Future of Therapy for Inborn Errors of Immunity

Elena Perez[1]

Abstract

Over the past 20 years, the rapid evolution in the diagnosis and treatment of primary immunodeficiencies (PI) and the recognition of immune dysregulation as a feature in some have prompted the use of "inborn errors of immunity" (IEI) as a more encompassing term used to describe these disorders [1, 2] . This article aims to review the future of therapy of PI/IEI (referred to IEI throughout this paper). Historically, immune deficiencies have been characterized as monogenic disorders resulting in immune deficiencies affecting T cells, B cells, combination of T and B cells, or innate immune disorders. More recently, immunologists are also recognizing a variety of phenotypes associated with one genotype or similar phenotypes across genotypes and a role for incomplete penetrance or variable expressivity of some genes causing inborn errors of immunity [3]. The IUIS classification of immune deficiencies (IEIs) has evolved over time to include 10 categories, with disorders of immune dysregulation accounting for a new subset, some treatable with small molecule inhibitors or biologics. [1] Until recently, management options were limited to prompt treatment of infections, gammaglobulin replacement, and possibly bone marrow transplant depending on the defect. Available therapies have expanded to include small molecule inhibitors, biologics, gene therapy, and the use of adoptive transfer of virus-specific T cells to fight viral infections in immunocompromised patients. Several significant contributions to the field of clinical immunology have fueled the rapid advancement of therapies over the past two decades. Among these are educational efforts to recruit young immunologists to the field resulting in the growth of a world-wide community of clinicians and investigators interested in rare diseases, efforts to increase awareness of IEI globally contributing to international collaborations, along with advancements in diagnostic genetic testing, newborn screening, molecular biology techniques, gene correction, use of immune modulators, and ex vivo expansion of engineered T cells for therapeutic use. The development and widespread use of newborn screening have helped to identify severe combined immune deficiency (SCID) earlier resulting in better outcomes [4]. Continual improvements and accessibility of genetic sequencing have helped to identify new IEI diseases at an accelerated pace [5]. Advances in gene therapy and bone marrow transplant have made treatments possible in otherwise fatal diseases. Furthermore, the increased awareness of IEI across the world has driven networks of immunologists working together to improve the diagnosis and treatment of these rare diseases. These improvements in the diagnosis and treatment of IEI noted over the past 20 years bring hope for a better future for the IEI community. This paper will review future directions in a few of the newer therapies emerging for IEI. For easy reference, most of the diseases discussed in this paper are briefly described in a summary table, in the order mentioned within the paper (Appendix).

Keywords Primary immunodeficiency · Inborn errors of immunity · Fusion protein · Monoclonal antibodies · Small molecule inhibitors · Gene therapy · Newborn screening

Targeting Immune Dysregulation

Advancements in the understanding of immune mechanisms of rheumatologic diseases have led to the development and application of novel therapeutics. Small molecule inhibitors, fusion proteins, and biologics are now being "borrowed" from other indications and used for the treatment of inborn errors of immunity that involve aspects of autoimmunity, lymphoproliferation, and malignancy. The term "precision medicine" describes the use of therapeutic agents to modulate intracellular pathways whose function is increased or diminished as a result of genetic defects. [6] This approach is starting to be applied in the treatment of some IEI. However, rare diseases such as inborn errors of immunity are inherently difficult to study in well-controlled clinical trials

✉ Elena Perez
  eperez@pballergy.com

[1] Allergy Associates of the Palm Beaches, North Palm Beach, FL, USA

and therefore need special attention from clinical immunologists to apply these new therapeutics in unique ways to improve outcomes in their patients.

Small Molecule Inhibitors

Small molecule inhibitors are low molecular weight-targeted therapies that can enter cells easily and modulate other proteins. In the treatment of inborn errors of immunity, small molecule inhibitors have been used in the context of STAT1 and STAT3 GOF mutations and are being studied for APDS (activated phosphoinositide 3-kinase syndrome) due to gain of function in either PIK3CD or PIK3R1 genes Table 1.

Jak Inhibitors (Jakinibs)

The JAK/STAT pathway transduces signals downstream of multiple cytokines [7]. At least 17 cytokines that bind to one of 6 distinct cytokine receptors and transmit signals through the Jak/Stat pathway modulate many types of immune responses including lymphocyte differentiation, innate immunity, erythro- and myelopoiesis, platelet production, antitumor and antiviral immunity, and acute phase responses. One consequence of dysregulated JAK/STAT pathways is autoimmunity, since cytokines involved in the pathogenesis of autoimmune and inflammatory diseases use JAKs and STATs to transduce intracellular signals. Some cytokines signal through specific JAK pathways, for example, the common gamma chain associates only with JAK3 and mediates signaling of IL-2, 4, 7, 15, and 21, while several cytokine receptors associate with JAK1 giving it a broader role [7]. Mutations in JAK/STAT genes cause a number of immunodeficiency syndromes, and polymorphisms in these genes are associated with autoimmune diseases [7, 8]. The success of small molecule JAK inhibitors (Jakinibs) in the treatment of rheumatologic disease demonstrated that intracellular signaling pathways can be targeted therapeutically to treat autoimmunity. JAK inhibitors have proven effective in the treatment of rheumatoid arthritis and other immune mediated diseases, and this paved the way for

their use to treat immune dysregulation in patients with gain of function (GOF) mutations in STAT1 and STAT3 [7, 8]. A comprehensive review of JAK/STAT signaling is available and beyond the scope of this article [7]. However, it is important to recognize that mutations or polymorphisms in JAK and STAT genes lead to several human diseases, for example, loss of function of JAK3 leads to autosomal recessive severe combined immune deficiency similar to common gamma chain deficiency, autosomal dominant LOF in STAT 1 leads to Mendelian predisposition to mycobacterial diseases, while GOF mutations in STAT1 cause chronic mucocutaneous candidiasis, susceptibility to viral and fungal infections, combined immune deficiency, along with organ-specific autoimmunity, and dominant negative mutations in STAT 3 lead to hyper-IgE syndrome, while GOF mutations in STAT3 lead to early-onset lymphoproliferation with multiorgan autoimmunity [7, 8].

The first two small molecule Jak inhibitors (ruxolitinib and tofacitinib) were FDA-approved for treatment of myeloproliferative neoplasm and RA, respectively [7]. Tofacitinib inhibits Jak1 and Jak3, while ruxolitinib preferentially blocks Jak1 and Jak2. The use of these Jakinibs in 17 patients with STAT1 GOF or STAT3 GOF showed symptomatic improvement in 14 of 17 patients treated. Three of the patients died due to complications of severe disease, and tocilizumab (monoclonal antibody against the IL-6 receptor) was used as an add-on therapy in the patients with STAT3 GOF [8]. Adverse events observed included thrombocytopenia, hyperbilirubinemia, transaminase elevations, viral respiratory infections, and herpes zoster. Nonetheless, remarkable improvements in immune dysregulation features of disease were observed with long-term treatment [8].

One challenge in the design of Jakinibs has been concern for potential off-target effects, since the current Jakinibs competitively block the adenosine triphosphate-binding site that is conserved in other Jaks and is structurally similar to other tyrosine kinases. [7] Future directions for jakinib development include (1) development and comparison of selective versus broad JAK inhibitors, (2) application to other diseases that are characterized by elevations in cytokines that signal through JAK/STAT, (3) topical application for psoriasis, atopic dermatitis and ocular diseases, (4) identification of biomarkers predictive of response in groups of patients, and (5) dosing strategies for remission and maintenance. Given the central role of JAK/STAT in cytokine signaling, as more inborn errors of immunity involving cytokine signaling pathways are identified, increased applications of small molecule JAK/STAT inhibitors are expected.

