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Review

Tailored therapies for primary immunodeficiencies

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Abstract. Primary immunodeficiency disorders (PIDs) are rare inherited monogenic disorders of the immune system, characterized by an increased risk of infection, immune dysregulation and malignancies. To date, more than 420 PIDs have been identified. The recent introduction of high throughput sequencing technologies has led to identifying the molecular basis of the underlying aberrant immune pathway, and candidate targets to develop precision treatment, aimed at modifying the clinical course of the disease. In PID, targeted therapies are especially effective to manage immune dysregulation and autoimmunity, also reducing the incidence of side effects compared to conventional treatments, sparing the use of steroids and immunosuppressive drugs. Moreover, in the last years, the approach of conventional treatments such as immunoglobulin replacement therapies has evolved and the indication has expanded to new diseases, leading to individualized strategies to both improve infection control and quality of life. Similarly, the new advent of gene therapy in selected PIDs has introduced the benefit to correct the immunological defect, reducing at the same time the complications related to the hematopoietic stem cell transplantation. Here, we illustrate the most recent findings on tailored treatments for PIDs. (www.actabiomedica.it)

Key Words: Primary immunodeficiencies, autoimmunity, immune dysregulation, target, tailored treatment, immunoglobulin, gene therapy

Introduction

Primary immunodeficiencies (PIDs) are genetic disorders affecting one of the components of the immune system. Over the last two decades, advancements in diagnostic genetic technologies, with whole exome and whole genome sequencing analysis, led to the discovery of an increasing number of PIDs. More than 420 responsible genes have been identified so far (1). Many of these new genetic disorders display a broad spectrum of features that include not only a higher susceptibility to infections but also immune dysregulation signs such as autoimmunity and/or autoinflammation, allergy and increased risk for malignancies, leading to the definition of Inborn Errors of Immunity (IEIs) (2).

The ability to precisely identify the molecular basis of an immunological disorder and to understand the underlying aberrant immune pathway enabled the development of target treatments, aimed at modifying the clinical course of the disease. This approach

represents one of the central components of precision medicine, that uses a specific molecular treatment, alone or in association with standard therapies, to correct or replace the activity of intracellular pathways whose function is altered as a consequence of a specific genetic defect.

Targeted therapies are especially effective in managing immune dysregulation and autoimmunity in PID-related conditions, also reducing the incidence of side effects compared to conventional treatments. Moreover, targeted treatments may contribute to decreasing the use of steroids and immunosuppressive drugs in PIDs with immune-dysregulation, reducing the incidence of infections and adverse events (3). Similarly, the recent advent of gene therapy (GT) in selected PIDs has introduced the benefit to correct the immunological defect, reducing at the same time the complications related to the hematopoietic stem cell transplant (HSCT) (4).

Moreover, in the last years, the approach of consolidated therapies such as immunoglobulin replacement treatment (IGRT) has also evolved, leading to individualized strategies to both improve infection control and minimize the burden of treatment, in order to ameliorate the quality of life in PID. Also, besides conventional use, the indication of IgG treatment is expanding, now including recently described monogenic IEIs with variable defects in qualitative and/or quantitative antibody response (5).

In this paper, we describe recently characterized PIDs and illustrate newly precision-based approaches aimed at targeting the molecular defect linked to each disorder. We also discuss the new tailored approach of validated old IGR therapies and we illustrate the gene therapy landscape for PIDs.

Targeted treatment for IEIs

Cytotoxic T-lymphocyte antigen 4 (CTLA-4)

Cytotoxic T-lymphocyte antigen 4 (CTLA-4) is a key checkpoint molecule, expressed on the surface of activated T cells and T regulatory cells (T regs), that down-regulates the immune response. It acts with different mechanisms, limiting the action of CD80 and CD86 co-stimulatory molecules expressed on the surface of antigen-presenting cells (APCs) and finally modulating the process of immune tolerance and homeostasis (6).

Heterozygous germline mutations in CTLA-4 result in a disease of immune dysregulation and susceptibility to infections (7).

The disease is characterized by incomplete penetrance and variable expressivity and the clinical phenotype includes recurrent infections, severe and life-threatening autoimmune cytopenia, respiratory and gastrointestinal disease. Respiratory involvement consists of recurrent lower and upper respiratory tract infections, granulomatous lymphocytic interstitial lung disease (GLILD), bronchiectasis, and idiopathic lung fibrosis. Enteropathy and Crohn-like disease are the most common and often severe gastrointestinal symptoms (8,9).

The immune phenotype is also variable, the main features being hypogammaglobulinemia, CD4+ T-cell lymphopenia, defective B cell maturation with progressive reduction of B cells, increased proportion of autoreactive $CD21^{low}$ B cells and impaired response to immunizations (10).

