Purpose of review

Primary immunodeficiency disorders (PIDs) are no longer defined by tendency for infections alone. First clinical sign or sequelae of PID may include autoimmunity, such as cytopenias, arthritis or enteropathy. This review addresses the latest in multidisciplinary approaches for expanding clinical phenotypes of PIDs with autoimmunity, including new presentations of known entities and novel gene defects. We also discuss diagnostic tools for identifying the distinct changes in immune cells subsets and autoantibodies, mechanistic understanding of the process, and targeted treatment and indications for hematopoietic stem-cell transplantation (HSCT).

Recent findings

In the past years, increased awareness and use of genetic screening, confirmatory functional studies and immunological biomarkers opened the door for early recognition of PIDs among patients with autoimmunity. Large cohort studies detail the clinical spectrum and treatment outcome of PIDs with autoimmunity with specific immune genes (e.g., CTLA4, LRBA, PI3Kδ, NFKB1, RAG). The benefit of early recognition is initiation of targeted therapies with precise re-balancing of the dysregulated immune pathways (e.g., biologics) or definitive therapy (e.g., HSCT).

Summary

Clinical presentation of patients with PID and autoimmunity is highly variable and requires in-depth diagnostics and precision medicine approaches.

Keywords

autoimmunity, immune dysregulation, primary immunodeficiency, targeted therapy, tolerance

INTRODUCTION

Primary immunodeficiencies (PIDs) are no longer defined by tendency for infections alone. PID patients with noninfectious complications are increasingly recognized with features of ‘immune dysregulation’ including autoimmunity, inflammation, lymphoproliferation or malignancy (Fig. 1) [1].

However, identifying an underlying PID in a heterogenous group of patients with a variety of autoimmune disorders can be a daunting task. Most pediatricians or specialists taking care of patients with autoimmune disorders may not consider immune evaluation in the initial workup and assume low probability. Therefore, it is not uncommon that the specific diagnosis of highly vulnerable patients with genetic immune deficiency disease is delayed.

In this review, we will focus on recent understanding of the most common clinical entities with PID where autoimmune complications dominate and highlight features that may distinguish these patients from the general population of autoimmune patients. We will also introduce a basic description of immune and genetic diagnostic tools that are essential for understanding the underlying immune defect. We will discuss the pathomechanism of autoimmunity in immune-deficient background, including both intrinsic and extrinsic factors. Lastly, we will...
KEY POINTS

- PIDs are no longer defined by infections alone: autoimmunity, such as cytopenias or early-onset inflammatory bowel disease can be first clinical signs.
- Accumulation of multiple autoimmune manifestations with age and family history of variable clinical presentation of immune dysregulation should increase clinical suspicion for underlying PID.
- Autoimmunity in PID emerges secondary to altered balance in immune pathways shaped by intrinsic and extrinsic factors that generate and/or sustain survival of autoreactive clones of lymphocytes.
- With the revolution of early genetic screening, specialties following patients with immune dysregulation can diagnose an underlying PID in increasing numbers.
- Treatment of PID patients with autoimmunity is most successful with narrow-spectrum immune modulation using biologicals specifically targeting immune pathways.
- Allogeneic HSCT and autologous HSCT with gene therapy are considered for genetically defined PID with autoimmunity and poor prognosis.

cites current literature on the decision-making process for targeted therapy and importance of a multidisciplinary approach for autoimmune disorders.