PI3Kδ Inhibitors

Activated phosphoinositide 3-kinase δ syndrome (APDS) is a combined immune deficiency disorder due to either GOF

Table 1 Examples of small molecule inhibitors and fusion proteins used in the treatment of IEI

Small molecule	IEI
Jakinibs: Tofacitinib (Jak1, Jak3) ruxolitinib (Jak1, Jak2)	STAT1 and STAT3 GOF
PI3Kδ inhibitors: leniolisib (under study) nemiralisib (under study)	APDS1 and APDS2
Fusion protein	**IEI**
Abatacept	CTLA-4 and LRBA deficiencies

mutations in PIK3Cδ [resulting in APDS1] or LOF mutations in PIK3R1 [resulting in APDS2]. PIK3Cδ codes for the p110δ catalytic subunit and PIK3R1 codes for the p85α regulatory subunit of PI3K, which is involved in downstream cellular pathways including mTOR [6]. The phenotypes of APDS1 and APDS2 overlap, with characteristics including T cell senescence, lymphoproliferation, autoimmunity, lymphoma, and infections with *S.pneumoniae* and *H. influenzae* as well as recurrent or persistent viral infections (EBV, CMV, HSV, and VZV) [6]. Until recently, treatment of APDS has been gammaglobulin replacement, antibiotic prophylaxis and immunosuppressive regimens, and, in some cases, HSCT with variable results [6]. Due to promising results in APDS with the use of mTOR inhibitors such as rapamycin, the use of selective PI3Kδ inhibitors is being studied in clinical trials of leniolisib and nemiralisib [6].

Biologics

Biologics are therapeutics that target cytokines or their receptors and include monoclonal antibodies and recombinant proteins. Biologics have been an important advancement in the treatment of autoimmune and inflammatory diseases, and new biologics are constantly emerging.

Monoclonal Antibodies and Fusion Receptors

Monoclonal antibodies have revolutionized targeted therapy and decreased the need for broadly immunosuppressive agents in the treatment of inflammation and autoimmune diseases. The nomenclature of monoclonal antibodies is reviewed in Table 2. Likewise, fusion receptors have significantly increased the ability to modulate the immune system by linking the extracellular domains of different transmembrane proteins to another molecule via a linker such as the Fc portion of human immune globulin, which itself can be engineered to be functional or not. The Fc domain increases the plasma half-life, prolongs therapeutic activity, and enables the molecules to interact with Fc receptors on immune cells [9]. Fusion proteins usually compete for binding of a ligand to its specific counter-receptor and, in most cases, prevent downstream effects, although depending on the molecule, they could be engineered to potentiate effects in certain situations [10].

TNF inhibitors include examples of both monoclonal antibodies, such as infliximab, and fusion receptors, such as etanercept. TNF inhibitors have been used clinically to treat rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, juvenile idiopathic arthritis, and psoriasis [10]. Similarly, over the past 20 years, agents inhibiting other proinflammatory cytokines including IL-1 and IL-6 have been developed. Anakinra (a recombinant IL-1rα) and rilonacept (a fusion protein composed of the EC domain of IL-1 accessory protein and the IL-1 receptor attached to the Fc portion of IgG1 that binds IL-1alpha and IL-1beta with high affinity) block IL-1 and have been used to treat cryopyrin-associated periodic fever syndromes. Tocilizumab (a humanized anti-IL-6 receptor mAb) binds to soluble and membrane bound IL-6 receptor and has shown promise in the treatment of RA. Fusion proteins and monoclonal antibodies have also been designed to inhibit T cells, B cells, IgE, and cell adhesion or migration [10]. Some examples (not all inclusive) are: basiliximab (antibody directed at activated T cell IL-2 receptor alpha chain), abatacept (soluble protein comprised of the EC domain of CTLA-4 linked to the Fc portion of IgG1) used in RA, but also "borrowed" for use in CTLA-4 deficiency and LRBA deficiency, rituximab (chimeric IgG1 mAb against CD20), used in non-Hodgkin B cell lymphoma and RA, along with a multitude of other off-label uses, including to treat granulomatous lymphocytic interstitial lung disease in CVID [11, 12], and omalizumab (targeting IgE) in allergic asthma among others [10].

CTLA-4 deficiency and LRBA deficiency are two examples of how the treatment of inborn errors of immunity has benefitted from a better understanding of genes involved in immunity, as well as from the development of newer agents to modulate immunity. A focus on common variable immunodeficiency phenotypes with autoimmunity as a feature has led to the discovery of these disorders, and an observation

Table 2 Nomenclature of monoclonal antibody therapies

	Partial name	Clinical use or characteristic
Beginning of name	Chosen by manufacturer	
Middle of name	-lim	-Immune/inflammatory
	-cir	-Cardiac disorder
	-tu	-Tumor or neoplasm
End of name	-ximab	Chimeric (murine variable region plus human Fc)
	-zumab	Humanized (murine complementarity determining region)
	-umab	Human

that up to 30–40% of patients with CVID may have a genetic defect [13]. Both CTLA-4 deficiency and LRBA deficiency benefit from treatment with abatacept given their closely related roles in T cell signaling and immune regulation. Abatacept is a soluble fusion protein comprised of the extracellular domain of the human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to the modified Fc (hinge, CH2 and CH3 domains) portion of IgG1 and is produced by recombinant DNA technology in a mammalian expression system. CTLA-4 "puts the brakes on" T cell activation and prevents autoimmune responses mediated by Treg cells. CTLA-4 is expressed on activated T cells and binds CD80/86 (the same ligand for CD28 required for "signal 2" of T cell activation) on antigen presenting cells with higher affinity than CD28. The downstream effect of CTLA-4/CD80/86 interaction is to limit proliferation and effector function. LRBA has a role in recycling CTLA-4 back to the cell surface and rescuing it from degradation,therefore, mutations leading to loss of LRBA result increase CTLA-4 degradation and impair T cell function.

Future directions in therapeutics with fusion proteins and monoclonal antibodies include (1) additional targets and functionalities, (2) safety considerations and balancing efficiency with side effects, (3) improved delivery whether IV or SC, and (4) possible enhancements to IVIG and vaccine development. Fusion proteins lend themselves to creativity in the design of molecules with particular specificities. Future directions in Fc-fusion proteins also include investigation of polymeric or monomeric versions, effects of different Ig class and selective binding to different Fc receptors, the role of glycosylation or sialylation in the function of Fc-fusion proteins, improvements in the expediency of "bench to bedside" development of human Fc fusion proteins with improved mouse models, and exploration of Fc fusions to antigens as vaccines. [9]

The use of "precision therapy" for inborn errors of immunity requires further study and collaboration in areas including prediction of the clinical manifestations that will respond to the therapy, and specifics such as dose and length of treatments required, and whether therapies may prevent expected symptoms of the disease over time or induce a sustained remission of a particular IEI. [6, 13–15] A formidable challenge in the study of these newer therapies for inborn errors of immunity is the very rarity of the conditions, making controlled studies difficult, and increasing the need for a thorough understanding of the underlying immunologic etiologies along with sound hypotheses regarding how modulation of the immune response in these conditions would impact the clinical course of disease. The agents used to treat IEI would most likely be "off label" unless a new approach is taken to approve them in the setting of rare diseases.