The identification of the CTLA4 role in modulating the immune response and its pathway of action led to the development of agents named abatacept and belatacept. These are fusion proteins containing the extracellular domain of CTLA-4 and the Fc portion of human IgG1 (CTLA-4-Fc-IgG1), that act as replacement inhibitors of T-cell activation by blocking the availability of CD80/CD86 ligands for CD28 (11). The first success of this therapy was reported in a Korean 14-years-old girl with autoimmune chronic diarrhea, hepatitis and hemolytic anemia, unsuccessfully treated with multiple other immunosuppressive drugs. Treatment with abatacept improved diarrhea, resolved hemolytic anemia, and led to discontinuation of other immunosuppressants (12).

Recently, Egg D et al (13), in an update of the therapeutic options for CTLA4, identified 29 patients, including 13 updated reports from Schwab et al (10), treated with abatacept, alone or in association with other immunosuppressants. Abatacept was described to be helpful in one case of chronic idiopathic thrombocytopenic purpura, in one case of chronic autoim-

mune hemolytic anemia, and one case of chronic pure red cell aplasia. Regarding GLILD, abatacept was used in 10 patients with a full resolution in five and a partial response in an additional two patients. Nine patients received abatacept for gastrointestinal disease, showing a response rate of 78%. Lastly, the drug was added to steroids in six cases of neurological involvement, four of them showed stabilization of neurological lesions and clinical improvement (14).

Another targeted therapy vedolizumab, an anti-integrin α4β7 monoclonal antibody with gut-specific immunosuppressive effects, firstly approved for Crohn's disease and ulcerative colitis, was successfully used to treat a CTLA4 patient with refractory autoimmune enterocolitis. However, it failed to reverse the hypogammaglobulinemia and pure red cell aplasia in the affected patient (15).

These treatments seem then effective in managing autoimmunity/immune dysregulation, with or without association with another immunosuppressant, but side effects are possible and related to the increased risk of infections and malignancy, limiting the use of this drugs for long periods (13).

Thus, HCT should be considered as a possible valid definitive therapy in CTLA4 haploinsufficiency patients with severe clinical manifestations and limited response to the treatment with immunomodulatory drugs (16).

Lipopolysaccharide-responsive beige-like anchor (LRBA)

The lipopolysaccharide (LPS)-responsive beige-like anchor (LRBA) protein is a cytosolic protein expressed in many tissues, regulating the trafficking of intracellular vesicles and involved in the endocytosis of ligand-activated receptors. LRBA has a crucial role in CTLA-4 regulation; CTLA-4 undergoes endocytosis within T cells where it is either recycled back to the plasma membrane thanks to the LRBA action or degraded within lysosomes. In the case of an LRBA mutation, CTLA4 is degraded and fails to control T-cell activation and maintain Treg-mediated tolerance (17).

First discovered in 2012, LRBA deficiency is an autosomal recessive combined immunodeficiency caused by biallelic mutations in the LRBA gene. The clinical phenotype is characterized by early-onset antibody deficiency with recurrent infections and autoimmunity (18,19). Nonmalignant lymphoproliferation with hepatosplenomegaly and lymphadenopathy, and immune dysregulation are also common. In particular, the latter is reported in almost all the patients and includes autoimmune cytopenia, enteropathy similar to Immunodysregulation-Polyendocrinopathy-Enteropathy-X-linked (IPEX) disease, but also autoimmune hepatitis, myasthenia gravis, uveitis, alopecia, polyarthritis and early-onset diabetes (20-23).

Respiratory complications include GLILD and bronchiectasis mainly related to viral and bacterial infections (21). Gastric adenocarcinoma has also been reported (24).

Laboratory features are hypogammaglobulinemia with normal B cell levels but low switched memory B cells and specific antibodies (20). Circulating T-cells quantities are normal in most cases but Treg cells are decreased (25), with increased CD25 and reduced CTLA4 and FOXP3+ expression (22), along with an increase in double-negative T cells (26) and circulating follicular helper T cells (cTFH) in some patients (27).

Due to the functional interplay between CLTA4 and LRBA, abatacept was used also in patients with LRBA deficiency with good results (28). In three patients it was able to reverse cytopenia, lymphocytic interstitial lung disease and improve lung function but not enteropathy, which required additional immunosuppressive treatments (29). Abatacept was efficacious also in treating enteropathy, lymphoproliferation and autoimmune cytopenia in a large Turkish cohort (30). Moreover, abatacept impacts immunophenotype, increasing naive effector T-cell ratios, functional antibody responses to polysaccharide vaccines, and reducing cTFH levels and markers of T cells activation (29).

Prolonged treatment over several years had minimal infectious or autoimmune complications (29). However, as in CTLA4 haploinsufficiency, HSCT is the only potentially definitive cure for LRBA deficiency but the experience is still limited (31).