INCREMENTAL AWARENESS FOR AUTOIMMUNITY: THE JANUS FACE OF PRIMARY IMMUNODEFICIENCY DISORDER

In the latter half of the 20th century, two rare classical endocrine monogenic autoimmune disorders were described. These two very early onset disorders are specific defects in regulatory T cells and/or elimination of autoreactive T cells, and are known as the syndromes of IPEX (immunodysregulation, polyendocrinopathy, enteropathy, X-linked) and APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy) (Fig. 2). APECED and IPEX are examples when pediatricians partnered in a multispecialty approach with endocrinologists and gastroenterologists for the care for complex monogenic autoimmune diseases. Once the underlying immune defect of autoimmune regulator (AIRE) (causing APECED) and forkhead box P3 (FOXP3) (causing IPEX) were discovered in 1997 and 2000 respectively, studies were initiated for insight into the disease biology, which informed clinical immunologists for both diagnosis and management of large numbers of patients and eventually enabled transplant specialists to justify the use of HSCT for IPEX cases. Similarly, clinical and research collaboration between pediatric hematologists/oncologists and immunologists began to properly care for patients with persistent multilinage cytopenias, lymphoproliferation, and tendency for malignancy with defects in immune cell apoptosis now termed as ALPS (autoimmune lymphoproliferative syndrome). Once genetic defects, biomarkers, and pathomechanism were better understood, diagnostic approaches and targeted therapies were developed successfully.

The need for a multidisciplinary approach for immune dysregulation among patients with autoimmunity continues on. Beyond IPEX, APECED, and ALPS, disorders with similar presentations (‘IPEX- or ALPS-like’) but different genetic causes have been steadily resurfacing. This group of Mendelian multiorgan autoimmune diseases are now coined as primary immune regulatory disorders (PIDR) with subgroups of dominantly regulatory T-cell defects (T-regopathies) and late-onset or profound combined immunodeficiency disorders where both T and B cells compartments are intrinsically autoimmune prone.

A recent French national study, which is the largest to date and includes all types of PID and autoimmune manifestations, has been published by Fischer et al. One or more autoimmune and inflammatory manifestations were noted in 26.2% of 2183 retrospectively screened PID patients. In particular, immune manifestation of dysregulation, such as autoimmune cytopenias, enteropathy, and skin disease, occurred in 50% of PID patients with T-cell deficiency (CID) by 40 years of age and 10–30% of children below 18 years of age depending on the underlying immunodeficiency (innate, B-cell or T-cell defects). This study highlights increased risk for autoimmune hemolytic anemia (AIHA) (830 times), inflammatory bowel disease (80 times), and arthritis (40 times) in children with PID compared with the general population. Although autoimmune manifestations occurred in patients with all types of PIDs, those with T-cell defects or common variable immunodeficiency (CVID) tended to have the highest risk for autoimmunity. Overall, this study well demonstrates that autoimmunity is a significant component of clinical presentation of all types of PIDs.
Clinically the most vulnerable group of young patients with PID and autoimmunity are those with reduced but not absent T-cell immunity. Unlike in severe combined immunodeficiency (SCID), these patients with LoCID and P-CID may only emerge after external triggers (viral infections or live

**FIGURE 1.** Precision medicine therapy for the diverse disease spectrum of primary immunodeficiency (PID). The variable clinical presentation of PID is influenced by environmental triggers as well as empirical therapy. For instance, rituximab therapy eliminates B cells and thus reduces autoantibodies but also increases risk of infections, whereas viral infections can stimulate dysregulated B cells and result in autoimmunity. The use of next-generation sequencing and functional immune studies can identify the precise molecular basis of disease and enable optimal treatment which targets the molecular defect and minimizes adverse effects.
vaccinations) have delayed diagnosis and may not be identified by newborn screening for SCID that is now implemented nationwide in the United States. Speckmann et al. [11] have published an interim analysis of an international prospective study on the natural history of 51 patients with P-CID. The age of diagnosis was delayed as late as 15 years of age, especially among those with undefined genetic cause. Curiously, within the first year of clinical presentation, over 50% of patients presented with signs of immune dysregulation and autoimmunity, especially autoimmune cytopenias (21%), which was a dominant feature and continued throughout their life [11]. Importantly, severe events of immune dysregulation resulted in hospitalizations in over half of the P-CID cases. Although autoimmune cytopenias are often dominant in the first clinical presentation, patients may eventually progress to autoimmune enteropathy, interstitial lung disease with or without granulomas or develop arthritis, alopecia, and lesions in the central nervous system. Two brief reports by Goda et al. [14] and Wu et al.
[15] illustrates well the autoimmune clinical presentation of young children with P-CID secondary to partial deficiency of recombinase activating gene (RAG). In the first case, the infant developed autoimmune thrombocytopenia (ITP) after varicella infection prompted the clinicians to screen for immunological biomarkers and genetic cause for presumed P-CID [14]. The second case describes a child with history of Kawasaki-like disease, arthritis, and alopecia followed by infections [15]. Both cases highlighted the importance of immune evaluation and biomarkers, to promote early genetic diagnosis in children who have early-onset autoimmune disease [14,15].