Prevention and Treatment of Infections

Innovations in Immune Globulin Replacement Therapy

Immune globulin replacement therapy has been the standard of care for deficiencies of antibody level and function and has been extensively reviewed [16–23]. Current gamma-globulin replacement therapies are based on purified IgG, but advances in IgA and IgM-enriched immunoglobulin replacement therapy are taking shape [24]. IgA and IgM have a multimeric structure, can agglutinate bacteria, and are involved in mucosal defense. Products in development are summarized in Table 3.

Therapeutic IgA

IgA is the main mediator of mucosal immunity and is secreted in the respiratory and gastrointestinal tracts. Functions of IgA include agglutination of bacteria, neutralization of toxins, and inhibition of bacterial adherence to

Table 3 IgA and IgM immune globulin products in development [24, 25]

Product	Description	Features	Use in humans?
Pentaglobin	IgA and IgM containing Ig preparation from Cohn Fraction III, (72% IgG, 12% IgM, and 16% IgA) for IV use	-Decreased aggregation -Effective reduction of endotoxin -Greater opsonic activity against *P.aeruginosa*, *S.aureus*, *E. coli* than conventional IVIG	Has been used in the treatment of persistent gastroenteric *C. jejuni* in 2 patients with hypogammaglobulinemia
Trimodulin	IgA and IgM containing Ig with 23% IgM and 21% IgA	-tenfold increase in opsonization of *E. coli* compared to pentaglobin	Phase II trial, which included 160 patients with severe community-acquired pneumonia
IgAbulin	IgA-enriched IgG preparation	-Might provide enhanced bacterial clearance and prevention of infection at mucosal surfaces	-When administered orally: -Prevented necrotizing enterocolitis in babies with low birth weight -Successfully treated children with chronic diarrhea

epithelium. IgA exists as monomers in the serum and dimers at mucosal surfaces in the form of secretory IgA [25]. The therapeutic potential of IgA was recently reviewed and is being explored in different areas including its possible role as an anti-infective or anti-inflammatory agent, as replacement therapy, and as an anti-tumor therapy [25]. Vaccines delivered to mucosal surfaces induce protective IgA responses. IgA also mediates anti-inflammatory responses through FcαR1 binding of monomeric IgA or anti-FcR1 Fab fragments, with therapeutic potential in diseases such as rheumatoid arthritis. Patients with primary antibody deficiency could theoretically benefit from IgA replacement given continued sinopulmonary infections, in some patients, despite IgG replacement. IgA could also be engineered to mediate ADCC by neutrophils through FcαR1 activation to have a powerful anti-tumor effect [25]. Several IgA or IgM enriched products have been studied and are summarized in Table 4. [24] Plasma-derived IgA can be bound to recombinant secretory component which increases its resistance to protease activity and resembles IgA at the mucosal surface. Oral preparations of these have prevented systemic dissemination of S. typhimurium in mice. Further work is needed to understand whether IgA enriched immune globulin replacement therapy could prevent infections in patients with IEI.

Viral-Specific T Cells

A healthy T cell response is important for defense against viral infections, and it is well-known that in patients with deficient T cell immunity, these infections can be fatal. Virus-specific T cells (VST) have been developed for use against viral infections including CMV, EBV, and adenovirus and used in various clinical trials in stem cell transplant patients. These cell products are derived from stem cell donors or third party partially HLA matched donors as "off the shelf" therapy. Recent trials show success rates from 75 to 92% [26]. VST have a promising role in treatment of patients with SCID and other immune deficiencies requiring transplant. Early VST were made from donor-derived EBV-transformed lymphoblastoid cell lines stimulated in culture. Later, peptide libraries representing multiple viral antigens were used to induce rapid expansion of VST targeting a wide range of viral targets in less than 2 weeks. Other advancements, such as the use of rapid selection technologies using MHC multimers or immunomagnetic bead separation techniques, have allowed for even faster VST production. As of 2018, at least 16 publications regarding the use of VST in immune deficiency described treating patients with viral infections and underlying IEI, including HIGM, various forms of SCID, CID, HLH, LAD, GATA2, CGD, CTPS1 deficiency, WAS, NK cell defect, SCAEBV, and XLP. [26] The majority of patients had favorable outcomes with control of infections, although there were some deaths reported. [26] The development of "third party" VST (rather than donor derived) from specialty T cell banks increases the availability of this therapy due to less time needed for production and requirement for only partial HLA-match. VST have been used to combat viral infections in both the pre- and post-transplant period. In phase I studies, VST appear to be safe, well-tolerated, and rarely induce graft versus host disease (GVHD) or cytokine release syndrome [26]. Cytokine release syndrome has been rare, but has been observed in patients with high viral loads. Alloreactivity is reduced in the VST product by using mainly T effector cells. It appears from phase I studies that GVHD when present after VST infusion is low grade [26]. Questions and challenges for the future use of VSTs include the need for randomized controlled studies assessing viral specificity/efficacy and safety, improved availability, added viral targets, improvements in manufacturing, strategies for the maintenance of antigen-specific responses, and cost.

Stem Cell Transplantation and Gene Therapy

Hematopoietic Stem Cell Transplant

Over the past decade, newborn screening for SCID and other T cell deficiencies has ushered in a new era of early detection and treatment with life-saving and curative transplant prior to the onset of severe infections [4]. The success of hematopoietic stem cell transplant (HSCT) for SCID greatly depends upon the age at diagnosis and the infection status of the patient. HSCT is now considered as a curative intervention in primary immune defects beyond SCID Table 4 [4, 5, 27, 28]. Improved outcomes for transplant may be

Table 4 Role of HSCT in various primary immune deficiencies (table [28]) adapted from

Role of HSCT	Immune deficiency
Curative	SCID, CID, CGD, DOCK8, DOCK2, IPEX, WAS, WIP, ARPC1B, CD40L, XLP1, XLP2, APDS, MHC class II, AD HIGE, CTLA4 haploinsufficiency, LRBA, HLH 1–5, GATA2, RAB27A, LAD1, RD
Partially curative	CHH, PGM3, STAT-1 and STAT-3 GOF, SCN, ADA2, C1Q, CD25, IL-10 & IL-10R deficiency, dsDNA break repair disorders
Controversial	CVID, Agammaglobulinemia, other complement deficiencies, DGS, IKBA deficiency, NEMO

attributed to advancements in high-resolution HLA typing, donor selection, choice of stem cell source, and refinements in reduced intensity conditioning for transplant and cellular engineering techniques [28]. Certain primary immune regulatory disorders (PIRD) are also increasingly being treated with HSCT, especially when immunosuppressive treatments are inadequate. [27] Of note, a PIDTC survey including 33 transplant centers, examining HCT between 1982 and 2017 identified that the majority of patients, who had an unknown genetic cause for PIRD at the time, had a CVID phenotype [27]. Autoimmune manifestations and immunodeficiency were the main indications for HCT. This survey also found that the survival rate in patients transplanted for PIRD was similar to another published report for transplant of autoimmune and inflammatory diseases from European centers, 70% at 5 years. [27, 29].

