second transplant. He had good donor chimerism at 95% and reasonable immune reconstitution at 4 months post-HCT. (24)

CD122 deficiency

CD122 deficiency is caused by homozygous mutations in the gene encoding interleukin-2 receptor beta *(IL2RB)*, resulting in an inability to respond to interleukin-2 (IL-2) stimulation. Zhang et al and Fernandez et al described a total of five kindreds (7 affected live born children and 3 perinatally affected fatalities) with autosomal recessive mutations in *IL2RB*, resulting in immunodeficiency and autoimmune disease. (25, 26) The hallmarks of the disease are enteropathy, skin abnormalities, autoimmune haemolytic anaemia, and hypergammaglobulinemia. Affected patients are susceptible to respiratory and herpesvirus infection. The severe and early onset autoimmune manifestations of *IL2RB* mutation resembles IPEX, but a distinctive feature of patients with IL2RB mutation is increased susceptibility to herpesviruses, especially cytomegalovirus (CMV) and Epstein-Barr virus (EBV). EBV, originally discovered in Burkitt lymphoma, is associated, even in people without genetic immune disorders, with Hodgkin's lymphoma, B cell lymphomas including Burkitt's, nasopharyngeal carcinoma, natural killer cell lymphomas, post-transplant lymphoproliferative disorders, and gastric adenocarcinoma carcinoma. Zhang et al also described HCT in two patients of eight affected individuals from four consanguineous families. The first patient presented at 5 months of age with failure to thrive, chronic diarrhoea, antineutrophil cytoplasmic antibody positive vasculitis, and recurrent infections including CMV pneumonitis, EBV viraemia, mucocutaneous candidiasis and pulmonary infections. The patient recovered with no sequalae after allogeneic HCT at 30 months of age. The second patient presented with profuse diarrhoea since birth and developed dermatitis, CMV viraemia and hepatitis, autoimmune haemolytic anaemia and positive ANA and anti-smooth muscle antibodies. The patient died of CMV pneumonitis during HCT.

Cytotoxic T-lymphocyte associated antigen-4 (CTLA-4)

Negative as well as positive costimulation play an important role in controlling T lymphocyte activation and peripheral T lymphocyte homeostasis. (27) These processes are mediated by cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) and CD28 upon interaction with the shared ligands CD80 and CD86 (also known as B7.1 and B7.2). CD28 provides a positive signal to T lymphocytes leading to T lymphocyte activation and effector cell differentiation, whereas the ligation of CTLA-4 to CD80 and CD86 delivers a negative signal which limits proliferation and survival of T lymphocytes and limits IL-2 production. (28) Studies in mice demonstrated that deficiency of CTLA-4 results in a lethal autoimmune phenotype. (29, 30) CTLA-4 is also important as a checkpoint inhibitor and target in tumour immunology. (31) Lymphoproliferation in CTLA-4-deficient mice has been shown to be mediated by costimulation-dependent activation of CD4+ lymphocytes. (32)

Heterozygous germline mutations in CTLA4 impair the suppressive function of T-lymphocytes and cause an immune dysregulation syndrome. These mutations behave in an autosomal dominant manner with incomplete penetrance, resulting in a complex immune dysregulation syndrome with disrupted T and B cell homeostasis. (33, 34) In the first reports in humans, Kuehn et al. identified 7 patients from 4 families with lymphoproliferation, organ infiltration, autoimmune cytopenias and B cell abnormalities7. Schubert et al. identified 14 patients from 6 families, of whom 11 had enteropathy and 10 hypogammaglobulinaemia; other manifestations included granulomatous lymphocytic interstitial lung disease, respiratory infections, organ infiltration, cytopenias, lymphadenopathy, skin diseases, autoimmune thyroiditis, arthritis and one case of solid cancer. (34) Cancer prevalence of 12.9% was documented in 184 CTLA-4 deficient patients. Ten of 17 affected patients had a lymphoma, 5 gastric adenocarcinoma, 1 multiple myeloma and 1 metastatic melanoma. Eight cases were associated with EBV, including 1 with both EBV and CMV and another with CMV alone, highlighting the increased risk for malignant transformation, especially EBV positive lymphomas and gastric cancers. (35)

Schwab et al. reported 133 people from 54 unrelated families with 45 unique heterozygous CTLA4 germline mutations. No association between genotype and onset of symptoms, penetrance or phenotype was found. Ninety were considered affected. Of these 15 (16%) died of disease or resulting complications at a median age of 23 years (14-60 years). The immunological characteristics of affected individuals were variable. Thirty-nine percent of those with available data had lymphopenia and hypogammaglobulinaemia was present in 84%. (36)

Slatter et al. reported 8 patients who received HCT. All received 10 out of 10 human leukocyte antigens (HLA) matched unrelated donor grafts following a variety of reduced intensity conditioning. All had received immunosuppressive therapy prior to transplant with a minimum of steroids and a calcineurin inhibitor. Five patients received peripheral blood HSC grafts and received cyclosporine and mycophenolate mofetil (MMF) for graft versus host disease (GvHD) prophylaxis. Three received bone marrow HSC grafts and had cyclosporine alone, cyclosporine and MMF, or methotrexate and tacrolimus. One patient died with transplant-related mortality of severe acute gut GvHD. Another patient did well post HCT, became total parenteral nutrition (TPN)-independent after 5 months, but unfortunately died from diabetic ketoacidosis 2.5 years post HCT. Five of 8 patients experienced GvHD despite having well-matched donors and receiving Alemtuzumab in 2 cases. The high levels of inflammation in which these patients enter the HCT process may promote the development of alloreactivity

and so patients are likely to benefit from either enhanced pre-HCT immunosuppression, or more aggressive post-HCT GvHD prophylaxis. Seven of 8 patients had complete resolution of severe enteropathy and cytopenias following HCT. All 8 patients had chimerism greater or equal to 85% donor. Complications such as diabetes are irreversible, highlighting the importance of early recognition and treatment. (37-40)