With the advance of genetic testing, we have the ability to group PIRD patients based on the underlying immune defect (Fig. 2). In recent years, several large studies have published on clinical characteristics of specific PIRD cohorts, in particular those with cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), lipopolysaccharide (LPS)-responsive and beige-like anchor protein (LRBA), nuclear factor (CTLA4), lipopolysaccharide (LPS)-responsive and with cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), lipopolysaccharide (LPS)-responsive and beige-like anchor protein (LRBA), nuclear factor κ-light-chain-enhancer of activated B cells 1 and 2 (NFκB1/NFκB2), activated phosphoinositide 3-kinase delta syndrome (APDS) and hypomorphic (partial) RAG and adenosine deaminase 2 (ADA2) deficiencies.

An international cohort of 133 patients with CTLA4 deficiency [16] shows unprecedented diversity of first symptoms of presentation including autoimmune cytopenia (33%), respiratory manifestations (21%), enteropathy (IBD) (17%), type 1 diabetes (T1DM) (8%), neurological symptoms (seizures, headache, and nausea; 6%), and in less than 5% of cases autoimmune thyroid disease (AIT), arthritis, alopecia, primary biliary cirrhosis and Addison disease. Only 61% of cases had history of infections (bacterial disease, herpes reactivation, and tuberculosis). Most autoimmune manifestations (cytopenia, gastrointestinal, and lung disease) were progressive and severe. Unlike other patients with CVID, there were a high fraction of cases (28%) with involvement of the central nervous system (CNS) either secondary to lymphocytic infiltration or hematological cause (e.g., bleeding, ischemia secondary to anemia, thrombosis). Beside the presence of multiple autoimmune disorders, CNS involvement may be a clinical diagnostic clue for CTLA4 deficiency. As inheritance is autosomal dominant, subsequent generations may be involved with variable penetrance of the clinical disease.

A systematic review of clinical features of 109 cases with LRBA deficiency also highlighted that the first presentation was often autoimmunity (42%) [17*]. Multiple autoimmune diseases occurred in 77% of patients, which were dominated by AIHA and ITP, followed by T1DM, AIT and IBD. Infections (16%) and chronic diarrhea (27%) were less frequent first signs of disease manifestation of PID. The primary clinical diagnosis of these LRBA deficient patients were CVID (43%), autoimmunity (28%), ALPS-like (8%), IPEX-like PID (7%), and LoCID (4%) [17*]. Lastly, a systematic review of 243 APDS patients also had autoimmune complications (28%); however, infections and lymphoproliferation (70%) were more dominant [18].

In the LoCID group, loss-of-function NFκB1 variants were published as most common monogenic cause of CVID in Europeans [19**]. Common clinical features included massive lymphadenopathy (24%), unexplained splenomegaly (48%), and autoimmune disease (48%) mainly AIHA and ITP, followed by alopecia, vitiligo, and AIT were also associated with worse prognosis. Among CID patients with immune dysregulation and hypomorphic SCID-associated genes, partial RAG deficiency tends to be the most common genetic cause. Two recent reports summarize the clinical presentation and treatment outcome of autoimmune complications. Both Delmonte et al. [20*] and Farmer et al. [21*] report broad clinical autoimmune presentations including autoimmune cytopenias, vitiligo, alopecia, vasculitis, and neurological disease. Farmer et al. [20*] showed that there is significant delay in molecular diagnosis (5 years or more) and often clinical decision for HSCT is made before full understanding of underlying cause. Overall, both studies emphasize that optimal bridge therapy is yet to be defined among partial RAG deficient patients [20*,21*].