Activated phosphoinositide 3-kinase δ syndromes (APDS)

Phosphoinositide-3-kinases (PI3Ks) are heterodimeric proteins composed of a p110a, p110b, or

p110d catalytic subunit associated with a p85 regulatory subunit, each having a role in signal transduction. PI3Kd is highly expressed in lymphocytes, it phosphorylates phosphatidylinositol-4,5 bisphosphate (PIP2) to phosphatidylinositol-3,4,5 trisphosphate (PIP3), an important mediator of PI3K downstream cellular pathways. Indeed PIP3, by attracting the PH domain-containing proteins, including phosphoinositide-dependent kinase-1 (PDK1) and protein kinase B (PKB or AKT), activate different molecules like the mammalian target of rapamycin (mTOR). The latter has a key role in the growth, proliferation and survival of B cells and contributes to the effector T-cell functions (32).

Thus, gain-of-function (GOF) mutations in the genes encoding for the PI3K subunits, PIK3CD or PIK3R1, are responsible for the combined immunodeficiency disorders named Activated phosphoinositide 3-kinase δ syndromes 1 and 2 (APDS1 and APDS2) respectively (33, 34).

Initially described in 2013, APDS clinical presentation includes recurrent sinopulmonary infections especially by encapsulated bacteria leading to bronchiectasis (35), and multiple noninfectious signs such as nonmalignant lymphoproliferation (lymphadenopathy, hepatosplenomegaly, nodular mucosal lymphoid hyperplasia of the gut and the airways), neurodevelopmental delay, and autoimmune and inflammatory diseases, including arthritis and enteropathy, glomerulonephritis and sclerosing cholangitis (36-38). Increased risk for lymphoma and other malignancies is observed (39). Recurrent and chronic viral infections due to Herpesviridae, mainly EBV, are also frequent (40,41).

Patients with APDS frequently display defects in class switching B cells leading to elevated serum IgM production with varied IgG and IgA deficiency, increased levels of transitional B cells and impaired vaccine responses, reduction of naïve CD4 and CD8 T-cells, and increased numbers of CD8 effector T-cells, high numbers of TFH cells and CD57+ senescent T cells (34,37,38, 42).

Standard therapy of APDS includes aggressive treatment of infections, antimicrobial prophylaxis and immunoglobulin replacement therapy. Immunosuppressive therapies, such as anti-CD20 monoclonal antibody (rituximab) and sirolimus, have been used effectively to control lymphoproliferation and autoimmunity (43).

HSCT has also been successful in several patients with APDS and can be considered as a curative option, leading to the resolution of infections and the lymphoproliferative process. However, a limited number of patients who underwent HSCT with elevated rates of post-transplant viral reactivation and engraftment failure at different time points have been reported (44,45). In another report, possibly due to the compromised conditions of affected patients undergoing HSCT, the outcome was less good than expected, with a 2-year overall and graft failure-free survival rates respectively of 86% and 68% (46).

Understanding the APDS mechanism of disease helped to create a personalized treatment in APDS. Considering the evidence of an increased AKT and S6 phosphorylation as a result of augmented mTOR signaling due to the GOF mutations, mTOR target therapy (i.e, rapamycin) has been used with good results in controlling non-neoplastic lymphoproliferative disease and enteropathy, but not for other manifestations like cytopenia (47). Recently, selective PI3Kd inhibitors have been introduced in different clinical trials. In a 12-week open-label study on 6 patients, leniolisib/CDZ173, an oral inhibitor of the p110d subunit of PI3Kd, showed normalization of immune phenotype with a reduction of circulating transitional B cells and senescent CD57+T cells, a decrease in previously elevated IgM and in inflammatory markers. Moreover, nearly all patients showed a significant reduction of lymphoproliferation and autoimmune manifestation. The drug was also well tolerated (48). Seletalisib, another selective PI3Kδ inhibitor was recently tested on seven patients in a phase 1b study showing an improvement of peripheral lymphadenopathy, lung function, thrombocyte levels, and chronic enteropathy. Also, percentages of senescent CD8 T cells and transitional B cells decreased and naive B cells increased. A favorable risk-benefit profile was maintained for ≤96 week (49).

Nemiralisib, an inhaled PI3Kδ inhibitor used to treat hyper inflammation in patients with chronic obstructive pulmonary disease (50), has been proposed to treat also APDS patients affected by lymphoproliferation and respiratory disease with infections and bronchiectasis.

Altogether, these data suggest that rapamycin and selective PI3Kd inhibitors could be effective in managing these patients, improving prognosis and quality of life. Long-term and more extensive data are needed to confirm these results (43).

Signal transducer and activator of transcription (STAT) defects

Members of the signal transducer and activator of transcription (STAT) protein family are intracellular transcription factors contained in most hematopoietic cells including immune cells that mediate many aspects of cellular immunity, proliferation, apoptosis and differentiation.