The approach for HSCT needs to be individualized depending on the underlying disease, comorbidities, availability of donor, and the state of health of the patient. Experience with transplant for some IEI diseases spans multiple decades, and best approaches for these are being refined, while in others, including PIRD, experience is less extensive, and approach to transplant is being developed. The evidence based on number of published patients regarding different approaches to hematopoietic stem cell transplant for individual primary immunodeficiencies was recently extensively reviewed [28]. A better understanding of the pathophysiology of the underlying disorders and the immune components affected has influenced the approach to transplant and improved survival over time. For example, the analysis of evidence available supports that conditioning is not required for T cell reconstitution in X-linked SCID, but functional B and NK cell reconstitution is not usually achieved without conditioning in X-linked SCID and JAK3 deficiency, whereas no or low-dose conditioning is indicated for IL-7R deficiency. For RAG deficiency, the use of reduced intensity conditioning is associated with better immune reconstitution, while for ADA deficiency, enzyme replacement therapy can be used as a bridge to transplant or gene therapy, and survival is better after unconditioned transplant than myeloablative or reduced intensity conditioning. Myeloablative conditioning regimens are required for myeloid engraftment in reticular dysgenesis. [28] Due to variations in the underlying defects, as well as individual patient differences even with the same disease, it is difficult to conform to a universal protocol for transplant of IEI. Earlier diagnosis and transplant in general results in better survival. The future challenges and directions for HCT are many and include analysis of long-term follow-up to continue to inform future innovations in HCT, improved identification of patients who would benefit from HCT, how best to handle transplant related complications, improvements in GVHD prophylaxis for example using potential

new strategies such as small molecule inhibitors, the use of VSTs as mentioned above, and development of clinical algorithms regarding treatment of the underlying condition with immune modulation, HCT, or gene therapy if available, and how these interventions might be used together.

Gene Therapy

Gene therapy describes the use of engineered viral vectors to deliver the desired corrected gene into autologous HSC which are then transplanted into the patient. The primary immune deficiency diseases most studied for gene therapy have been X-linked SCID, ADA-SCID, X-linked CGD, and WAS. [30–40] Over the past 25 years, work in the field of gene therapy for primary immunodeficiencies has made significant progress and also expanded the possibilities to include treatments for other diseases. Early gene therapy using gammaretroviral vectors was associated with insertional mutagenesis near proto-oncogenes, resulting in malignancy in some patients. The use of self-inactivating lentiviral vectors has proven to be generally safer and more efficient. Recent advances in gene therapy include improvement in vector safety, protocols for manufacturing high quality virus, and automated CD34 cell purification among others. [37] Numerous clinical trials have shown promise for gene therapy as a viable and possibly more efficient and consistent treatment for primary immune deficiencies. Lentiviral vectors can accommodate large genes (up to 8 kb) and efficiently transduce hematopoietic stem and progenitor cells. [40] Integration profiles of lentiviral vectors are safer than retroviral vectors, and no serious adverse events have been reported after 12 years from the start of the first lentiviral clinical trial. [40].

The first successful retroviral gene transfer into murine hematopoeitic stem cells took place in 1983, and since then the field has made significant progress including HSC gene therapy in X-SCID and ADA-SCID, but also has suffered setbacks and challenges Table 5. [31, 32, 41] Over the following 37 years, the concept of gene therapy has evolved from work with retroviral or lentiviral gene delivery to actual gene editing to correct disease causing genes using techniques including zinc finger nucleases (ZFN), transcript activator like effector nucleases (TALEN), or clustered regularly interspersed short palindromic repeats and CRISPR-associated protein 9 (CRISPR/Cas9). Gene editing eliminates the need for viral vector integration and expression, and instead is based on creating a site-specific double-stranded DNA break by engineered nucleases, which then trigger endogenous DNA repair mechanisms to edit the genome in a permanent and site-specific manner via non-homologous end joining (NHEJ) and homology-directed repair (HDR) mechanisms [37]. The combination of gene editing with autologous HSC transplantation could

Table 5 History of viral vector technology for human gene therapy (adapted from [35, 37])

Year	Gene therapy landmark or setback	Year	Gene editing advances
1983	Successful retroviral gene transfer to murine HSCs	1983	
1990–1996	First attempted T lymphocyte and HSC gene therapy for ADA-SCID	1996	ZFN architecture described
1997	First attempted HSC gene therapy in CGD	1997	
1997–2000	Introduction of conditioning regimens to gene therapy protocols	1997–2000	
2000–2002	Successful HSC gene therapy in SCID-X1 and ADA-SCID Mapping of human genome completed	2000–2002	
2002–2003	Development of SIN gammaretroviral and lentiviral vector systems for applications to PID	2002–2003	
2003	First report of LTR-mediated insertional mutagenesis leading to leukemia	2003	
2006	First retroviral vector trial for WAS started	2009	TALEN code described, first ZFN gene edited T cells infused (CCR5/HIV)
2010	Insertional mutagenesis in gammaretroviral trials for WAS and CGD reported	2012	CRISPR/Cas9 system described
2013–2015	Successful SIN gammaretroviral and lentiviral gene therapy in several PIDs	2013	Cas9-gRNA used in mammalian cells
2014	First report of successful ZFNs-mediated editing in HSPCs	2014	ZFN-modified T cell trial reports safety Preclinical HSC gene correction for X-SCID published
2015	Efficacy of lentiviral gene therapy for WAS published	2015	AAV6 identified as a HDR donor delivery platform
2016	First licensed ex vivo gene therapy Strimvelis™ for ADA-SCID	2016	CRISPR/Cas9 efficiency increases using RNP delivery
2017	In vivo retinal gene therapy approved in US (Luxturna-LCA), Kymriah and Yescarta CAR T cell products approved in US	2017	First in vivo ZFN administration (Hunters syndrome)
2019	Zynteglo approved in Europe (LV/beta-thal)	2018	First ex vivo CRISPR gene edited HSC trial initiated (SCD, beta-thal)
2020	Successful LV gene therapy for CGD reported	2019	First in vivo CRISPR/Cas9 administration (LCA10)

potentially provide an ideal therapeutic option for primary immune deficiencies and would constitute a major development in the field in the future. [37].

Advances in Gene Therapy for ADA Deficiency

Treatment options for ADA deficiency include enzyme replacement therapy (ERT), HSCT, or gene therapy. The first-line curative therapy for ADA is considered HSCT. The use of ERT with PEG-ADA can stabilize patients in the short term, but in the long term, it is very expensive and may decrease efficacy due to decreased thymic output over time. In the earlier trials of gene therapy with retroviral vector, the continued PEG replacement may have impaired the selective growth advantage of gene corrected cells. Later trials discontinued enzyme replacement after gene correction and used non-myeloablative conditioning to improve engraftment. Strimvelis, the first ex vivo gene therapy product to receive regulatory approval in the world, was approved in Europe in 2016, based on data from 18 patients with ADA-SCID who were treated from 2000 to 2011 with a median follow-up of 7 years, showing 100% survival and evidence of long-term gene correction in T cells and maintenance of immune reconstitution [35, 37–42]. Until recently, there had been no reports of insertional oncogenesis or leukemic proliferation observed in greater than 40 ADA patients treated with gamma-retroviral vector gene therapy, but it has been recently reported that a patient treated with Strimvelis for ADA-SCID was diagnosed with T cell leukemia and the cause is under investigation. [35] The most recent trials, which are ongoing in the UK and US, are using a safer self-inactivating lentiviral vector with codon optimized cDNA for adenosine deaminase under control of an elongation factor (elongation factor 1α) promoter with continuation of ERT for one month after gene therapy. For up to 3 years of follow-up, the 30 treated patients have shown excellent efficacy and no associated genotoxicity. [37].