Twelve patients were identified in Schwab's report, who had received HCT between 10 and 50 years of age. Five of these were in the previously published series including the death from GvHD and from diabetic ketoacidosis. (40) Nine were alive, the additional death also being due to GvHD. Three survivors were more than 5 years post-transplant and were well, off all medication. (36) Other therapeutic options proposed for CTLA4 deficient patients include soluble CTLA4 fusion proteins (abatacept and belatacept), which bind to CD80 and CD86 and inhibit immune activation. (41) In some cases these treatments could be used as a bridge to HCT to optimise the condition of patients prior to HCT.

Lipopolysaccharide (LPS)-responsive and beige-like anchor protein (LRBA)

A novel gene designated *lba*, short for LPS-responsive, beige-like anchor gene was first described in mice, flies and humans in 2001. Expression of *lba* was shown to be induced after LPS stimulation of B cells and macrophages. In addition, *lba* was found to be expressed in many other tissues in the body. (42) Dysregulated expression of *LRBA* has been shown to facilitate cancer cell growth. (43) The LRBA gene which is a member of the beige and Chediak Higashi – tryptophan (w) aspartic acid (D) 40 amino acid (BEACH-WD40) protein family, is involved in signal transduction, vesicular trafficking, autophagy and apoptosis. WD-40 indicates a protein that contains an evolutionarily conserved repeated structural motif of 40 amino acids terminating in tryptophan (written in one letter short form as W) and aspartic acid (written in one letter short form as D). (44)

LPS-responsive beige-like anchor protein (LRBA) deficiency was first reported in 5 individuals from 4 families with childhood-onset humoral immune deficiency and features of autoimmunity. (45) A separate report described 5 affected individuals from 2 branches of a large consanguineous family with features of common variable immune deficiency (CVID), immune dysregulation, or both manifesting as inflammatory bowel disease with chronic diarrhea, autoimmune cytopenia, and EBV-induced lymphoproliferative disease. Combined exome sequencing and autozygome filtration in this consanguineous family revealed a null mutation in LRBA. (46) Absence of LRBA leads to decreased CTLA4 expression and so the clinical features of immune dysregulation and autoimmunity are similar to those of CTLA4

insufficiency. Like CTLA4 insufficiency there is high variability in the phenotype even within affected families.

Various immunosuppressive agents are commonly used including steroids and sirolimus. The soluble CTLA4 immunoglobulin fusion protein abatacept partially restores T regulatory cell function, but as with its use in CTLA4 insufficiency this may not prevent problems in the long-term, but is useful as a bridge to HCT in appropriate cases. (47)

Tesch et al. reported 76 patients from 29 centres worldwide. (48) Forty-seven had been treated with immunosuppressive therapy and 24 had undergone HCT. Five, identified by family screening had mild or no symptoms and required no treatment. There was no genotype – phenotype correlation. Eight patients died in the allogeneic HCT group giving an overall survival at time of analysis of 70.8%. All the deaths occurred in the first 3 months post HCT from transplant related mortality. Nine of 52 who were conventionally treated also died giving a survival at time of analysis of 82.7%, but the risk of mortality remained constant and these patients had an increased disease burden compared to the HCT survivors. All 16 patients that died had lung involvement and autoimmune cytopenia also significantly correlated with death. In the HCT group 9 patients developed GVHD including 3 with grade IV gastrointestinal GVHD. Graft failure occurred in 2 patients both of whom died (one following a second procedure), but 10 of 11 for whom information was available had full donor chimerism. Importantly the overall survival was better in patients transplanted within 3 years of the onset of disease symptoms. The numbers are small but outcome was not related to donor type, donor carrier status, conditioning regimen or age at HCT.

An immune deficiency and dysregulation activity (IDDA) score was developed which graded organ involvement depending on the severity and need for treatment, weighted by performance indices. A score for number of days of hospitalisation, need for intensive care, and number of infections was added. The IDDA score for patients prior to HCT was significantly higher than the group treated with conventional therapy. The score decreased significantly in all HCT survivors. A lower score pre HCT was associated with a higher probability of survival. The IDDA score of patients who survived in the group with conventional therapy was significantly higher than that of the HSCT survivors. The use of abatacept led to a decrease in the IDDA score.

All patients with a residual expression of LRBA protein survived, whereas absent protein expression was associated with a worse outcome. Therefore, this is a useful test to guide clinicians with treatment decisions and can be monitored over time. (48)

Fifteen LRBA-deficient patients from 13 families with a diagnosis of CVID or possible

autoimmune lymphoproliferative syndrome (ALPS) were found to have LRBA deficiency reported by Cagdas et al.(49) Seven of these patients underwent HSCT with matched family donors, six with busulfan, fludarabine and ATG one with melphalan, fludarabine and ATG conditioning. All survived with a median follow up of 2 years.

Deciding which patients should be offered HCT and when is difficult. High transplant related mortality is seen when HCT is performed late in patients with a high burden of disease and so transplantation should be considered before the disease progresses.