Unique cohorts are now described with ADA2 deficiency and may also present with CVID-like disease [22]. This is the first monogenic vasculitis syndrome with highly pleiotropic clinical features of autoinflammation, autoimmunity (ITP, arthritis), vasculopathy, vasculitis and strokes [22,23]. Some of the earliest onset PIRDs are those with STAT3 gain-of-function (GOF) or NFκB2 variants. As high as 80% of NFκB2 deficient patients develop autoimmunity (alopecia, arthritis, cytopenia) with unique features of adrenocorticotropic hormone deficiency (44%) [24]. Fabre et al. [25] have published a comprehensive review of 42 children with STAT3 GOF pathogenic variants and very early onset autoimmunity (0.5–5 years of age) including cytopenias, interstitial lung disease, and endocrine complications (diabetes, thyroiditis, and growth failure). Lastly, Chinn et al. [26] have summarized in an excellent comprehensive review of the genetic causes of specific clinical autoimmune presentations among patients with PIDs managed by multiple specialists (hematologist, endocrinologist, dermatologist).
In summary, PIRD groups with specific gene defects share similar features (IPEX, ALPS, CVID/CID-like) with combinations of multiple autoimmune diseases. Referral to the immunologist and diagnosis of PID is often delayed as the presenting symptoms are often autoimmune-related with no significant history of infections.

**GENETIC AND IMMUNOLOGICAL DIAGNOSTIC TOOLS**

A genetic revolution has occurred in recent years regarding PID diagnosis. Panels with 200–300 PID genes are now more affordable and broadly available on clinical grounds. These panels are helpful to identify the most common PIDs linked to autoimmunity and discover ‘new face of old disorders’ (such as RAG deficiency). However, the quest often needs to continue in ‘PID-panel’ negative cases with whole exome and/or genome sequencing approaches as novel genes are being discovered. For example, Fernandez et al. [27] recently described a homozygous IL2RB pathogenic variant from two infant siblings, which manifested as multisystem autoimmunity (enteropathy, lymphocytic interstitial pneumonitis, Coombs+) and susceptibility to cytomegalovirus (CMV) infection. There are specific clinical target groups with autoimmunity where genetic testing proved to be fruitful. Among pediatric patients with Evans syndrome, there is a high probability of finding an underlying PID based on recent studies from France [28**,29]. In a prospective cohort of 203 pediatric patients with Evans syndrome, 80 patients underwent genetic testing, which revealed 32 (40%) had an underlying pathogenic mutation. The affected genes included TNFRSF6, CTLA4, STAT3, PIK3CD, CBL, ADAR1, LRBA, RAG1, and KRAS [28**]. One of the largest studies on genetic defects in PID patients has been the ‘Houston project’ by the teams of Jordan Orange and James Lupski (2017). They investigated 278 families from 22 countries by whole-exome sequencing. This project highlighted that 5% of patients had two distinct PID disease genes shaping their clinical and immune phenotype (mixed phenotype). Genes linked to autoimmune diseases spanned several categories (autoimmune disease, CID, CVID, defects of innate immunity) and were identified in more than 23 cases (8%). Genetic causes included COPA, CTLA4, FOXP3, STAT1, STAT3, RAG1, CCDC40, CASP10, PLCG2, FALG, and CBL [30]. Lastly, an eloquent case report of a mother and child by Le Coz et al. [31] highlights CD40L duplication in human autoimmune diseases including autoimmune cytopenias (AICs) and AIT, and discusses the relevance of epigenetic control in disease progression, CD40L overexpression and CD40/CD40L interaction as previously seen in lupus.

In case of variants of uncertain significance, functional studies are needed to confirm the link between the clinical phenotype and genetic findings. Therefore, immunologists and other specialists need to be prepared to initiate evaluation for protein expression and function such as CTLA4 or LRBA expression, STAT1 or STAT3 phosphorylation, B or T-cell repertoire or in vitro recombination activity testing (RAG and DNA deficiencies). Unfortunately, most of these assays are only available on a research basis in collaboration with expert centers. A practical approach to genetic testing for PID has been recently summarized by the Clinical Immunology Society [32,33].