Other advancements and lessons regarding gene therapy for ADA are that the use of low-dose busulfan prior to infusion of gene-modified stem and progenitor cells is required for engraftment, that the use of ERT for 1 month after gene therapy does not blunt the selective advantage of the

ADA expressing cells and may improve outcome, and that improvements in quality of life for patients with ADA-SCID need to be addressed because the presence of neurologic, auditory, and behavioral problems may persist after therapy (either insufficient restoration of ADA expression or CNS damage that has already occurred) [40].

Advances in Gene Therapy for X-Linked SCID

The first gene therapy for X-SCID was carried out in Paris between 1999 and 2002 in 10 infants using a murine leukemia virus based gamma-retrovirus expressing the common gamma chain driven by the viral promoter LTR and without preconditioning. A similar trial in London in 10 patients used a gibbon ape leukemia virus pseudo-typed gamma-retroviral vector also without preconditioning. Seventeen out of twenty patients had recovery of the functional T cell compartment with polyclonal and functioning T cells and only partial restoration of humoral immunity. However, there were 5 patients who developed acute T cell lymphoblastic leukemia due to insertional mutagenesis within a few years, and one of these patients died. [37] Later, parallel trials in Europe and the USA using a self-inactivating gamma-retroviral vector without conditioning in 9 patients had 7 of 8 surviving patients (one died of infection prior to immune reconstitution) showing recovery of functional T cells without recovery of humoral immune function and had improved safety as shown by less clustering of integrations near lymphoid proto-oncogenes. The most recent lentiviral vector in trials is a self-inactivating lentiviral vector with codon optimized cDNA for the common gamma chain, flanked by insulators and driven by an EF1α promoter, used with non-myeloablative busulfan conditioning. So far, patients treated have had selective expansion of gene marked T, B, and NK cells, restoration of humoral responses to immunization, and no vector related adverse events. [37].

Challenges in Gene Therapy for WAS and CGD

Available treatments for chronic granulomatous disease include lifelong prophylactic antibiotics, interferon gamma and, when possible, early myeloablative allogeneic HSCT. Chronic granulomatous disease lends itself to gene therapy, due to the small amount of superoxide production, needed that could result in clinical improvement. However, gene therapy for chronic granulomatous disease has remaining challenges to overcome. Early gene therapy trials demonstrated that conditioning is important for X-CGD gene therapy and that safer vector design is needed, due to leukemic events observed in three patients. A new self-inactivating lentiviral gene therapy expressing gp91phox under control of a myeloid-specific chimeric promoter showed preferential activity during terminal myeloid differentiation, resulting in increased expression of gp91phox in differentiated myeloid cells, rather than other targets. Ongoing trials using this vector are underway, and so far, are showing stable persistence of oxidase positive neutrophils. [37] For Wiskott Aldrich syndrome (WAS), early gene therapy studies showed that the use of gammaretroviral vector for treatment of WAS carried a high level of insertional oncogenesis risk. More recently, a trial using a lentiviral vector encoding WAS performed in Milan, Paris, London, and Boston showed restoration of T and B compartment with only partial correction of the platelet compartment. Longer term follow-up is needed, and so far, most patients treated showed clinical improvement, and one died of infectious complications [37, 40].

Future directions in gene therapy for primary immune deficiencies include (1) optimization of safer vector design to limit adverse events due to insertional mutagenesis, (2) improved transduction processes to increase yield (e.g., improving efficacy for transduction of quiescent stem cells), (3) development of culture supplements to enhance transduction while maintaining engraftment potential of stem cells), (4) characterization of transduced cells, (5) enrichment of stem cells, (6) commercialization and biomanufacturing to increase accessibility, (7) development of GMP cryopreserved cell products for wider distribution, and (8) novel approaches such as in vivo gene therapy [37, 40].

Gene Editing

Gene editing has the potential to cure primary immune deficiencies by providing the correct gene in its natural context. [39] Gene editing may be a safer alternative for the treatment of some primary immunodeficiencies, since aberrant gene expression from viral vectors is avoided. Gene editing approaches create a DNA double-strand break, providing a substrate for the endogenous DNA repair pathways to either knock out genes or insert therapeutic DNA by providing a suitable donor containing sequence homologous to the cleaved ends, thereby conserving the native regulatory motifs surrounding the gene. [35] Zinc finger nucleases (ZFN), transcript activator-like effector nucleases (TALEN), and clustered regularly interspersed short palindromic repeats and CRISPR-associated protein 9 (CRISPR/Cas9) are the currently available platforms available to accomplish gene editing Table 6. The first trial of zinc finger nucleases (ZFN) in humans used ZFN to knock out CCR5 in T cells for patients with HIV, demonstrating that gene editing can be safe in T cells. [35] TALEN and CRISPR are being used in immunotherapy products, such as CAR T cells. X-SCID HSC have been corrected using ZFN and non-integrating lentiviral vectors in a mouse model, and CRISPR/Cas9 along with adeno-associated virus type 6 (AAV6) homology donors are showing promise with levels as high as 50% gene correction in hematopoietic stem cells (HSC) [35].

Table 6 Platforms for gene editing (table [37]) adapted from

Platform	Details
Zinc finger nucleases (ZFN) and transcription activator like effector nucleases (TALEN)	ZFNs and TALENs are fusions between arrays of zinc fingers or TALEN DNA-binding domains and the dimerization-dependent FokI nuclease domain They are directed to site-specific targets of genomic DNA and create a dsDNA break at the site Both require extensive engineering and optimization for each new target
Clustered regularly interspersed short palindromic repeats/Crispr-associated protein 9 (CRISPR/Cas9)	CRISPR/Cas9 is an RNA-guided endonuclease A 23 nucleotide long RNA linked to the CRISPR-domain (gRNA), guides the CRISPR-Cas9 to find the complementary protospacer DNA target in a genome where it cuts the double-stranded DNA precisely 3 base pairs upstream of a PAM (protospacer adjacent motif)

Broken DNA ends generated by these are repaired either by:
Non-homologous end joining (NHEJ) resulting in small insertion/deletions (indels) to disrupt target allele], or by homology directed repair (HDR) to precisely replace desired nucleotides with delivery of the homologous DNA template

Future directions for the optimization of gene editing efficiency in HSC include improving ex vivo expansion of HSC while preserving their primitive phenotype, optimizing the ex vivo expansion of HSC cells, improving transfection techniques including using mRNA encoding the nucleases to avoid toxicity from plasmids, improving donor template platforms such as CRISPR/Cas9 plus AAV6 donor template and assessment of off-target effects, improving sustained levels of corrected cells over time, and conducting preclinical safety and tumorgenicity studies. [37].

Hematopoeitic Cell Therapy vs Medical Therapy and the Need for Genetic Testing

The management of inborn errors of immunity have been discussed in terms of a spectrum from conditions requiring exclusive medical therapy to conditions requiring exclusive hematopoietic cell therapy and those in between [43]. These conditions are subject to change depending on future treatment advances and summarized in their current categories in Table 7 [43]. Alternative treatments to HCT should be considered if available and allow a good quality of life. HCT should not be considered for conditions such as pure antibody deficiencies, including XLA, or for disorders, such as thymic dysfunction or complement deficiencies, for which the underlying defect is not correctable with HCT. Patients with diseases, for which other effective, well-tolerated therapies are available, should also not be considered for HCT–for example, patients with certain autoinflammatory syndromes that are treatable with IL-1 blocking antibodies or an rIL-1R antagonist. In patients with CVID plus complications such as immune dysregulation, refractory cytopenias, autoimmune hepatitis, and colitis, HCT may be a consideration [43].