STAT3 gain-of-function

The signal transducer and activator of transcription (STAT) family of transcription factors are activated in the cytoplasm by Janus kinases (JAKs) in response to cytokines, hormones and growth factors binding to their respective receptors. Mutations resulting in reduced or increased activity of STAT proteins have been implicated in immunodeficiency and immune dysregulatory syndromes. Two of those, STAT3 gain-of-function mutations and STAT5b deficiency, are characterized by low numbers of regulatory T cells, and can thus be classified as 'IPEX-like' diseases.

STAT3 gain-of-function mutations can result in severe early-onset autoimmunity such as type 1 diabetes and enteropathy, eczema, autoimmune cytopenia, interstitial lymphocytic pneumonia, lymphoproliferation, short stature and recurrent infections (50-52). The immunological phenotype includes T cell lymphopenia, reduced regulatory T cells, reduced T helper 17 (Th17) lymphocytes and hypogammaglobulinemia. Some individuals from affected families have few or no symptoms, suggesting incomplete penetrance. The degree of penetrance of specific STAT3 mutations may be due to differences in constitutional transcriptional activity and kinetics of STAT3 phosphorylation in response to stimuli (53).

Patients with STAT3 gain-of-function mutations are often treated with immunosuppressive agents to ameliorate autoimmune and immune dysregulation features of the disease. IL-6 signals via STAT3 and treatment with tocilizumab, an IL-6 receptor antibody, has resulted in an increase in regulatory T cells and clinical improvement (54). Forbes et al reported on six patients who received a JAK inhibitor, before, after or concomitantly with treatment with tocilizumab, with three patients significantly improving (55).

Five patients with STAT3 gain-of-function have been reported to have received an allogeneic hematopoietic stem cell transplantation. (51, 55-57) The indications for HCT were refractory autoimmunity in 4/5 and hemophagocytic lymphohistiocytosis (HLH) in 1/5 patients. Unfortunately, all but one patient died due to complications of HSCT. As evidenced by one

patient with long term survival however, it is a potentially curative option for patients with STAT3 gain-of-function. In addition, 18 patients transplanted for STAT 3 GOF from 11 centres worldwide has 11 patients alive (OS 61%) at a median follow up of 2.5 years, with reversal of the underlying immune dysfunction (personal communication Lisa R. Forbes). Further studies are needed to determine if better pre-HCT disease control results in better outcome.

Haematopoietic Stem cell transplantation in autoimmunity with or without lymphoproliferation

Tripeptidyl-peptidase II deficiency

The discovery of tripeptidyl-peptidase II (TPP II) was reported in 1983. (58) As the name implies, TPPII is present in the cytosol of most eukaryotic cells and removes tripeptides sequentially from the free N-termini longer peptides with a broad specificity. Overexpression of TTP II leads to accelerated cell growth, genetic instability and resistance to apoptosis, whereas inhibition or down-regulation of TPPII renders cells sensitive to apoptosis. (59) Patients with autosomal recessive loss of function mutations in the TPP2 gene suffer from autoimmunity, recurrent infections and neurodevelopmental delay.

Lu et al and Stepensky et al first described TPPII deficiency in six patients from three families who were affected by combined immunodeficiency, severe autoimmunity and developmental delay. (60, 61) Lu et al showed that a major function of TPPI in mammalian cells is to maintain amino acid levels and that TPPII-deficient cells compensate by increasing lysosome number and proteolytic activity. Increasing lysosomes results in deranged cellular metabolism by consuming the key glycolytic enzyme hexokinase-2 via chaperone-mediated autophagy, leading to reduced glycolysis and impaired production of effector cytokines, including interferon-gamma (IFN-□) and IL-1□. TPPII is important for homeostasis of intracellular amino acid availability, lysosomal number and glycolysis which is important for innate and adaptive immunity and neurodevelopment. (60) Stepensky et al demonstrated TPPII deficiency results in premature cellular immunosenescence in T- and B-lymphocytes, leading to phenotypic alternations, defects in apoptosis and proliferation and functional effector skewing. (61) Three patients from these studies underwent HCT, one was alive with successful correction of autoimmunity and immunodeficiency, one was alive but with no long-term disease outcome data, and one died of adenovirus infection. Long-term disease outcome data are required to study the impact of HCT on developmental outcome.

Prolidase deficiency

Prolidase enzyme hydrolyses dipeptides containing C-terminal prolife proline and hydroxyproline residues. Prolidase deficiency is a rare disorder with an autosomal recessive mutation in prolidase gene, peptidase D (PEPD), resulting in massive excretion of urinary iminodipeptides. The clinical features of prolidase deficiency are widely variable, including intractable skin ulcers of lower extremities, unusual facial, ocular abnormalities, deafness, splenomegaly, obesity, often with mental retardation and history of recurrent infection. (62)

Caselli et al described the first transplant in an 8-year old child with compound heterozygous mutations in PEPD who presented with recurrent deep ulcerations complicated by infection. She underwent HCT using her matched sibling donor who was confirmed to be a carrier. Post-transplant monitoring of erythrocyte prolidase activity showed that the child had converted to a heterozygous pattern and reduction of excreted urine dipeptides. Unfortunately, the patient died of invasive fungal infection 3 months post-HCT. This study provided the first evidence that allogeneic HCT has the potential to reverse the biochemical features of patients with prolidase deficiency. (63)

Haematopoietic Stem cell transplantation in autoimmune lymphoproliferative disease