Six STAT proteins have been described (STAT1-6), which are activated through 4 Janus kinases (Jak1, Jak2, Jak3, Tyk2). Janus kinases are activated after a specific cytokine bind to a transmembrane receptor which stimulates the activation of receptor-bound JAKs. STAT proteins are then recruited and phosphorylated, dimerize, and translocate into the nucleus of the cell where they alter the gene expression of various immune and inflammatory pathways (51). Mutations in several Jaks and STATs and, in particular, both loss-of-function (LOF) and GOF mutations in STAT1 and STAT3 cause immunodeficiency.

STAT1

STAT1 is activated by type I and II interferons (IFN), interleukin (IL) 6, g chain cytokines, IL-10, and IL-23, promoting the expression of genes involved in the IFN-pathway, important for viral and mycobacterial defense. Moreover, when activated, STAT1 inhibits IL-17 pathway balancing the STAT3 activity, to control the inappropriate immune response in particular against Candida infection (52). Thus, LOF STAT1 mutations cause severe susceptibility to viral and mycobacterial infections, whilst GOF STAT1 mutations cause hyperphosphorylation of STAT1 and inhibition of the development of IL-17-producing T cells (TH17), resulting in chronic mucocutaneous candidiasis (53). Nevertheless, GOF STAT1 disease presents a wide spectrum of clinical manifestations. The infection susceptibility includes not only candida infections but also other fungal infections like coccidioidomycosis and histoplasmosis (54), skin and respiratory bacterial infections, mainly due to S. aureus and viral infections, especially due to Herpesviridae (55). Autoimmunity and immune dysregulation (hypothyroidism, cytopenia, diabetes, systemic lupus erythematosus, enteropathy, arthritis, and multiple sclerosis) have also been observed as well as cerebral aneurysms and vasculopathy (56,57).

Clinical disease reflects the immunological impairment detected. Laboratory immune features are variable and include decreased numbers and/or function of T, B, and/or NK cells, hypogammaglobulinemia, low memory B cells levels in some patients and decreased Th17 cells and IL17 production in peripheral blood (58, 59).

First-line treatments are aimed to prevent and treat systemic infections with antimicrobial drugs and immunoglobulin replacement therapy, despite the lack of antibody deficiency in all patients (56). Patients with autoimmune disease require immunosuppressive medications. However, despite treatment, the clinical outcome of GOF STAT1 patients is poor.

HSCT is the only curative treatment, being attempted with variable success depending on patient clinical conditions and age at the time of the transplant (56, 60, 61).

Knowledge of the molecular mechanism of JAK-STAT activation led to the development of mechanism-based precision therapies for the treatment of STAT1-GOF.

Five small molecule inhibitors of the JAK-STAT activation, defined jakinibs, have been recently designed and tested: tofacitinib acts as a JAK 2 and JAK3 inhibitor, ruxolitinib and baricitinib are two JAK1 and JAK2 inhibitors, filgotinib and upadacitinib are more selective JAK1 inhibitors, and new other jakinibs are under clinical trials. (62). Experience with jakinibs is still low but their use seems to be effective in the improvement of immune-dysregulation features, like cytopenia and interstitial lung disease, and in preventing infection rather than reverse an active disseminated infection (63). It was observed also a reduction of the IFN signature and downstream IFN activation in a patient after treatment with baricitinib (64). Moreover, treatment with ruxolitinib partially reversed functional

NK cell deficiency (65) and normalized dysregulated Th responses (66) in two different patients.

Side effects and complications of these drugs include mild thrombocytopenia and elevated liver enzymes.

Considering the description of Herpes zoster infections in two patients, viral monitoring and prophylaxis especially against Herpesviridae are recommended, especially if more than one immunosuppressive agent is administered in combination with Jakinibs (63).

STAT3

STAT3 is a transcription factor that transmits signals to the cell nucleus after activation by a large number of cytokines and growth factors, including IL-2, IL-6, IL-10, IL-12, IL-15, IL-21, IL-23, and IL-27. Through its regulation of gene activity, the STAT3 protein is involved in the regulation of inflammation and control of cell growth and proliferation, migration and apoptosis of different cells, including T cells and B cells (67). In particular, STAT3 activation favors Th17 cell response and balancing of regulatory T cell development (68).

LOF mutations in STAT3 cause a decrease in the number of Th 17 lymphocytes and consequently of IL-17, essential in the defense against infections mainly by bacteria and extracellular fungi. On the contrary, STAT3 GOF mutations promote inflammatory dysregulation with impaired Th17 and differentiation and Treg control (69). Despite incomplete penetrance and variable expressivity observed in family members with GOF STAT3 mutations, the most common disease manifestations include early-onset autoimmunity such as diabetes, enteropathy, hypothyroidism, cytopenia, nonmalignant lymphoproliferation with lymphadenopathy, hepatosplenomegaly and lymphocytic interstitial pneumonia, and recurrent infections due to nontuberculous mycobacteria, fungi, and viruses (70-72). Postnatal short stature is also a typical feature of the disease and is possibly due to the associated reduced levels of phosphorylated STAT5 (73).