Immune phenotyping is of utmost importance in identifying or confirming the underlying PID among the heterogeneous group of patients with autoimmunity. Immunoglobulin levels can identify patients with CVID and CID, and a simple test of the ratio of naïve and memory T cells (CD45RA/CD45RO) may distinguish those with LoCID or P-CID [10,11,34].

There are specific subsets of T and B cells that have been linked to PID with autoimmunity. These include the expansion of TCRAβ CD4+ CD8– (double negative) T cells in ALPS, CD19lo21hi B cells in CVID with autoimmunity, abnormal count of regulatory T cells (Treg) in Tregopathies, Th17 cells in STAT1 GOF patients, and expanding follicular helper T cells (Thf) in CTLA4 and LRBA deficiency [35**]. Changes in these subsets may also predict progression of autoimmune complications or response to therapy.

Patients with PID tend to have broad selection of autoantibodies as seen in RAG deficiency with AICs [20]. Further, in some PIDs, particular antibodies with unique self-reactivity occur and may serve as biomarkers. Beyond antibodies to IFNα, IFNβ and IL-12 in patients with partial RAG deficiency [14,36] and APECED [37], Rosenberg et al. [38] reported neutralizing anti-IFNα antibodies among patients with IPEX in two large cohorts from Seattle Children’s Hospital and San Raffaele Hospital (Milan, Italy). Anti-IFNα antibodies were recently described in a patient with NFκB2 deficiency after herpes virus infection [39]. In addition, novel autoantibodies against lung-specific bactericidal/permeability-increasing fold-containing protein B1 (BPIFB1) and the potassium channel regulator protein (KCNFG), have been linked to onset of autoimmune pneumonitis in disorders of central T-cell tolerance (APECED, RAG deficiency, and thymoma) [39]. It is intriguing that presence of anticytokine antibodies are also proposed as markers of prognosis in APECED, as they noted negative correlation of anti-IFNα antibodies and the incidence of T1DM [40,41].
PATHOMECHANISM OF AUTOIMMUNITY IN IMMUNE-DEFICIENT BACKGROUND

Many patients with immunodeficiency harbor autoreactive T and B cells secondary to abnormal pruning of naturally occurring polyreactive clones in the bone marrow (B cells) or thymus (T cells). As these autoreactive cells fail central tolerance checkpoints secondary to intrinsic abnormalities, they spill to the periphery. If peripheral tolerance checkpoints are intact, these clones can become dormant. Additional triggers (extrinsic factors) may revive these clones (Fig. 3). In particular, autoreactive B cells have a second chance to undergo somatic hypermutation (SHM) of their B-cell receptor (BCR) during a process known as clonal redemption and lose self-reactivity [42]. If this process is impaired, autoreactive B cells remain activated and convert into plasma cells to generate autoantibodies. In particular, among patients with CVID and AIC, translocated microbiome or its components (e.g., LPS) have been proposed as triggers for self-reactive immunoglobulin heavy chain variable gene segment 4-34 (IgH-V4-34) expressing B-cell clones capable of binding both commensal bacteria and red blood cells [43**]. Likewise, herpes virus infections as triggers are also well described and linked to onset of autoimmune complications [14,20*]. In many of these patients, germinal centers are hyperplastic but likely inefficient as B cells display low SHM of BCR suggestive of abnormal clonal redemption [43**]. Tfh cells are being recognized as important cellular players in immune dysregulation [44], as overproduction of Tfh cells has been associated with the generation of autoantibodies and autoimmunity. The phenomenon of Tfh expansion has been highlighted in a mouse model [45] and among patients with CVID with AIC [43**], LRBA [35**], CTLA4 deficiencies [46] and APDS [47]. Thauland et al. [47] have highlighted the importance of a new pathway for expansion of Tfh cells in APDS, which involved intracellular osteopontin and p85α.