Autoimmune lymphoproliferative syndrome (ALPS) represents a failure of apoptotic mechanism leading to defective lymphocyte homeostasis, resulting from mutations in the Fas pathway. Fas is short for FS-7-Associated Surface protein and was first identified as binding a monoclonal antibody from mice immunized with the human fibroblast FS-7 cell line. (64)The surface receptor Fas when bound to Fas ligand (FasL) transmits a death inducing (apoptosis) signal to the Fas expressing cell. ALPS-FAS and ALPS-sFAS are the most common types of ALPS are caused by germline and somatic mutations in the FAS gene. In rare cases, ALPS is caused by mutations in the genes encoding Fas ligand (ALPS-FASLG) or caspase 10 (ALPS-CASP10). The defective apoptosis of lymphocytes mediated through the Fas/FasL pathway leads to accumulation of lymphoid mass and persistence of autoreactive cells. The Fas pathway also appears to play a role in suppression of malignant transformation of lymphocytes. The consequences of defects in this pathway include lymphoproliferative disease, manifested by lymphadenopathy, hepatomegaly, splenomegaly and an increased risk of lymphoma, as well as autoimmune multilineage cytopenias. The diagnosis of ALPS is based upon strict criteria that include clinical findings (lymphadenopathy and/or splenomegaly); laboratory abnormalities including presence of alpha beta double negative T cells, elevated levels of ALPS biomarkers (vitamin B12, IL-10, IL-18 and Fas ligand (FAsL) in serum/plasma), and

defective in vitro Fas-mediated apoptosis; and identification of mutations in genes relevant for the Fas pathway of apoptosis including FAS, FASLG and CASP10. (65)

Management of ALPS focuses upon three aspects: treatment of disease manifestations, prevention and treatment of complications, and curative therapy with allogeneic HCT. While some ALPS patients required no treatment, many require immunosuppression, particularly to treat cytopenias. Sirolimus and mycophenolate mofetil have been studied for long-term management of patients with ALPS. (66) In many ALPS patients the clinical symptoms are moderate or decrease after childhood and adolescence. In HCT perspectives, HCT is the only curative treatment for ALPS but the experience overall is limited and careful consideration is needed given the significant risks associated with allogeneic HSCT. Benkerrou et al and Sleight et al reported two patients who underwent successful HSCT to correct Fas deficiency. (67, 68) The indication for HCT seems therefore limited although it is clear that HSCT could correct the immune defect. HCT can be considered in patients with lymphoma, severe and refractory autoimmune cytopenia, significant immunodeficiency, severe phenotypes or recurrent severe invasive bacterial infection or sepsis. (65, 69)

HCT in other monogenic autoimmune diseases

RAG1 and 2 deficiency

Recombinase activating genes (RAG1 and RAG2) play a pivotal role in the V(D)J recombination process producing clonotypic T and B lymphocyte antigen receptors, thus generating a diverse immune repertoire. Null mutations in RAG have been shown to cause severe combined immune deficiency (SCID) characterized by a complete lack of T and B lymphocytes. (70) Hypomorphic RAG mutations resulting in residual protein function occur with a higher frequency compared to null mutations (71) and have been associated with a broad spectrum of clinical manifestations including Omenn syndrome, atypical SCID, combined immune deficiency with autoimmunity, and common variable immune deficiency. (72-76)The hypomorphic mutations in the RAG genes have been demonstrated to impact on disturbances in both central and peripheral T- and B-cell tolerance. (77-79)

Reports on the HCT indications and outcome in hypomorphic RAG deficiency are limited. In 2016, John et al. reviewed thirteen published cases, all except one transplanted because of worsening immune dysregulation. A variety of conditioning regimens and donors were used. Eleven of thirteen patients were transplanted above the age of six years (range 29 months to 19 years). Infectious and immune dysregulation complications occurred in almost half of the patients. Two patients died of transplant-related complications both in the context of chronic GVHD and 8 were reported alive and well at last follow-up (range 0.5-10 years). (80)

Farmer et al reported on 85 patients with RAG mutations. Autoimmune and/or hyperinflammatory complications were identified in 57 patients and included autoimmune cytopenias (n=33, 57.9%), granulomas (n=9, 15.8%), skin disease (n=8, 14.0%), vasculitis (n=3, 5.3%), neuropathy (n=3, 5.3%), interstitial lung disease (ILD) (n=2, 3.5%), and myopathy (n=1, 1.8%). Skin manifestations included vitiligo, psoriasis, and alopecia. More than half of the patients had more than one disease manifestation. Infections frequently preceded the onset of autoimmune and/or hyperinflammatory manifestations. Autoimmune hemolytic anemia (AIHA) was the most frequent autoimmune complication with a median age at onset of 1.9 years. Therapy-refractoriness to first and second line treatment occurred in two-thirds of the patients and was a major indication for HCT. In about three quarters of the patients with refractory cytopenia stable remission was achieved following HCT. Similarly, HCT was required and successful in three patients with refractory vasculitis and enteropathy. Notably, a median 5-year interval existed between the clinical recognition of immune dysregulation (immunodeficiency and/or autoimmunity) and the final diagnosis of RAG deficiency.(81)

Lawless et al. published results on fifteen adult, late onset, RAG deficient patients from two large PID cohorts thus coming up with an estimated prevalence of RAG deficiency in adult PID in the range of 1%–1.9%. The large majority had developed inflammatory autoimmune complications and autoimmune cytopenias were reported in 40%. Progressive inflammatory lung involvement was the main cause of morbidity and mortality. Five patients were transplanted of whom three survived well and two died of transplant-related infectious complications. (82)

Replacement of T and B cell progenitors in the thymic and bone marrow niches respectively seems pivotal for both proper reconstitution of a donor immune system and elimination of residual recipient hypomorphic RAG-elements that may cause persistent or recurrent immune dysregulation. Given the considerable clinical heterogeneity in patients, even within affected families, testing candidate stem cell donors within those families is mandatory (Schuetz et al. 2014). (83) Early recognition of RAG defects underlying the often complex immune dysregulation and autoimmune disease manifestations is pivotal for proper management of these patients and timely consideration of HCT.

