Tailored therapies for primary immunodeficiencies

Bianca Cinicola1,2, Federica Pulvirenti3, Giulia Brindisi1,4, Gian Luigi Marseglia5,6, Riccardo Castagnoli5,6, Thomas Foiadelli5,6, Carlo Caffarelli7, Amelia Licari5,6, Michele Miraglia Del Giudice8, Anna Maria Zicari1, Marzia Duse1,2, Fabio Cardinale9

1Department of Maternal Infantile and Urological Sciences, Sapienza University of Rome, Rome, Italy; 2 Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy; 3 Department of Internal Medicine and Infectious Diseases, Regional Reference Centre for Primary Immune Deficiencies, Azienda Ospedaliera Universitaria Policlinico Umberto I, Rome, Italy; 4 Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy; 5 Pediatric Clinic, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; 6 Pediatric Unit, Department of Clinical, Surgical, Diagnostic, and Pediatric Sciences, University of Pavia, Pavia, Italy; 7 Pediatric Clinic, Department of Medicine and Surgery, University of Parma, Parma, Italy; 8 Department of Woman, Child and of General and Specialized Surgery, University of Campania ‘Luigi Vanvitelli’, Naples, Italy; 9Department of Pediatrics, Giovanni XXIII Pediatric Hospital, University of Bari, Bari, Italy

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 CD21low 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 phosphorlates 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 naïve 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 PI3Kδ 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 binds 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 non-tuberculous 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 TCR$\alpha\beta^+$ 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
| 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 (lymphadenopathy, 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 (lymphadenopathy, hepatosplenomegaly and focal nodular lymphoid hyperplasia), autoimmunity/immune dysregulation (including cytopenia, arthritis, enteropathy, glomerulonephritis and sclerosing cholangitis), increased risk of lymphoma and malignancies, 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 PI3Kδ 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 TCRβ+ T cells and decreased TH17 cells, terminal B cell maturation arrest | Antimicrobial prophylaxis, immunoglobulin replacement therapy, Immunosuppressants, tocolizumab, 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** |
| Agammaglobulinemia (X-linked, AR) | Lack of B cells | Effective in reducing infections (pneumonia, meningitis/encephalitis, septic arthritis) | IIb | B |
| 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** |
| HlGm | Abnormal B-cell signaling resulting in defective CSR and SHM | Effective | IIb | B |
| 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

| Condition | Symptoms | Treatment and Prognosis |
|-----------|----------|-------------------------|
| **CVID with complications**<br>(splenomegaly, granuloma, autoimmune, 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** | |  |
| 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** | |  |
| Selective antibody deficiency | Defective CSR reported; anti-PPS antibodies measured by ELISA do not reflect functionality | Antibiotic prophylaxis might be equally effective |
| **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 |
| IgG subclass deficiency | One or more IgG subclass affected | Immunoglobulin replacement only if a significant antibody deficiency is demonstrated |
| 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 |

*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 | Stable IgG serum concentrations between consecutive infusions | Similar to IVIG but more delayed peak and slow decline over the next 3-4 weeks |
|                          | end of infusion, rapid fall in the subsequent 48 h, and slower 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