AUTOIMMUNITY INCREASES MORTALITY IN PRIMARY IMMUNODEFICIENCY DISORDER: HOW TO OPTIMIZED TREATMENT

Cunningham-Rundles et al. [48] have established high mortality among CVID patients with noninfectious complications. Recently, Farmer et al. [49] at Massachusetts General Hospital studied 142 patients with genetically undefined CVID and concluded that both presence of AIHA and/or ITP increase risk of mortality. Similarly, Fisher et al. [13*] in the French national study discussed above concluded that any types of PID with autoimmunity have increased mortality and complications post-HSCT. Even carriers can be at risk. Schwab et al. [16*] described that both affected CTLA4 patients and their carrier family members (‘unaffected’ or not seeking medical attention) had decreased survival compared with the general population.

It has been described that many PID patients are seen and receive immune modulatory treatment for immune dysregulation before full evaluation or discovery of the underlying immune defect [20*]. As

![Figure 3. Intrinsic and extrinsic phases of autoimmunity in PID. Autoimmunity in PID arises because of impaired tolerance checkpoints resulting from both intrinsic (genetic susceptibility) and extrinsic (environmental) causes.](image-url)
these treatments result in an altered immune status, it is often unclear to the specialists if immunodeficiency is induced by immune modulation or preexisted before therapy. This enigma can only be resolved if a pathogenic genetic defect causing an aberrant immune response is identified and proven by functional studies (as discussed in the genetic and diagnostic tool section). These variants may result in low (loss of function) or excessive response (gain of function) of a specific immune signaling pathway. The identification of pathogenic genetic defects can facilitate the use of targeted agents specific for the defect or group of defects that share similar pathophysiologic mechanisms.

Immune modulation is a major therapeutic challenge in the PID population and reflects the importance of precision medicine where narrow-spectrum immune modulation delicately balances infectious susceptibility. Most of biologicals are developed and received approval of the Federal Drug Administration for patients with cancer or rheumatologic conditions where safety profile is established (Table 1). In contrast, these biologicals are used off label with unclear safety profile in the PID population. There are excellent recent reviews in the literature discussing targeted therapies for immune dysregulation in PIDs [1,50–54]. Recent cohort studies highlight the use anti-IL-6 receptor and Janus kinase inhibitor biologics in STAT3GOF patients [5], CTLA4 Ig in CTLA4 deficiency [16], and a small molecule inhibitor, leniolisib, in activated protein I3 kinase delta syndrome (APDS or PI3Kδ) deficiency [55]. Monitoring Tfh cells is proposed as a cellular marker to assess control for immune dysregulation [35**]. In patients with deficiency of adenosine deaminase 2 deficiency, TNFα blockade is first-line therapy for vasculopathy and autoinflammation [22,23].

In the era of genetic revolution, genetically defined PID patients with immune dysregulation are increasingly considered for definitive therapy with the ultimate goal to correct the underlying defect, primarily by HSCT. Hematopoietic stem cells (HSCs) may originate from a healthy donor (allogeneic) or the patient itself when genetic defect is repaired by viral transduction of the correct gene (autologous gene therapy). Furthermore, genetic defect in HSC may also be corrected via guide RNA that interacts with the cell’s own DNA repair machinery [Clustered Regularly Interspaced Short Palindromic Repeats and CRISPR associated protein 9 (CRISPR-Cas9) gene editing]. Conditioning regimens need to consider the inflammatory state of the patient as the risk of graft failure is high in these circumstances. Targeted therapy for immune dysfunction serves as a bridge until the definitive treatment with HSCT can be pursued safely. Indication to pursue HSCT in a child with autoimmune complications and underlying PID has not been fully delineated. Only a few large cohort studies and case series on HSCT for autoimmune complications have been published among patients with partial RAG and ADA2 deficiencies [20*,22,23,56,57]. A recent report of allogeneic HSCT for chronic arthritis in children is intriguing. In a retrospective study by Silva et al. [58], allogeneic HSCT was performed in 11 patients with systemic and five with polyarticular rheumatoid factor negative juvenile idiopathic arthritis after patients failed multiple medications considered to be the standard of treatment or failed autologous HSCT, or developed life-threatening complications such as macrophage activation syndrome. Eleven of 14 surviving patients were reported to be in drug-free remission at the last follow-up. Common complications were severe infections (viral reactivation) and even autoimmunity during and after the transplant. Notably, in these reports, there was no search for underlying PID on immunological or genetic grounds. The authors argued that identifying the predictive markers of medical treatment failure in these patients would allow for early selection of candidates for HSCT, fewer HSCT-related complications and less disability.