ZAP-70 deficiency

Zeta-Chain Associated Protein Kinase 70kDa (ZAP-70) is a rare combined immunodeficiency caused by recessive homozygous/compound heterozygous loss of function mutations in the ZAP70 gene. In a recent systemic review by Sharifinejad et al which examines the clinical, immunological and genetic features of 49 patients with ZAP-70 deficiency, affected patients

had a broad spectrum of clinical manifestations including recurrent respiratory infection (82%), cutaneous involvement (58%), lymphoproliferation (32%), autoimmunity (19%), enteropathy (18%), and increased risk of malignancies (8%). The predominant immunological features were low CD8+ T cell counts, defective antibody production and decreased lymphocyte responses to mitogenic stimuli. (84)

Cuvelier et al and Brager et al. reported a total of 24 patients with ZAP70 deficiency who under HCT. Ten had matched sibling donors (MSD), 6 matched unrelated donors (MUD), 3 mismatched family donors (MMFD) and 3 haploidentical donors. The median age at HSCT was 10 months (range, 6.7 to 17.2 months). Survivals were 90% for MSD, 100% for MUD, 33% for MMFD and 100% for haploidentical donors. (85, 86). Patients who received myeloablative conditioning achieved complete immune reconstitution. In Cuvelier's report, one patient required a second transplant for primary graft failure after receiving serotherapy only for first HCT.

Sharifinejad et al has shown that the survival after HCT (n=25) was 90%, compared to 40% in non-transplanted patients (n=24). (84) These data support that HCT can lead to a more favourable outcome.

STAT1 gain-of-function

Activating mutations in STAT1 result in an autosomal dominant inherited immunodysregulatory syndrome. Also termed chronic mucocutaneous candidiasis disease (CMCD), recurrent and refractory fungal and staphylococcal infections are a prominent feature in many patients and the diagnosis of combined immunodeficiency is often made. Clinical autoimmune features and/or autoimmune antibodies are present in 43% of patients in one large case series (87). Also, at least in some patients, the mucosal lesions are not due to primary candidiasis infection, but are presumed to be an autoimmune feature, as evidenced by a good response to immunosuppressive treatment (88). Other reported autoimmune features include thyroid disease, enteropathy, autoimmune cytopenia, diabetes mellitus, Addison's disease, SLE, alopecia and autoimmune hepatitis. Additional features of the disease are cerebral aneurysms and an increased risk of malignancy.

Leiding et al reported on 15 patients with STAT1 gain-of-function mutations who underwent allogeneic hematopoietic stem cell transplantation (89). Indication for HCT was therapy refractory IPEX-like disease in 5/15 patients, with enteropathy, type 1 diabetes, thyroiditis, autoimmune cytopenia as most common auto-immune features. Other indications for HCT were combined immunodeficiency, HLH and recurrent severe infections. Two additional reports describe three patients with STAT1 gain-of-function mutations with a combined

immunodeficiency (CID) phenotype who received hematopoietic stem cell transplant, of whom two survived (90, 91). In total, 18 patients were reported to have received 22 hematopoietic transplants, of whom eight patients (44%) survived. Patients who died were generally older than patients who survived (mean age at first SCT 15.5 years vs. 9.2 years). Myeloablative conditioning was associated with worse survival. Two patients died of HLH post-transplant, both had a CID phenotype with HLH prior to transplant. Nine of 18 patients had graft-versus-host disease (skin grades 1-3 in seven patients, gastrointestinal GvHD in two patients, liver graft-versus-host disease in one patient). Graft failure was common, with primary graft failure occurring in three transplant procedures in two patients, and secondary graft loss occurring in six patients.

The patients with IPEX-like disease seemed to have a better outcome than patients with CID, HLH or recurrent infections. However, this may also be due to the fact that these patients were generally younger at time of transplant, since four of five patients with IPEX-like phenotype were younger than 12 years of age at time of HCT, as compared to seven of thirteen patients with other disease phenotypes. All surviving patients who engrafted with almost complete donor chimerism had complete resolution of auto-immunity.

In conclusion, although overall survival in the reported transplanted patients with STAT1 gain-of-function mutations is poor at 44%, patients with IPEX-like disease seem to do better than patients with other disease manifestations and HCT resulted in complete resolution of autoimmunity in patients with (near-)complete donor chimerism.

Complement deficiency

C1q is the recognition molecule of the classical pathway of the complement system and together with C1r and C1s it forms the C1 complex. This complex is important for recognizing e.g. immune complexes and to activate the complement system. C1q is mainly produced by macrophages and immature dendritic cells. C1q is important to clear necrotic cells or apoptotic blebs from the circulation and therefore lack of C1q may predispose to development of autoimmunity like in SLE. In most identified C1q deficient individuals the clinical presentation is towards autoimmunity and the development of SLE, whereas a minor group presents with recurrent infections. The treatment of C1q deficient patients has mainly been aimed at the symptoms, although fresh frozen plasma containing C1q is applied in a subset of the patients. In an international survey, Schaarenburg et al reported 45 C1q deficient patients. The median age at diagnosis was 9 years but with a large age range. Most patients (36/45) were diagnosed during a work-up for SLE or SLE plus infections and 6/45 for recurrent infections only. In this cohort 9 patients had died, all except one before the age of 20, mainly due to infections/sepsis. (92) Studies in C1q deficient mice have