References

1. Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2019 update on the classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol 2020;40:24-64.
2. Castagnoli R, Lougaris V, Giardino G, et al. Inborn errors of immunity with atopic syndromes: a practical guide for allergists. World Allergy Organ J 2021;14:100513.
3. Heimall J. Genetic testing to diagnose primary immunodeficiencies and to identify targeted therapy. Immunol Allergy Clin North Am 2019;39:95-111.
4. Wasserman RL. Personalized therapy: immunoglobulin replacement for antibody deficiency. Immunol Allergy Clin North Am 2019;39:95-111.
5. Wasserman RL. Personalized therapy: immunoglobulin replacement for antibody deficiency. Immunol Allergy Clin North Am 2019;39:95-111.
6. Chikuma S. CTLA-4, an essential immune-checkpoint for T-cell activation. Curr Top Microbiol Immunol 2017;410:99-126.
7. Mitsuiki N, Schwab C, Grimbacher B. What did we learn from CTLA-4 insufficiency on the human immune system? Immunol Rev 2019;287:33-49.
8. Schubert D, Bode C, Kenecke R, et al. Autosomal dominant immune dysregulation syndrome in humans with CTLA4 mutations. Nat Med 2014;20:1410–6.
9. Kuehn HS, Ouyang W, Lo B, et al. Immune dysregulation in human subjects with heterozygous germline mutations in CTLA4. Science 2014;345:1623–7.
10. Schwab C, Gabrys A, Olbrich P, et al. Phenotype, penetrance, and treatment of 133 cytotoxic T-lymphocyte antigen 4-insufficient subjects. J Allergy Clin Immunol 2018;142:1932-46.
11. Pombo-Suárez M, Gomez-Reino JJ. Abatacept for the treatment of rheumatoid arthritis. Expert Rev Clin Immunol 2019;15:319-26.
12. Lee S, Moon JS, Lee CR, et al. Abatacept alleviates severe autoimmune symptoms in a patient carrying a de novo variant in CTLA-4. J Allergy Clin Immunol 2016;137:327-30.
13. Egg D, Rump IC, Mitsuiki N, et al. Therapeutic options for CTLA4 insufficiency. J Allergy Clin Immunol 2021;S0091-6749(21)00891-5. Epub ahead of print.
14. van Leeuwen EM, Cuadrado E, Gerrits AM, Witteveen E, de Bree GJ. Treatment of intracerebral lesions with abatacept in a CTLA4-haploinsufficient patient. J Clin Immunol 2018;38:464-7.
15. Navarini AA, Hruz P, Berger CT, et al. Vedolizumab as a successful treatment of CTLA-4-associated autoimmune enterocolitis. J Allergy Clin Immunol 2017;139:1043-6.
16. Slatter MA, Engelhardt KR, Burroughs LM, et al. Hematopoietic stem cell transplantation for CTLA4 deficiency. J Allergy Clin Immunol 2016;138:615-9.
17. Hou TZ, Verma N, Wanders J, et al. Identifying functional defects in patients with immune dysregulation due to LRBA and CTLA-4 mutations. Blood 2017;129:1458-68.
18. Lopez-Herrera G, Tampella G, Pan-Hamarstrom Q, et al. Deleterious mutations in LRBA are associated with a syndrome of immune deficiency and autoimmunity. Am J Hum Genet 2012;90:986-1001.
19. Alkhairy OK, Abolhassani H, Rezaei N, et al. Spectrum of phenotypes associated with mutations in LRBA. J Clin Immunol 2016;36:33-45.
20. Habibi S, Zaki-Dizaji M, Rafemanesh H, et al. Clinical, immunologic, and molecular spectrum of patients with LPS-responsive beige-like anchor protein deficiency: a systematic review. J Allergy Clin Immunol Pract 2019;7:2379-86.
21. Gamez-Diaz L, August D, Steppensky P, et al. The extended phenotype of LPS-responsive beige-like anchor protein (LRBA) deficiency. J Allergy Clin Immunol 2015;135:217–27.
22. Charbonnier LM, Janssen E, Chou J, et al. Regulatory T-cell deficiency and immune dysregulation, polyendocrinopathy, enteropathy, X-linked-like disorder caused by loss-of-function mutations in LRBA. J Allergy Clin Immunol 2015;135:217–27.
23. Levy E, Stolzenberg MC, Bruneau J, et al. LRBA deficiency with autoimmunity and early onset chronic erosive polyarthritis. Clin Immunol 2016;168:88-93.
24. Bratnic N, Kovac J, Pohar K, et al. Multifocal gastric adenocarcinoma in a patient with LRBA deficiency. Orphanet J Rare Dis 2017;12:131.
25. Azizi G, Mirshafiey A, Abolhassani H, et al. The imbalance of circulating T helper subsets and regulatory T cells in patients with LRBA deficiency: correlation with disease severity. J Cell Physiol 2018;233:8767-77.
26. Revel-Vilk S, Fischer U, Keller B, et al. Autoimmune lymphoproliferative syndrome-like disease in patients with LRBA mutation. Clin Immunol 2015;159:84-92.
27. Alroqi FJ, Charbonnier LM, Baris S, et al. Exaggerated follicular helper T-cell responses in patients with LRBA deficiency caused by failure of CTLA4- mediated regulation. J Allergy Clin Immunol 2018;141:1050–9.
28. Jamee M, Hosseinzadeh S, Sharifinejad N, et al. Comprehensive comparison between 222 CTLA-4 haploinsufficiency and 212 LRBA deficiency patients: a systematic review. Clin Exp Immunol 2021;205:28-43.
29. Lo B, Zhang K, Lu W, et al. Autoimmune disease. Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy. Science 2015;349:436-40.
30. Kiykim A, Ogulur I, Dursun E, et al. Abatacept as a long-term targeted therapy for LRBA deficiency. J Allergy Clin Immunol Pract 2019;7:2790–800.
31. Tesch VK, Abolhassani H, Shadur B, et al. Inborn errors, clinical, and registry working parties of the European Society for Blood and Marrow Transplantation and the European Society for Immunodeficiencies. Long-term outcome of LRBA deficiency in 76 patients after various treatment modalities as evaluated by the Immune Deficiency and Dysregulation Activity (IDDA) score. J Allergy Clin Immunol 2020;145:1452–63.