The immunological phenotype may be characterized by a variable degree of T/B/NK-cell lymphopenia with a low number of Treg cells, increased levels of double-negative TCRαβ+ T cells and decreased TH17 cells, hypogammaglobulinemia with terminal B cell maturation arrest, and a decreased number of circulating dendritic cells and eosinophils (72,74).

Treatment of GOF STAT3 patients should be focused on treating autoimmune/immune dysregulation manifestations with immunosuppressive agents. Moreover, patients with antibody deficiency, lymphopenia, or functional defects could benefit from IGRT and antimicrobial prophylaxis.

Little experience is on HSCT, attempted in very few patients until now with controversial results (71,72).

Considering the important signaling role of IL-6 through STAT3, treatment with tocilizumab (an anti-IL6R monoclonal antibody) was attempted, with significant clinical improvement of patients with autoimmunity and lymphoproliferation like severe erosive arthritis and scleroderma-like disease in one case (72), hepatitis and enteropathy, lymphoproliferation, cytopenia and interstitial lung disease in others (75).

Recently, adding jakinibs to tocilizumab has been successful at reversing and/or controlling immune dysregulation in patients where the only treatment with tocilizumab was not completely efficacious (63).

These data suggest that this combination of therapies could be a promising effective treatment strategy, and both agents should be considered for use together in the treatment of immune dysregulation in these patients.

Clinical manifestations, immunophenotype and treatment options of the described diseases are summarized in Table 1.

Immunoglobulin replacement therapy

Immunoglobulin G is indicated as replacement therapy (IGRT) for patients with PIDs characterized by absent or deficient antibody production. Since its introduction three decades ago, its benefits have been proven (76) and PID developed an FDA/EMA-approved indication of immunoglobulin, for which all currently available products are licensed (77).

The mainstream use of IGRT includes treatment of agammaglobulinemia due to the absence of B cells

Table 1. Characteristics and treatment options in PIDs with autoimmunity/immune dysregulation

Disease	Gene mutation /Inheritance	Clinical features	Immune phenotype	Treatment options
CTLA4 deficiency	CTLA4/ AD	Recurrent infections, autoimmunity/ immune dysregulation (cytopenia, enteropathy, GLILD)	Hypogammaglobulinemia, CD4+ T-cell lymphopenia, defective B cell maturation with progressive B lymphopenia and impaired response to immunizations	Antimicrobial prophylaxis, immunoglobulin replacement, Immunosuppressants, rituximab, abatacept, belatacept, vedolizumab HSCT
LRBA deficiency	LRBA/AR	Recurrent infections, autoimmunity/ immune dysregulation (including cytopenia, enteropathy, GLILD, hepatitis, myasthenia gravis, uveitis, alopecia, polyarthritis and diabetes) Nonmalignant lymphoproliferation (lympadenopathy, hepatosplenomegaly) Increased risk of gastric adenocarcinoma and other malignancies	Hypogammaglobulinemia with normal B cell levels but low memory B cells and impaired response to immunizations. Normal T cell levels but decreased Tregs and increased double-negative T cells and cTFH	Antimicrobial prophylaxis, immunoglobulin replacement, Immunosuppressants, rituximab, abatacept HSCT
APDS 1 and 2	PIK3CD, PIK3R1/AD	Recurrent bacterial and viral infections, nonmalignant lymphoproliferation (lympadenopathy, hepatosplenomegaly and focal nodular lymphoid hyperplasia), autoimmunity/ immune dysregulation (including cytopenia, arthritis, enteropathy glomerulonephritis and sclerosing cholangitis), increased risk of lymphoma and malignances, developmental delay (APDS 2)	Hypogammaglobulinemia (variable degree of low IgG and IgA and high IgM levels), low memory B cells, high transitional B cells and impaired response to immunizations, low naïve CD4 and CD8 T-cells, and increased CD8 effector T-cells, TFH cells and CD57+ senescent T cell levels	Antimicrobial prophylaxis, immunoglobulin replacement, Immunosuppressants, rituximab, mTOR target therapy (i.e, rapamycin), selective PI3Kd inhibitors (i.e. leniolisib, seletalisib nemiralisib under trials) HSCT
STAT1 GOF disease	STAT1/AD	Recurrent infections, chronic mucocutaneous candidiasis Autoimmunity/ immune dysregulation (including hypothyroidism, cytopenia, diabetes, systemic lupus erythematosus, enteropathy, arthritis, and multiple sclerosis), Increased risk of cerebral aneurysms and vasculopathy	Hypogammaglobulinemia, variable decreased levels and/ or function of T, B, and/or NK cells, decreased Th17 cells and IL17 production	Antimicrobial prophylaxis, immunoglobulin replacement therapy, immunosuppressants, jakinibs (i.e. tofacitinib, ruxolitinib and baricitinib, filgotinib and upadacitinib), HSCT
STAT3 GOF disease	STAT3/AD	Recurrent infections, Autoimmunity/immune dysregulation (including diabetes, enteropathy, hypothyroidism, cytopenia), nonmalignant lymphoproliferation (lymphadenopathy, hepatosplenomegaly and lymphocytic interstitial pneumonia), short stature	Hypogammaglobulinemia, variable degree of T/B/ NK-cell lymphopenia with a low number of Treg cells, increased levels of double-negative TCRαβ+ T cells and decreased TH17 cells, terminal B cell maturation arrest	Antimicrobial prophylaxis, immunoglobulin replacement therapy, immunosuppressants, tocilizumab, jakinibs