demonstrated that C1q levels could be restored by bone marrow transplantation (93, 94), thus providing the rational for HCT in C1q deficient patients. Arkwright reported HCT with an HLA identical sibling in a 17 year old boy with a positive family history suffering from complicated SLE. Following myeloablative conditioning withtreosulfan, fludarabine, thiotepa and alemtuzumab full donor chimerism was achieved. Restoration of normal C1q levels was associated with resolution of clinical SLE manifestations and autoantibodies. (95) Olsson et al. reported HCT in two unrelated patients, a 9 year old boy with therapy-resistant cerebral SLE and a 12 year old girl with therapy-resistant discoid lupus. The first patient received conditioning with treosulfan, fludarabine and ATG plus etopside because of secondary hemophagocytosis followed by a matched unrelated donor marrow graft. Restoration of C1q levels and functionality of the classical complement pathway was demonstrated. The patient unfortunately succumbed from refractory GvHD related complications following donor lymphocyte infusion to treat post-transplant lymphoproliferative disease. The second patient received a bone marrow graft from her HLA-identical sister after treosulfan, fludarabine and ATG conditioning. Hematopoietic reconstitution with stable mixed chimerism was reported with concomitant restoration of (sub) normal C1q levels and resolution of SLE activity. (96) Although the number of reported clinical cases is limited, it is clear that HCT can correct C1q deficiency and result in resolution of autoimmune disease manifestations. Given the clinical heterogeneity, even within families, counselling of C1q deficient patients for allogenic HCT remains a challenge.

Calcium Chanel Defects: ORAI1 deficiency and STIM1deficiency

Mutations in *ORAI1* or *STIM1* genes in human patients are associated with a unique clinical phenotype that is characterized by immunodeficiency, autoimmunity, lymphoproliferation, muscular hypotonia, and ectodermal dysplasia with defects in sweat gland function and dental enamel formation. (97, 98) The Paris group reported the first two patients who underwent HCT for ORAI1 mutation and a recent update showed that these patients were alive 16 years post-HSCT, but they have persistent myopathy and ectodermal dysplasia. (99) Chou et al presented a patient who had refractory CMV pneumonitis and hypotonia at 3 months of age. The patient was confirmed to have a homozygous mutation in *ORAI1*. After myeloablative unrelated donor HCT at 9 months of age, he had resolution of his recurrent infection but his hypotonia persists. (100) HCT outcomes from *STIM1*-LOF mutation showed the same pattern with resolution of infection but persistent muscular hypotonia. (101, 102). These reports showed that HCT is able correct the defect immunity but muscular dystrophy and ectodermal dysplasia persist after HCT.

Concluding remarks

Monogenic autoimmune diseases are rare disorders but the number of patients who are diagnosed with such diseases is rapidly increasing with the expanding use of molecular diagnostic tools such as next generation sequencing as well as with growing awareness among clinicians taking care of these often-complex patients. To make further advances in timely diagnosis and optimizing management of patients with these rare diseases, multidisciplinary specialized teams in dedicated expert centers as well as collaborations between these institutions are pivotal. Further progress in our understanding of the molecular basis and pathophysiology of monogenic autoimmune diseases remain crucial to guide clinical decision making and thus optimize long-term disease outcome. Monogenic autoimmune disease stemming from defects in the HSCs can often be corrected by allogeneic HCT, but immunological diseases due to thymic stromal (such as APECED) or other extra-haematopoietic defects are unlikely to be cured by HCT.

The use of biologic agents as a bridge to transplant might ameliorate symptoms or achieve disease remission and optimize patient performance prior to transplant, such as abatacept in CTLA-4 haploinsufficiency. Disease-activity index or clinical scoring system are being developed to evaluate the extent of immunodeficiency and immunodysregulation in order to facilitate the decision of HCT timing and monitor treatment outcome.

In the last decade important progress has been made in overall safety and efficacy of allogeneic HCT procedures. Still, optimal clinical management of patients with these monogenic diseases including the decision-making process which patients qualify for and benefit from HCT remains challenging as these diseases have a heterogenous spectrum, variable penetrance and lack of predictive markers in most diseases. Short-term transplant survival must be carefully distinguished from long-term disease outcomes, late effects of transplant, and quality of life from the patients' perspective. Novel transplant strategies, including minimal toxic conditioning regimens, pharmacokinetic targeted drug doses, graft manipulation and better GvHD prevention, are required to prevent/reduce late effects. Advances in the field of both stem cell and somatic cell gene therapy are likely to provide attractive therapeutic alternatives for selected patients with monogenic autoimmune diseases. In all cases, patients suffering from these complex diseases as well as their families deserve careful counselling, execution of the HCT procedure as well as multidisciplinary long-term follow-up in specialized PID transplant centres.