32. Cantley LC. The phosphoinositide 3-kinase pathway. Science. 2002;296:1655–71.

33. Angulo I, Vadas O, Garcon F, et al. Phosphoinositide 3-kinase delta gene mutation predisposes to respiratory infection and airway damage. Science 2013;342:866–71.

34. Lucas CL, Kuehn HS, Zhao F, et al. Dominant-activating germline mutations in the gene encoding the PI(3)K catalytic subunit p110delta result in T cell senescence and human immunodeficiency. Nat Immunol 2014;15:88–97.

35. Brodsky NN, Lucas CL. Infections in activated PI3K delta syndrome (APDS). Curr Opin Immunol 2021;72:146–57.

36. Elgizouli M, Lowe DM, Speckmann C, et al. Activating PI3Kδ mutations in a cohort of 669 patients with primary immunodeficiency. Clin Exp Immunol 2016;183:221–9.

37. Elkaim E, Neven B, Bruneau J, et al. Clinical and immunologic phenotype associated with activated phosphoinositide 3-kinase δ syndrome 2: a cohort study. J Allergy Clin Immunol 2016;138:210–8.

38. Coulter TI, Chandra A, Bacon CM, et al. Clinical spectrum and features of activated phosphoinositide 3-kinase δ syndrome: A large patient cohort study. J Allergy Clin Immunol 2017;139:597–606.

39. Durandy A, Kracker S. Increased activation of PI3 kinase-δ predisposes to B-cell lymphoma. Blood 2020;135:638–43.

40. Edwards ES, Bier J, Cole TS, et al. Activating PIK3CD mutations impair human cytotoxic lymphocyte differentiation and function and EBV immunity. J Allergy Clin Immunol 2019;143:276–91.

41. Carpenter JM, Lucas CL. Epstein–Barr virus susceptibility in Activated PI3Kδ Syndrome (APDS) immunodeficiency. Front Immunol 2018;8:2005.

42. Jameel TI, Nanda A, Zhang Y, et al. Clinical, immunological, and genetic features in patients with activated PI3Kδ syndrome (APDS): a systematic review. Clin Rev Allergy Immunol 2020;59:323–33.

43. Coulter TI, Cant AJ. The treatment of activated PI3Kdelta syndrome. Front Immunol 2018;9:2043.

44. Nademi Z, Slatter MA, Dvorak CC, et al. Hematopoietic stem cell transplant in patients with activated PI3K delta syndrome. J Allergy Clin Immunol 2017;139:1046–9.

45. Okano T, Imai K, Tsujita Y, et al. Hematopoietic stem cell transplantation for progressive combined immunodeficiency and lymphoproliferation in patients with activated phosphatidylinositol-3-OH kinase δ syndrome type 1. J Allergy Clin Immunol 2019;143:266–75.

46. Dimitrova D, Nademi Z, Maccari ME, et al. International retrospective study of allogeneic hematopoietic cell transplantation for activated PI3K-delta syndrome. J Allergy Clin Immunol 2021;S0091-6749(21)00810-1. Epub ahead of print.

47. Maccari ME, Abolhassani H, Ahamohammadi A, et al. Disease evolution and response to rapamycin in activated phosphoinositide 3-Kinase δ syndrome: the European Society for Immunodeficiencies-activated phosphoinositide 3-Kinase δ syndrome registry. Front Immunol 2018;9:1–8.

48. Rao VK, Webster S, Dalm V, et al. Effective “activated PI3Kdelta syndrome”-targeted therapy with the PI3Kdelta inhibitor leniolisib. Blood 2017;130:2307–16.