CTLA4, Cytotoxic T-lymphocyte antigen 4; *LRBA*, Lipopolysaccharide-responsive beige-like anchor; *APDS,* Activated phosphoinositide 3-kinase δ syndrome; *PIK3*, Phosphoinositide-3-kinases; *STAT,* Signal transducer and activator of transcription; *GLILD,* Granulomatous and Lymphocytic Interstitial Lung Disease; *GOF,* gain of function; *AD,* autosomal dominant; *AR*, autosomal recessive; *HSCT*, hematopoietic stem cell transplantation.

(such as X Linked (XLA) and autosomal recessive (AAR) agammaglobulinemia) and hypogammaglobulinemia with poor antibody function (including common variable immunodeficiency (CVID), hyper IgM syndrome and Good Syndrome) (78-80). In these conditions, due to the risk for pulmonary deterioration because of chronic or subclinical infection (81, 82), early recognition of the diagnosis and initiation of IGRT therapy is crucial. In severe combined immunodeficiency (SCID) with defective T and B-cell function, IGRT is warranted at diagnosis, due to the disappearance of transplacental maternal IgG over time, and until B-cell function is restored in the post-transplantation period, during gene therapy or enzyme replacement (83). Furthermore, selected patients require IGRT indefinitely if B-cell function is never restored (84).

More recently, high-throughput gene sequencing has contributed to individuate additional genetically complex PIDs involving defects in antibody function who may also benefit from IGRT. Many diagnoses have low total levels of IgG, but some have a normal level with documented specific antibody deficiency. Levels of evidence for IGRT in PID are summarized in Table 2 (76, 85, 86). Since the effects of the newly described gene defects on the humoral immune system may not be fully qualified by antibody serum level, functional antibody responses assays and microbiological characterization of the recurrent infections in antibody deficient patients are needed (87).

Although it has been initially supposed that progressive increases in dosage may reduce lung infections and chronic damage, the dosage of IGRT remains an open question (88). For CVID, no correlation was

Table 2. Indication of immunoglobulin replacement for PIDs with antibody deficiency

	Mechanism leading to antibody defect.	**Efficacy of IGRT**	**Evidence Category**	**Strength of the evidence**
1. PID with absent B cells			IIb	B
Agammaglobulinemia (X-linked, AR)	Lack of B cells	Effective in reducing infections (pneumonia, meningitis/encephalitis, septic arthritis)		
Good syndrome	B- and T-cell defects	Effective in reducing infections		
XLP with EBV-induced loss of B cells	Antibody deficiency caused by reduced number of B cells; defective cytotoxic T cells, NK cells	Effective in reducing infections, no effect on EBV-related pathology		
SCID	Severe B- and T-cell deficiency	Temporary benefit while waiting for and during HSCT/GT		
SCID after HSCT without B-cell engraftment	Mixed chimera with donor T cells and recipient B cells	Effective		
2.PID with hypogammaglobulinemia and impaired specific antibody production		Effective	IIb	B
HIgM	Abnormal B-cell signaling resulting in defective CSR and SHM	Effective		
	T/B-cell interaction leading to abnormal CSR and SHM; defect in macrophage activation (CD40L and CD40 deficiency)	Effective, No effective on susceptibility to opportunistic infections		
CVID (including defect of CD19, CD20, CD21, CD80, ICOS, TACI, or BAFF-R)	Hypogammaglobulinemia, antibody deficiency, often CSR affected	Effective		

Table 2. Indication of immunoglobulin replacement for PIDs with antibody deficiency