Multiple questions must be considered in assessing risk of treatment modalities whether medical or transplant-based, particularly, (1) is the disease state treatable with conservative measures or does the condition require transplant for survival, (2) does the genotype and phenotype of the underlying disease respond better to either transplant or medical therapy and is malignancy a risk if the gene defect is treated vs definitively corrected, (3) for conditions needing transplant, is a donor available, (4) what are the risks to the patient regarding conditioning therapy, (5) what co-morbidities are present that would increase risk of transplant, (6) is the transplant center experienced with the particular inborn error of immunity, and (7) have economic consequences of transplant been considered and is there access to care where the patient lives? [43]. Often the clinical immunologist must weigh the benefit of treatment options for patients based on published evidence of efficacy and risks of the particular therapy used in other disease states against the risks of leaving the condition untreated. Clinical immunologists rely on networks and societies to share clinical expertise and on colleagues to publish case series and case reports, which may become valuable to others as commonalities in presentation are observed in groups of patients with similar genetic findings. Discussions with patients and families regarding off-label medical therapies are crucial to shared decision making in the management of patients with inborn errors of immunity. [43].

Table 7 Spectrum of inborn errors of immunity treated with medical therapy or hematopoietic cell therapies ([43] adapted from)

Treatment for inborn errors of immunity from medical management to hematopoietic cell therapy

Medical therapies:	Exclusively medical	Mostly medical	"In between"	Mostly HCT	Exclusively HCT	Hematopoietic cell therapies: allogeneic HCT Gene therapy
IgG replacement	XLA	ALPS	LRBA deficiency	CD40/CD40L	SCID	
Antibiotics	IgAD	STAT3 LOF	CTLA4 haploinsufficiency	CGD	WAS	
Biologic therapies	APECED	CVID (no genetic dx)	PI3K GOF disorders	GATA2	IPEX	
Immune modulators	Complement deficiencies	Interferonopathies	STAT1 GOF	C1Q deficiency	CD25 deficiency	
Enzyme replacement	DiGeorge	ADA2 deficiency	STAT3 GOF	NEMO	XLP	
Small molecule inhibitors	Thymic defects	MSMD		XIAP Deficiency	IL-10/IL-10R deficiency	
	FMF	Partial LAD-1		DOCK8 deficiency	Primary HLH	
	CAPS	CARD 11 DN		CARMIL2 deficiency	Severe LAD-1	
	DIRA	NLRC4 GOF		STAT1 LOF		
		PLCG2				

ADA2 Adenosine deaminase 2, *ALPS* Autoimmune lymphoproliferative syndrome, *APECED* Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy, *CAPS* Cryopyrin-associated periodic syndrome, *CARD11 DN* Caspase recruitment domain family, member 11 dominant negative, *CARMIL2* Capping protein regulator and myosin linker 2, *CGD* Chronic granulomatous disease, *CTLA-4* Cytotoxic T-lymphocyte associated protein 4, *CVID* Common variable immune deficiency, *DGS* DiGeorge syndrome, *DIRA* Deficiency of interleukin-1 receptor antagonist, *DOCK8* Dedicator of cytokinesis 8, *FMF* Familial Mediterranean fever syndrome, *GATA2* GATA-binding factor 2, *HLH* Hemophagocytic lymphohistiocytosis, *IgAD* IgA deficiency, *IPEX* Immunodysregulation, polyendocrinopathy, enteropathy X-linked, *LRBA* Lipopolysaccharide-responsive and beige-like anchor protein, *MSMD* Mendelian susceptibility to mycobacterial diseases, *NEMO* NF-kappa-B essential modulator, *NLRC4* NLR family CARD domain-containing 4, *LAD-1* Leukocyte adhesion deficiency-1, *PI3K* Phosphatidylinositol-3-kinase, *SCID* Severe combined immune deficiency, *STAT1* Signal transducer and activator of transcription 1, *STAT3* Signal transducer and activator of transcription 3, *WAS* Wiskott Aldrich syndrome, *XIAP* X-linked inhibitor of apoptosis protein, *XLA* X-linked agammaglobulinemia, *XLP* X-linked lymphoproliferative disease

Current and Future Challenges

Progress in the field of clinical immunology necessitates collaboration among clinicians, geneticists, and laboratory-based immunologists. The many advancements in targeted therapies and increased ease of genetic testing have ushered in an era of clinical immunology in which there is a greater demand for accurate genetic diagnosis in order to continue to improve treatments, provide counseling, and understand the prognosis for our patients [5]. At the same time, new challenges in diagnostics, therapeutics, and bioethics have emerged and have been recently reviewed [3, 44, 45]. Some of the challenges center around diagnostics–for example, the inability to identify multigenic disorders, mosaics, somatic, and epigenetic disease-causing variants. Advances in bioinformatics are required to keep genomic libraries up to date, improve diagnostic accuracy, and help to distinguish disease causing variants from variants of uncertain significance [44, 45]. Specialized in vitro testing beyond the usual commercially available tests is also needed to define observed genetic changes as disease causing variants, but is mainly available only at academic research institutions. The diagnosis and care of patients with inborn errors immunity requires an understanding of disease pathogenesis along with personalized approaches that are not supported by large studies or evidence-based medicine. Ethical concerns also exist,

for example, regarding newborn screening for SCID, which may detect other diseases without clear benefit from early detection. [3, 44] The clinical approach to inborn errors of immunity may optimally involve three components: clinical evaluation, immunologic phenotype, and genetic assessment [3]. The future of clinical immunology will continue to rely on the improved characterization of immune defects through genetic testing coupled with scientific observation and reporting on cases and collaboration among clinicians and researchers in the field.

Declarations

Appendix Quick reference guide to the IEI mentioned in the text of this review

Disease	Gene	Clinical findings
STAT-1 GOF	STAT-1	• Chronic mucocutaneous candidiasis • Recurrent respiratory infections • Organ specific autoimmunity • Combined immune deficiency
STAT-3 GOF: early-onset lymphoproliferation with multiorgan autoimmunity	STAT-3	• Early-onset recurrent infections • Lymphadenopathy • Hepatosplenomegaly • Autoimmune disorders (hemolytic anemia, thrombocytopenia, neutropenia, enteropathy, type I diabetes, scleroderma, arthritis, atopic dermatitis, and inflammatory lung disease) • Failure to thrive • Decreased regulatory T cells • Hypogammaglobulinemia • Low memory B cells
APDS1 and APDS2 (activated phosphoinositide 3-kinase syndrome)	PIK3CD (GOF) PIK3R1 (LOF)	• Lymphoproliferation • Recurrent sinopulmonary infections • Airway damage • Chronic herpesvirus viremia • ± elevated IgM