49. Diaz N, Juarez M, Cancrini C, et al. Scleralisib for activated PI3Kδ syndromes: open-label phase 1b and extension studies. J Immunol 2020;205:2979–87.

50. Cahn A, Hamblin JN, Begg M, et al. Safety, pharmacokinetics and dose–response characteristics of GSK2269557, an inhaled PI3Kdelta inhibitor under development for the treatment of COPD. Pulm Pharmacol Ther 2017;46:69–77.

51. Harrison DA. The Jak/STAT pathway. Cold Spring Harb Perspect Biol 2012;4:a011205.

52. Zhang Y, Ma CA, Lawrence MG, et al. PD-L1 up-regulation restrains Th17 cell differentiation in STAT3 loss- and STAT1 gain-of-function patients. J Exp Med 2017;214:2523–33.

53. Zhang W, Chen X, Gao G, et al. Clinical relevance of gain- and loss-of-function germline mutations in STAT1: A systematic review. Front Immunol 2021;12:654406.

54. Sampio EP, Hsu AP, Pecharcek J, et al. Signal transducer and activator of transcription 1 (STAT1) gain-of-function mutations and disseminated coccidioidomycosis and histoplasmosis. J Allergy Clin Immunol 2013;131:1624–34.

55. Mizoguchi Y, Okada S. Inborn errors of STAT1 immunity. Curr Opin Immunol 2021;72:59–64.

56. Toubiana J, Okada S, Hiller J, et al. International STAT1 gain-of-function study group. Heterozygous STAT1 gain-of-function mutations underlie an unexpectedly broad clinical phenotype. Blood 2016;127:3154–64.

57. Uzel G, Sampio EP, Lawrence MG, et al. Dominant gain-of-function STAT1 mutations in FOXP3 wild-type immune dysregulation polyendocrinopathy enteropathy-X-linked-like syndrome. J Allergy Clin Immunol 2013;131:1611–23.

58. Baris S, Alroqi F, Kiykim A, et al. Severe early-onset combined immunodeficiency due to heterozygous gain-of-function mutations in STAT1. J Clin Immunol 2016;36:641–8.

59. Ma CS, Wong N, Rao G, et al. Monogenic mutations differentially affect the quantity and quality of T follicular helper cells in patients with human primary immunodeficiencies. J Allergy Clin Immunol 2015;136:993–1006.

60. Kiykim A, Charbonnier LM, Akcay A, et al. Hematopoietic stem cell transplantation in patients with heterozygous STAT1 gain-of-function mutation. J Clin Immunol 2019;39:37–44.

61. Aldave JC, Cachay E, Núñez L, et al. A 1-year-old girl with a gain-of-function STAT1 mutation treated with hematopoietic stem cell transplantation. J Clin Immunol
2013;33:1273-5.
62. Gadina M, Chisolm DA, Philips RL, McInness IB, Changelian PS, O’Shea JJ. Translating JAKs to jakinibs. J Immunol 2020;204:2011-20.
63. Forbes LR, Vogel TP, Cooper MA, et al. 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 2018;142:328-30.
65. Vargas-Hernandez A, Mace EM, Zimmerman O, et al. Ruxolitinib reverses dysregulated T helper cell responses and controls autoimmunity caused by a novel signal transducer and activator of transcription 1 (STAT1) gain-of-function mutation. J Allergy Clin Immunol 2017; 139:1629-40.
67. Vogel TP, Milner JD, Cooper MA. The ying and yang of STAT3 in human disease. J Clin Immunol 2015;35:615-23.
68. Sharma S, Saikia B, Goel S, et al. TH17 cells in STAT3 related hyper-IgE syndrome. Indian J Pediatr 2016;83:110-4.
69. Chandrasekaran P, Zimmerman O, Paulson M, et al. Distinct mutations at the same positions of STAT3 cause either loss or gain of function. J Allergy Clin Immunol 2016;138:1222-4.
70. Flanagan SE, Haapaniemi E, Russell MA, et al. Activating mutations in STAT3 cause early-onset multi-organ autoimmune disease. Nat Genet 2014;46:812-4.
71. Fabre A, Marchal S, Barlogis V, et al. Clinical aspects of STAT3 gain-of-function mutations: a systematic review. J Allergy Clin Immunol Pract 2019;7:1958-69.
72. Milner JD, Vogel TP, Forbes L, et al. Early-onset lymphoproliferation and autoimmunity caused by germline STAT3 gain-of-function mutations. Blood 2015; 125: 591-9.
73. Gutiérrez M. Activating mutations of STAT3: impact on human growth. Mol Cell Endocrinol 2020; 518: 110979.
74. Haapaniemi EM, Kaustio M, Rajala HL, et al. Autoimmunity, hypogammaglobulinemia, lymphoproliferation, and mycobacterial disease in patients with activating mutations in STAT3. Blood 2015; 125: 639-48.
75. Wang W, Liu L, Hui X, et al. Efficacy of tocilizumab therapy in a patient with severe pancytopenia associated with a STAT3 gain-of-function mutation. BMC Immunol 2021;22:19.
76. Ammann AJ, Ashman RF, Buckley RH, et al. Use of intravenous gamma-globulin in antibody immunodeficiency: results of a multicenter controlled trial. Clin Immunol Immunopathol 1982;22:60-7.
77. European Medicine Agency. Core summary of product characteristics for human normal immunoglobulin for intravenous administration (IVIg). Available at https://www.ema.europa.eu/en/core-summary-product-characteristics-human-normal-immunoglobulin-intravenous-administration-ivig. Accessed on 28 July 2021.
Biologic IgG level in primary immunodeficiency disease: the IgG level that protects against recurrent infection. J Allergy Clin Immunol 2008;122:210-2.