CVID with complications (splenomegaly, granuloma, autoimmunity, cancer)	Hypogammaglobulinemia, antibody deficiency, CSR and SHM defective, often T-cell defect (abnormal CD40L expression, decreased CD4/CD8 ratio)	Effective in reducing infections but not autoimmunity and granuloma or incidence of malignancy		
3.Clinically and genetically well-described PID with variable defect in antibody qualitative and quantitative response		Might be beneficial	IV	D
WAS, deletion 22q11.2, STAT3 deficiency, AT, VODI, DKC, ICF, Netherton syndrome	Defective antibody responses associated with other immune defects; characteristic syndromic defects	Partially effective; disease-specific strategies required		
CID (including mutations in PNP, ZAP70)	B- and T-cell defects, hypogammaglobulinemia	Limited benefit but HSCT should be considered		
Hypomorphic mutations in RAG1/2, IL2RG, ADA, RMRP, Artemis, and DNA ligase IV	Hypogammaglobulinemia, CID, low B-cell numbers	Limited benefit; HSCT indicated		
Complement deficiencies (C3, C4, C5-9), properdin deficiency	Variable abnormal antibody responses	Might be beneficial; other prophylactic strategies may be considered (hyperimmunization, antibiotic prophylaxis)		
4.PID with normal IgG levels and impaired specific antibody production		Probably beneficial	III	C
Selective antibody deficiency	Defective CSR reported; anti-PPS antibodies measured by ELISA do not reflect functionality	Antibiotic prophylaxis might be equally effective	IV	D
5.Other primary antibody defect				
Transient hypogammaglobulinemia of infancy with severe recurrent infections	Hypogammaglobulinemia, generally normal antibody production	Immunoglobulin replacement not indicated except if antibody production is demonstrated to be temporarily defective	IIb-III	C
IgG subclass deficiency	One or more IgG subclass affected	Immunoglobulin replacement only if a significant antibody deficiency is demonstrated	III	C
Asymptomatic hypogammaglobulinemia and normal antibody responses; selective immunoglobulin deficiencies	Normal B- and T-cell numbers, normal antibody responses; selective IgM, IgA, and IgE deficiency	Immunoglobulin replacement not indicated	IV	D

XLP, X linked lymphoproliferative syndrome; *SCID,* severe combined immunodeficiency*; HIgM,* Hyper IgM syndrome; *CVID,* common variable immunodeficiency; *WAS,* Wiskott-Aldrich Syndrome; *AT,* Ataxia-Telangiectasia; *VODI,* Hepatic veno-occlusive disease with immunodeficiency; *DKC*, Dyskeratosis congenita; *ICF,* Immunodeficiency, Centromeric region instability, Facial anomalies syndrome; *CID,* combined immunodeficiency; *AR*, autosomal recessive; EBV, Epstein-Barr virus; *HSCT,* hematopoietic stem cell transplantation; *GT,* gene therapy; *CSR*, class-switch recombination; *SHM,* somatic hypermutation.

found between IgG trough level and the incidence of pneumonia and serious infections for trough levels (TL) raised over 400 mg/dl (89). Differently, retrospective analyses of data from XLA children revealed that the number and severity of infections are inversely correlated with the dose of IGRT administered (90). At now, most of the experts considered the biologic IgG level that keeps PID patient infection-free extremely variable, suggesting that immunoglobulins dose should be adjusted based on monitored trough serum IgG concentrations and rate of infections (91).

The decision about setting (hospital, hospital outpatient, or home-based setting) and the route of IgG administration should be based on the patient's characteristics, lifestyle, and expectation (92-94). Efficacy has been demonstrated in PIDs either for intravenous immunoglobulin (IVIG) or subcutaneous (SCIG) route and for subcutaneous IgG facilitated by hyaluronidase (fSCIG), with differences in the resultant pharmacokinetic and adverse effect profiles (Table 3). Reasons for a preference for SCIG may include the desire to be autonomous with self-infusions, difficulty with intravenous access, preference for a home setting, decreased need to travel and time off from school/work, and concern for systemic adverse effects with IVIG. Preference for healthcare professionals to be responsible for IGRT administrations, lack of desire to self-administer, less frequent administration, concern for local site reactions with SCIG, and fewer needle sticks, make IVIG an attractive choice (95, 96).

In addition to the function of replacing the missing immunoglobulins, the immunomodulatory effect of IGRT should be also considered. Anti-inflammatory properties of high dose IgG (1-2 gr/kg) are an established treatment for signs of immune dysregulation (i.e. autoimmune cytopenias) also in PIDs. However, the anti-inflammatory effect has been shown also for IGRT (dosage 400 mg/Kg/month) (97).