Table 1 Monogenic autoimmune diseases: disease characteristics and HCT outcome

Disease OMIM/ inheritance/ gene Estimated prevalence	Hallmarks	Immunodeficiency features	AI features	Immunology features	Mechanisms of autoimmunity	HSCT data	Outcome	Remarks	Ref
Regulatory T cell defects									
IPEX 304790/XLR/*FOXP3* Estimated <1:1,000,000	Early onset enteropathy, type 1 DM	Combined, variable severity	Enteropathy, early onset diabetes, endocrinopathies, cytopenia, hepatitis, skin (eczema, rash, vitiligo), elevated IgE and IgA	T↔; B ↔ Lack of (and/or impaired function of) $CD4^+$ $CD25^+$ $FOXP3^+$ Tregs	T regulatory cell deficiency or loss-of-function	n=5 n=7 n=58	All survived with resolution of enteropathy 3 alive OS 73.2%	Many features of IPEX remit after HCT. Endocrinopathies frequently persist due to permanent organ damage	(10) (11) (12)
CD25 deficiency 606367/AR/*IL2RA* Unknown prevalence	IPEX-like Profound susceptibility to viral, fungal and bacterial infections	Combined, variable severity	Enteropathy, cytopenia, thyroiditis, growth retardation	T ↔/↓; B ↔ Impaired T cell proliferation in vitro No $CD4^+$ $CD25^+$ cells with impaired function of Tregs	Impaired CD25-mediated T-regulatory cell function	n=1	Resolution of enteropathy and dermatitis	Need more data on long-term follow-up	(23)
CD122 deficiency 618495/AR/*IL2RB* Unknown prevalence	Enteropathy, skin abnormalities, AIHA	Recurrent viral (EBV, CMV) infections	Lymphoproliferation, dermatitis, enter-opathy, cytopenia	↑ memory CD8 T cells ↑ Tregs ↑ memory B cells ¯ IL2Rβ expression ↓ Dysregulated signalling in response to IL-2/ IL-15 ↑immature NK cells	Impaired CD122-mediated T-regulatory cell function	n=2	Resolution of symptoms in one patient. Another patient died of CMV pneumonitis during HCT	Need more data on long-term follow-up	(24)

Disease OMIM/ inheritance/ gene Estimated prevalence	Hallmarks	Immunodeficiency features	AI features	Immunology features	Mechanisms of autoimmunity	HSCT data	Outcome	Remarks	Ref
CTLA4 deficiency 123890/AD/*CTLA4* Estimated <1:1,000,000	Progressive loss of B cells, hypogamma-globulinaemia	Upper and lower respiratory tract infection	Autoimmune cytopenias, enteropathy, interstitial lung disease, extra-lymphoid lymphocytic infiltration, recurrent infections	↓T and B cell counts Impaired function of Tregs	T regulatory cell defect, impaired T cell help for B cells	n=8 All MUD n = 12	7 survived and all had resolution of enteropathy and cytopenia 9 survived	HCT is an option for severe cases	(39) (35)
LRBA deficiency 606453/AR/*LRBA* <1:1,000,000	Enteropathy, ALPS/CVID overlap syndrome	Bacterial and opportunistic infection	Enteropathy, cytopenia, arthritis, myasthenia gravis, neurological manifestation (encephalitis, cerebellitis, CNV lymphoma), lymphoproliferation	CD4 ↔/↓; B ↔/↓ T cell dysregulation	CTLA4-dependent T regulatory cell defect, impaired autophagy, autoreactive B cells	n=24 n=7	71% survived All survived	High TRM is seen when HCT is performed late in patients with a high burden of disease	(46) (47)
STAT3 GOF 102582/AD/*STAT3* Unknown prevalence	Early-onset, IPEX-like	Recurrent infections	Enteropathy, endocrinopathies, cytopenia, pneumonitis, hepatitis, lymphoproliferation	T ↔/↓; B ↔	T cell differentiation towards IL-17 production, perturbed T regulatory cell function	n=5 n=18	One survived 11 alive, reversal of immune dysfunction	HCT is potential curative therapy for STAT3 GOF	(49, 53, 54, 100) Personal communi-cation with Forbes

Disease OMIM/ inheritance/ gene Estimated prevalence	Hallmarks	Immunodeficiency features	AI features	Immunology features	Mechanisms of autoimmunity	HSCT data	Outcome	Remarks	Ref
BACH2 deficiency 605394/AD/*BACH2* Unknown prevalence	Enteropathy	Recurrent respiratory tract infection	Enteropathy, lymphoproliferation	Progressive T lymphopenia Impaired memory B lymphocyte development	Haploinsufficiency for a critical lineage specification transcription factor	No report	NR	None	(101, 102)
DEF6 deficiency 610094/AR/*DEF6* Unknown prevalence	Enteropathy, HSM	Recurrent infections	Enteropathy, autoimmune cytopenia	Mild ↓ CD4 & CD8 ⟷/↓ B lymphocyte Impaired Treg function	Impaired CTLA-4 surface trafficking with reduced functional CTLA4 availability	No report	NR	None	(103)
Autoimmunity with or without lymphoproliferation									
APECED 240300/AR/*AIRE* 1-10:1,000,000	Ectodermal dystrophy, 21-hydroxylase autoantibodies	Candidiasis	Endocrinopathies, skin (eczema, rash, vitiligo, alopecia, oral ulcerations, mucocutaneous candidiasis)	T ⟷ B ⟷	Central tolerance defect, anticytokine, enzyme- and tissues-directed autoantibodies	No indication	NR	NR	(104)
ITCH deficiency 613385/AR/*ITCH* Unknown prevalence	Multisystemic autoimmune disease, dysmorphism, developmental delay	None	Early onset chronic lung disease (interstitial pneumonitis), autoimmunity (thyroiditis, IDDM, enteropathy, and hepatitis)	Not evaluated	May cause immune dysregulation by affecting both anergy induction in auto-reactive effector T cells and generation of Tregs	No report	NR	NR	(105-107)