Disease	Gene	Clinical findings
CTLA-4 deficiency	CTLA-4	• Autoimmune cytopenias • Lymphoproliferation • Hypogammaglobulinemia • Lymphocytic infiltration of non-lymphoid organs • Increased risk of lymphoma
LRBA deficiency	LRBA	• Lymphoproliferation • Autoimmunity • Hypogammaglobulinemia • Recurrent infections • Increased risk of lymphoma
CVID (common variable immune deficiency)	Multifactorial	• Hypogammaglobulinemia, low IgA or M • Poor response to vaccines • Low memory B cells • Recurrent sinopulmonary infections, bronchiectasis • Autoimmunity
HIGM (hyper-IgM syndrome)		
	CD40L CD40	• Recurrent sinopulmonary infections • Susceptibility to opportunistic infections • Neutropenia • Autoimmunity
	AID UNG	• Recurrent sinopulmonary infections • Gastrointestinal infections (*Giardia* or viruses) • Splenomegaly • Lymphadenopathy • Autoimmune cytopenia • Hepatitis • Inflammatory bowel syndrome • Arthritis
SCID (severe combined immune deficiency)		• Severe recurrent infections • Failure to thrive • Thrush • Diarrhea
	IL2-Rγc-chain JAK3	• T-B+NK-
	IL7Rα def	• T-B+NK+
	RAG1/2	• T-B-NK+
	ADA	• T-B-NK- • Deficiency of adenosine deaminase is toxic to lymphocytes • Neurodevelopmental deficits • Sensorineural deafness • Skeletal abnormalities • Hepatic abnormalities
HLH (hemophagocytic lympho-histiocytosis)	**Familial:** 1: chromsm-9 2: PRF1 3: UNC13D 4: STX11 5: STXBP2 **X-linked (XLP):** SH2D1A XIAP	• Fever • Hepatomegaly/splenomegaly • Rash • Lymphadenopathy • Thrombocytopenia • Kidney abnormalities • Cardiac • Increased risk for certain cancers

Disease	Gene	Clinical findings
GATA2 deficiency	GATA2	• *Monocytopenia and Mycobacterial infection syndrome*: dendritic cell, monocyte, B and NK lymphoid deficiency • *Familial myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML)* • *Emberger syndrome:* deafness-lymphedema-leukemia syndrome • *NK cell deficiency* • Variable symptoms: o Severe infections (viral or nontuberculous mycobacterial infections) o Respiratory problems o Hearing loss o Lymphedema o Myelodysplasia, acute myeloid leukemia, or chronic myelomonocytic leukemia
CGD (chronic granulomatous disease), (defects in genes for subunits of NADPH oxidase)	CYBA CYBB NCF1 NCF2 NCF4	• Indolent bacterial and fungal infections • Granulomas of the gastrointestinal tract and the genitourinary system • Abscesses of lungs, liver, spleen, bones, or skin • Lymphadenopathy • Diarrhea • [CYBB form is x-linked, others are AR recessive]
CTPS1 deficiency (rare type of SCID)	CTPS1	• Early-onset, severe viral infections with EBV and VZV • Recurrent sinopulmonary bacterial infections • Defective T and B cell proliferation
WAS (Wiskott Aldrich syndrome)	WAS	• Thrombocytopenia, bleeding • Eczema • Combined immunodeficiency • opportunistic infections • Autoimmunity: autoimmune hemolytic anemia, neutropenia, vasculitis, inflammatory bowel disease, renal disease, and arthritis • High risk of B cell lymphomas
NK cell deficiencies	FCGR3A	• Recurrent infections, (herpes, papillomavirus) • Lymphoproliferation • Decreased or normal NK cell number • Defective NK function in spontaneous cellular cytotoxicity • Antibody-dependent cellular cytotoxicity unaffected
	GATA-binding protein 2 gene	• Pulmonary alveolar proteinosis • Aplastic anemia • Recurrent infections (viruses and fungi, mycobacteria) • Cytopenia: monocytes, dendritic cells, neutrophils, and B cells • Decreased NK cells and NK cell precursors • Deficient NK cell-mediated and antibody-mediated cytotoxicity • Susceptibility to myelodysplasia and myeloid leukemia

References

1. Tangye SG, Al-Herz W, Bousfiha A et al (2020) Human inborn errors of immunity: 2019 update on the classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol 40(1):24–64. https://doi.org/10.1007/s10875-019-00737-x

2. Castagnoli R, Notarangelo LD (2020) Updates on new monogenic inborn errors of immunity. Pediatr Allergy Immunol 31(Suppl 26):57–59. https://doi.org/10.1111/pai.13365

3. Abraham RS, Butte MJ (2021) The new "wholly trinity" in the diagnosis and management of inborn errors of immunity. J Allergy Clin Immunol Pract 9(2):613–625. https://doi.org/10.1016/j.jaip.2020.11.044

4. Hale JE, Platt CD, Bonilla FA et al (2021) Ten years of newborn screening for severe combined immunodeficiency (SCID) in Massachusetts. J Allergy Clin Immunol Pract. https://doi.org/10.1016/j.jaip.2021.02.006

5. Heimall J (2019) Now is the time to use molecular gene testing for the diagnosis of primary immune deficiencies. J Allergy Clin Immunol Pract 7(3):833–838. https://doi.org/10.1016/j.jaip.2018.12.022

6. Delmonte OM, Castagnoli R, Calzoni E, Notarangelo LD (2019) Inborn errors of immunity with immune dysregulation: from bench to bedside. Front Pediatr 7:353. https://doi.org/10.3389/fped.2019.00353

7. Banerjee S, Biehl A, Gadina M, Hasni S, Schwartz DM (2017) JAK-STAT signaling as a target for inflammatory and autoimmune diseases: current and future prospects. Drugs 77(5):521–546. https://doi.org/10.1007/s40265-017-0701-9

8. Forbes LR, Vogel TP, Cooper MA et al (2018) Jakinibs for the treatment of immune dysregulation in patients with gain-of-function signal transducer and activator of transcription 1 (STAT1) or STAT3 mutations. J Allergy Clin Immunol 142(5):1665–1669. https://doi.org/10.1016/j.jaci.2018.07.020

9. Czajkowsky DM, Hu J, Shao Z, Pleass RJ (2012) Fc-fusion proteins: new developments and future perspectives. EMBO Mol Med 4(10):1015–1028. https://doi.org/10.1002/emmm.201201379

10. Lee SJ, Chinen J, Kavanaugh A (2010) Immunomodulator therapy: monoclonal antibodies, fusion proteins, cytokines, and immunoglobulins. J Allergy Clin Immunol 125(2 Suppl 2):S314–S323. https://doi.org/10.1016/j.jaci.2009.08.018

11. Chase NM, Verbsky JW, Hintermeyer MK et al (2013) Use of combination chemotherapy for treatment of granulomatous and lymphocytic interstitial lung disease (GLILD) in patients with common variable immunodeficiency (CVID). J Clin Immunol 33(1):30–39. https://doi.org/10.1007/s10875-012-9755-3

12. Verbsky JW, Hintermeyer MK, Simpson PM et al (2021) Rituximab and antimetabolite treatment of granulomatous and lymphocytic interstitial lung disease in common variable immunodeficiency. J Allergy Clin Immunol 147(2):704-712 e17. https://doi.org/10.1016/j.jaci.2020.07.021

13. Leiding JW, Ballow M (2019) Redefining precision medicine in disorders of immune dysregulation. J Allergy Clin Immunol Pract 7(8):2801–2803. https://doi.org/10.1016/j.jaip.2019.07.026

14. Delmonte OM (2020) Immunodeficiency and disorders of immune dysregulation. Pediatr Allergy Immunol 31(Suppl 24):8–10. https://doi.org/10.1111/pai.13163

15. Leiding JW, Forbes LR (2019) Mechanism-based precision therapy for the treatment of primary immunodeficiency and primary immunodysregulatory diseases. J Allergy Clin Immunol Pract 7(3):761–773. https://doi.org/10.1016/j.jaip.2018.12.017