Table 3. Clinical implication of route for immunoglobulin administration

	IVIG	**SCIG**	**fSCIG**
Efficacy	Proven in PID	Proven in PID	Proven in PID
Dosage	Every 3 to 4 weeks	Daily to biweekly	Every 3 to 4 weeks
Pharmacokinetics	High peak right after the end of infusion, rapid fall in the subsequent 48 h, and slower decline over the next 3-4 weeks	Stable IgG serum concentrations between consecutive infusions	Similar to IVIG but more delayed peak and slow decline over the next 3-4 weeks
Adverse systemic events (rate per-infusion - prescribing information)	Frequent (17-42%*)	Infrequent (2,5-5%**)	Less frequent than IVIG (20%***)
Local site reaction	Rare	Frequent	Frequent
IV access	Yes	No	No
Administration	By trained healthcare professionals only	Self-infusion (by trained patient /caregiver)	Self-infusion (by trained patient /caregiver)
Setting	Hospital (most common), hospital outpatient, or home-based setting	Home (most common)	Home (most common)
Need to travel	Yes	No	No
Time off from school/work	Yes, day(s) of IVIG administration	No	No
Person managing immunoglobulin and materials supplying	Healthcare professionals	Patient /caregiver	Patient /caregiver

IVIG, intravenous immunoglobulin; *SCIG*, subcutaneous immunoglobulin; *fSCIG,* facilitated subcutaneous immunoglobulin. *Gammagard, Privigen, Gammunex, IgVena; ** Hizentra, Cuvitru; ***Hyqvia

Gene therapy

Allogenic HSCT (alloHSCT) is the only curative therapy for many PIDs. However, it is burdened by post-transplant complications due to immunological differences between the patient and the HSC donor, such as rejection of the donor HSC or graft versus host disease (GVHD), or for the toxicity related to the immunosuppressive agents used (98).

Thus, thanks to the genetic and molecular understanding of the mechanisms of PIDs and the identification of the underlying genetic defect, gene therapy (GT) has been developed and offers a valid alternative where a suitable HLA-matched donor is unavailable.

GT consists of the genetic modification of autologous hematopoietic stem and progenitor cells of the patient (HSPCs) with a vector containing the corrected gene product. The CD34+ cells are mobilized from the bone marrow into the peripheral blood after using most commonly a combination of granulocyte colony-stimulating factor and plerixafor, and then harvested through apheresis. Then, they are selected, cultured ex vivo and manipulated to insert corrected gene through transduction of the patients' HSPCs with a vector carrying one or more copies of a therapeutic gene. The patients undergo conditioning to receive their own genetically modified HSPCs that once reinfused, replicate transferring the corrective gene to all immune-hematopoietic lineages, restoring a fully functioning system (99).

The first gene therapy trials on X-linked severe combined immunodeficiency (SCID-X1), and adenosine deaminase (ADA) SCID used gammaretroviral vectors (γRV) with a certain degree of efficacy on gene correction and improvement in immune function but, several years later, this technique complicated with cases of acute myeloid and lymphoid leukemias, as a result of activation of pro-oncogenes adjacent to insertion points of the γRV vector. (100).

Thus, GT using self-inactivating-gamma-retroviral (SIN-cRV) and SIN-lentiviral (LV) vectors (LVs) were optimized to improve the safety and efficacy of the gene transduction into HSPCs, decreasing insertional mutation risk (101,102).

In the context of PIDs, in May 2016 Strimvelis, a SIN-cRV-based product, received regulatory approval by the EMA and is now available for the GT of patients with ADA-SCID who lack a suitable donor for alloHSCT (103), and many other clinical trials are also in advanced stages in Europe and the United States for PIDs, including SCID- X1, ADA- SCID, Wiskott–Aldrich syndrome and chronic granulomatous disease. GT for Artemis and CD18 deficiencies but also for several other PIDs are currently under investigation with promising results (4, 104).

However, patients receiving GT need long-term monitoring to evaluate safety and efficacy for the risk of late insertional mutagenesis. Moreover, further improvements in GT techniques will lead to expanding its application to new PIDs.

Conclusion

It has been recognized that, depending on the specific gene defect, signs of immune dysregulation, such as autoimmunity and hyper inflammation, may be associated and, in some cases, be the predominant clinical manifestations associated with PIDs. As most patients with PIDs present alterations in antibody quantity or quality and display severe recurrent infections, IGRT remains the main supportive and preventive therapeutic tool, together with antimicrobial prophylaxis. IGRT can be used also for its immunomodulatory effects to treat signs of immune dysregulation. This treatment should be personalized based on the patient's characteristics, lifestyle, and expectations.

However, the increasing identification and characterization of the underlying molecular mechanisms led to the development of novel precise therapeutic strategies to modulate the immune system and normalize or, at least, ameliorate the disease-related manifestations. Moreover, despite HSCT remains the best curative therapy thanks to advances in source manipulation and conditioning strategies, GT is showing success in different diseases and hopefully will provide a safe and effective alternative treatment for many PIDs. New and long-term studies would be needed to evaluate the side effects and benefits of these tailored treatments.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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