Disease OMIM/ inheritance/ gene Estimated prevalence	Hallmarks	Immunodeficiency features	AI features	Immunology features	Mechanisms of autoimmunity	HSCT data	Outcome	Remarks	Ref
Tripeptidyl-peptidase II deficiency 190470/AR/*TPP2* Unknown prevalence	Lymphoproliferation, cytopenia	Recurrent infection	Lymphoproliferation, severe autoimmune cytopenias,	T ↓ B ↓ Hypergammaglobulinemia	TPP2 deficiency results in premature immunosenescence and immune dysregulation	3 patients	2 alive	1 had successful correction of autoimmunity and immunodeficiency 1 did not have long-term disease survivor Long-term outcome data are important to study impact of HCT on developmental outcome	(59)
JAK1 GOF 147795/AD/*JAK1* Unknown prevalence	Dermatitis, profound eosinophilia, eosinophilic infiltration of liver and gut, massive HSM	Viral infection	Autoimmune thyroid diseases	Not evaluated	Hyperactive JAK1	No report	NR	NR	(108)
Prolidase deficiency 613230/AR/*PEPD* Unknown prevalence	Intractable skin ulcers, dysmorphism, deafness, mental retardation	Recurrent infection	Autoantibodies	T ↔ B ↔	Loss of immune tolerance	n=1	Died of fungal infection at 3 months post-HCT	HCT was able to correct biochemical features of patients with prolidase deficiency	(61)

Disease OMIM/ inheritance/ gene Estimated prevalence	Hallmarks	Immunodeficiency features	AI features	Immunology features	Mechanisms of autoimmunity	HSCT data	Outcome	Remarks	Ref
Autoimmune lymphoproliferative syndrome									
ALPS Estimated >1 to 5:100,000 FAS: 134637/AD or AR/*TNFRSF6* FASLG: 134638/AR/ *TNFSF6* Caspare10: 601762/AD/ *CASP10* Caspase 8: 601763/ AR/ *CASP8* FADD: 602457/AR/ *FADD*	Adenopathy, splenomegaly, autoimmune cytopenia	Rare	Cytopenia, endocrinopathies, kidney disease (glomerulonephritis), lymphoproliferation, lymphoma	↑ TCR αβ+ $CD4^-$ $CD8^-$ double negative T cells B⟷	Apoptosis defects, immature and senescent T cell phenotype, autoreactive T and B cells, impaired debris clearance	n=2	2 alive	HCT is able to correct Fas deficiency	(64, 65)
Other IEI with prominent autoimmunity									
RAG1 and 2 deficiency RAG1: 179615/AR/ *RAG1* RAG2: 179616/AR/ R*AG2*	Autoimmune cytopenia Combined immunodefi-ciency	Recurrent infection	Autoimmune cytopenia, granuloma, vasculitis, neuropathy, interstitial lung disease, myopathy, vitiligo, psoriasis, alopecia	T↓↓ B↓↓ Normal NK cell number	Disturbances in central and peripheral T- and B-cell tolerance	n=12 n=46 n=5 (adult)	8 alive and well 31 alive 3 alive and well	Increased risk of graft rejection, possibly due to activated NK cells, radiation sensitivity	(77) (78) (79)

Disease OMIM/ inheritance/ gene Estimated prevalence	Hallmarks	Immunodeficiency features	AI features	Immunology features	Mechanisms of autoimmunity	HSCT data	Outcome	Remarks	Ref
ZAP-70 deficiency 269840/AR/*ZAP70* Unknown prevalence	Cutaneous involvement, lymphoproliferation	Recurrent respiratory infection	Lymphoproliferation, autoimmunity, enteropathy	↓ CD8 ⟷ CD4 but poor function	Defective T cell developmental and function	n=24	90% MSD (n=10) 100% MUD (n=6) 33% MMFD (n=3) 100% haplo (n=3)	Survival after HCT was 90%, compared 40% in non-transplanted patients	(81-83)
STAT1 gain-of-function 600555/AD/*STAT1* Unknown prevalence	Chronic mucocutaneous candidiasis	Fungal, bacterial, mycobacterial, herpesvirus infection	Autoimmune cytopenia, endocrinopathies	T ⟷ B ⟷	Impaired development of interleukin-17 producing cells	n=18	8 survived	HCT resulted in complete resolution of autoimmunity in patients with near/ complete donor chimerism	(109-111)
C1q deficiency 120500/AR/*C1QA* 125070/AR/*C1QB* 120575/AR/*C1QC* Unknown prevalence	SLE	Infections with encapsulated organism	Features of SLE	T ⟷ B ⟷ Absent CH50 haemolytic activity	Defective activation of classical pathway, diminished clearance of apoptotic cells	n=1	Alive and well	HCT can correct C1q deficiency	(92) (93)

Disease OMIM/ inheritance/ gene Estimated prevalence	Hallmarks	Immunodeficiency features	AI features	Immunology features	Mechanisms of autoimmunity	HSCT data	Outcome	Remarks	Ref
Calcium channel defects ORAI1: 610277/AR/ *ORAI1* STIM1: 605921/AR/ *STIM1* Unknown prevalence	Autoimmunity, ectodermal dysplasia myopathy	Recurrent infection	Lymphoproliferation, autoimmunity	T ⟷; defective TCR mediated activation B ⟷	Defective T cell activation	n=3 (ORAI1 deficiency) n=5 (STIM1 deficiency)	All alive 3 alive	HCT corrects the defect immunity Myopathy and ectodermal dysplasia persist after HCT	(96-99)

AD: autosomal dominant; AIHA: autoimmune haemolytic anaemia; AR: autosomal recessive; DM: Diabetes mellitus; haplo: haploidentical donor; HSM: hepatosplenomegaly; IBD: Inflammatory bowel disease; IDDM: insulin dependent diabetes mellitus; IL: interleukin; MMFD: mismatched family donor; MUD: matched unrelated donor; MSD: matched sibling donor; NR: not relevant; OS: overall survival; XLR: X-linked recessive; SLE: systemic lupus erythematous; TRM: transplant-related mortality; « normal; ↑ increase; ↓ decrease

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