16. Ameratunga R, Woon ST, Gillis D, Koopmans W, Steele R (2013) New diagnostic criteria for common variable immune deficiency (CVID), which may assist with decisions to treat with intravenous or subcutaneous immunoglobulin. Clin Exp Immunol 174(2):203–211. https://doi.org/10.1111/cei.12178

17. Hanitsch L, Baumann U, Boztug K et al (2020) Treatment and management of primary antibody deficiency: German interdisciplinary evidence-based consensus guideline. Eur J Immunol 50(10):1432–1446. https://doi.org/10.1002/eji.202048713

18. Jolles S, Chapel H, Litzman J (2017) When to initiate immunoglobulin replacement therapy (IGRT) in antibody deficiency: a practical approach. Clin Exp Immunol 188(3):333–341. https://doi.org/10.1111/cei.12915

19. Perez EE, Orange JS, Bonilla F et al (2017) Update on the use of immunoglobulin in human disease: a review of evidence. J Allergy Clin Immunol 139(3S):S1–S46. https://doi.org/10.1016/j.jaci.2016.09.023

20. Sriaroon P, Ballow M (2015) Immunoglobulin replacement therapy for primary immunodeficiency. Immunol Allergy Clin North Am 35(4):713–730. https://doi.org/10.1016/j.iac.2015.07.006

21. Yang L, Wu EY, Tarrant TK (2016) Immune gamma globulin therapeutic indications in immune deficiency and autoimmunity. Curr Allergy Asthma Rep 16(8):55. https://doi.org/10.1007/s11882-016-0632-7

22. Cunningham-Rundles C (2011) Key aspects for successful immunoglobulin therapy of primary immunodeficiencies. Clin Exp Immunol 164(Suppl 2):16–19. https://doi.org/10.1111/j.1365-2249.2011.04390.x

23. Jolles S, Orange JS, Gardulf A et al (2015) Current treatment options with immunoglobulin G for the individualization of care in patients with primary immunodeficiency disease. Clin Exp Immunol 179(2):146–160. https://doi.org/10.1111/cei.12485

24. Langereis JD, van der Flier M, de Jonge MI (2018) Limited innovations after more than 65 years of immunoglobulin replacement therapy: potential of IgA- and IgM-enriched formulations to prevent bacterial respiratory tract infections. Front Immunol 9:1925. https://doi.org/10.3389/fimmu.2018.01925

25. Sterlin D, Gorochov G (2021) When therapeutic IgA antibodies might come of age. Pharmacology 106(1–2):9–19. https://doi.org/10.1159/000510251

26. Harris KM, Davila BJ, Bollard CM, Keller MD (2019) Virus-specific T cells: current and future use in primary immunodeficiency disorders. J Allergy Clin Immunol Pract 7(3):809–818. https://doi.org/10.1016/j.jaip.2018.10.049

27. Chan AY, Leiding JW, Liu X et al (2020) Hematopoietic cell transplantation in patients with primary immune regulatory disorders (PIRD): a primary immune deficiency treatment consortium (PIDTC) survey. Front Immunol 11:239. https://doi.org/10.3389/fimmu.2020.00239

28. Castagnoli R, Delmonte OM, Calzoni E, Notarangelo LD (2019) Hematopoietic Stem Cell Transplantation in primary immunodeficiency diseases: current status and future perspectives. Front Pediatr 7:295. https://doi.org/10.3389/fped.2019.00295

29. Greco R, Labopin M, Badoglio M et al (2019) Allogeneic HSCT for autoimmune diseases: a retrospective study from the EBMT ADWP, IEWP, and PDWP working parties. Front Immunol 10:1570. https://doi.org/10.3389/fimmu.2019.01570

30. Aiuti A, Roncarolo MG (2009) Ten years of gene therapy for primary immune deficiencies. Hematology Am Soc Hematol Educ Program 682–9. https://doi.org/10.1182/asheducation-2009.1.682

31. Booth C, Gaspar HB, Thrasher AJ (2011) Gene therapy for primary immunodeficiency. Curr Opin Pediatr 23(6):659–666. https://doi.org/10.1097/MOP.0b013e32834cd67a

32. Booth C, Romano R, Roncarolo MG, Thrasher AJ (2019) Gene therapy for primary immunodeficiency. Hum Mol Genet 28(R1):R15–R23. https://doi.org/10.1093/hmg/ddz170

33. Bloomer H, Smith RH, Hakami W, Larochelle A (2020) Genome editing in human hematopoietic stem and progenitor cells via CRISPR-Cas9-mediated homology-independent targeted integration. Mol Ther. https://doi.org/10.1016/j.ymthe.2020.12.010

34. De Ravin SS, Brault J (2019) CRISPR/Cas9 applications in gene therapy for primary immunodeficiency diseases. Emerg Top Life Sci 3(3):277–287. https://doi.org/10.1042/ETLS20180157

35. Houghton BC, Booth C (2021) Gene therapy for primary immunodeficiency. Hemasphere 5(1):e509. https://doi.org/10.1097/HS9.0000000000000509

36. Kohn DB, Kuo CY (2017) New frontiers in the therapy of primary immunodeficiency: from gene addition to gene editing. J Allergy Clin Immunol 139(3):726–732. https://doi.org/10.1016/j.jaci.2017.01.007

37. Zhang ZY, Thrasher AJ, Zhang F (2020) Gene therapy and genome editing for primary immunodeficiency diseases. Genes Dis 7(1):38–51. https://doi.org/10.1016/j.gendis.2019.07.007

38. Ferrua F, Aiuti A (2017) Twenty-five years of gene therapy for ADA-SCID: from bubble babies to an approved drug. Hum Gene Ther 28(11):972–981. https://doi.org/10.1089/hum.2017.175

39. Fischer A, Hacein-Bey-Abina S (2020). Gene therapy for severe combined immunodeficiencies and beyond. J Exp Med 217(2). https://doi.org/10.1084/jem.20190607

40. Cavazzana M, Bushman FD, Miccio A, Andre-Schmutz I, Six E (2019) Gene therapy targeting haematopoietic stem cells for inherited diseases: progress and challenges. Nat Rev Drug Discov 18(6):447–462. https://doi.org/10.1038/s41573-019-0020-9

41. Thrasher AJ, Williams DA (2017) Evolving gene therapy in primary immunodeficiency. Mol Ther 25(5):1132–1141. https://doi.org/10.1016/j.ymthe.2017.03.018

42. Aiuti A, Roncarolo MG, Naldini L (2017) Gene therapy for ADA-SCID, the first marketing approval of an ex vivo gene therapy in Europe: paving the road for the next generation of advanced therapy medicinal products. EMBO Mol Med 9(6):737–740. https://doi.org/10.15252/emmm.201707573

43. Cooper MA, Zimmerman O, Nataraj R, Wynn RF (2021) Lifelong Immune Modulation Versus Hematopoietic cell therapy for inborn errors of immunity. J Allergy Clin Immunol Pract 9(2):628–639. https://doi.org/10.1016/j.jaip.2020.11.055

44. Arkwright PD, Walter JE (2021) Introducing a new epoch in inborn errors of immunity. J Allergy Clin Immunol Pract 9(2):660–662. https://doi.org/10.1016/j.jaip.2020.11.022

45. Sullivan KE (2021) The scary world of variants of uncertain significance (VUS): a hitchhiker's guide to interpretation. J Allergy Clin Immunol 147(2):492–494. https://doi.org/10.1016/j.jaci.2020.06.011