92. Lechanska-Helman J, Sobocinska A, Jerzynska J, Stelmach I. The influence of hospital-based intravenous immunoglobulin and home-based self-administrated subcutaneous immunoglobulin therapy in young children with primary immunodeficiency diseases on their parents’ / caregivers’ satisfaction. Pediatr Int 2020;62:316-8.

93. Anterasian C, Duong R, Grueneheimer P, Ernst C, Kitsen J, Geng B. Quality of life differences for primary immunodeficiency patients on home SCIG versus IVIG. J Clin Immunol 2019;39:814-22.

94. Ameratunga R, Ahn Y, Steele R, Woon ST. The natural history of untreated primary hypogammaglobulinemia in adults: implications for the diagnosis and treatment of Common Variable Immunodeficiency Disorders (CVID). Front Immunol 2019;10:1541.

95. Berger M. Choices in IgG replacement therapy for primary immune deficiency diseases: subcutaneous IgG vs. intravenous IgG and selecting an optimal dose. Curr Opin Allergy Clin Immunol 2011;11:532-8.

96. Pulvirenti F, Cinetto F, Pecoraro A, et al. Health-related quality of life in patients with CVID under different schedules of immunoglobulin administration: prospective multicenter study. J Clin Immunol 2019;39:159-70.

97. Matucci A, Maggi E, Vultaggio A. Mechanisms of action of Ig preparations: immunomodulatory and anti-inflammatory effects. Front Immunol 2015;5:690.

98. Gennery AR, Albert MH, Slatter MA, Lankester A. Hematopoietic stem cell transplantation for primary immunodeficiencies. Front Pediatr 2019;7:445.

99. Ferrari G, Thrasher AJ, Aiuti A. Gene therapy using haematopoietic stem and progenitor cells. Nat Rev Genet 2021;22:216-34.

100. Dunbar CE, High KA, Joung JK, Kohn DB, Ozawa K, Sadelain M. Gene therapy comes of age. Science 2018;359:eaan4672.

101. Houghton BC, Booth C. Gene therapy for primary immunodeficiency. Hemasphere 2020;5:e509.

102. Kohn DB, Booth C, Shaw KL, et al. Autologous ex vivo lentiviral gene therapy for adenosine deaminase deficiency. N Engl J Med 2021;384:2002-13.

103. European Medicine Agency. Strimvelis. Available at https://www.ema.europa.eu/en/medicines/human/EPAR/strimvelis. Accessed on 31 July 2021.

104. Fox TA, Booth C. Gene therapy for primary immunodeficiencies. Br J Haematol 2021;193:1044-59.

Correspondence:
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Bianca Cinicola, Department of Maternal Infantile and Urological Sciences, Sapienza University of Rome Viale Policlinico 155, Rome, Italy
Phone +393408442354
Email: biancacinicola@gmail.com