Preventing development of autoimmunity in PID is a far-reaching goal, as it is unclear, which PID patients will progress into clinical autoimmune disease even among those with a genetic defect linked to immune dysregulation. Monitoring prognostic biomarkers of development to autoimmunity could improve early interventions and slow or reverse disease progression. These may be cellular (e.g., Tfh/Treg ratio, autoimmune prone B-cell subsets) or serum markers (e.g., antibodies targeting self-antigens including cytokines).

**CONCLUSION**

The face of PID is rapidly changing with increased awareness, availability of genetic testing, and in-depth immune phenotyping. A multidisciplinary approach is needed to expedite prompt diagnosis. Once multiple autoimmune complications are present, care of these patients is likely shared by multiple specialists (e.g., in hematology, rheumatology, neurology). At that point, reevaluation of the patient’s immune system is of high importance. The primary pediatrician needs to advocate for prompt immune evaluation and genetic testing in this multidisciplinary setting to optimize the diagnostic and treatment approach for these vulnerable patients.
| Target               | Agent                 | Structure                                   | Approved indication by FDA           | Used in PID patients off label or in clinical trials |
|----------------------|-----------------------|---------------------------------------------|--------------------------------------|------------------------------------------------------|
| **Cellular lymphocytes** |                       |                                             |                                      |                                                      |
| CD52                 | Alemtuzumab           | anti-CD52 mAb                               | MS                                   | pt with HLH                                          |
| **B cells**          |                       |                                             |                                      |                                                      |
| CD20                 | Rituximab             | chimeric mouse/human anti-CD20 mAb         | RA, polyJIA                          | ITP, AIHA, GLILD [pts with CVID/CID, APDS/PASLI]    |
| Ofatumumab           |                      | human anti-CD20 mAb                         | adult refractory CLL                |                                                      |
| Obinutuzumab         |                      | humanized anti-CD20mAb                     | adult de novo CLL                   |                                                      |
| CD22                 | Epratuzumab           | humanized anti-CD22mAb                     | B cell malignancies                 |                                                      |
| BAFF                 | Belimumab             | human anti-BAFF mAb                         | SLE                                  |                                                      |
| CD38                 | Daratumumab           | human anti-CD38 mAb                         | MM                                   | AIHA (pts with WAS s/p HSCT)                         |
| **Proteosome inhibitor** |                       |                                             |                                      |                                                      |
| Bortezomib           |                      | pyrazine and boronic acid derivative        | MM, MCL                             |                                                      |
| Carfilzomib          |                      | epoxomicinderivate                         | MM                                  |                                                      |
| Ixazomib             |                      | second generation boron containing peptide | MM, MCL                             |                                                      |
| **T cells**          |                       |                                             |                                      |                                                      |
| m-TOR                | Sirolimus (rapamycin) | S6K/m-TOR inhibitor                         | LAM, T/OR                           | ITP, AIHA [pts with CTLA4/LRBA def, ALPS, APDS]      |
| m-TOR                | Everolimus            | S6K/m-TOR inhibitor                         | BrCA, TS, T/OR                      | CTLA4/LRBA def                                      |
| IMD                  | Mycophenolic acid     | reversible inhibitor of IMD                 | kidney, heart, liver transplant     | ITP, AIHA [pts with CTLA4/LRBA def, ALPS, APDS]      |
| CD28                 | Abatacept             | human CTLA4-IgG fusion protein with extracellular domain of CTLA4 and IgG1 Fc | RA, polyJIA                          | pts with CTLA4, LRBA def                            |
| p110β                | Leniolisib (CDZ173)   | small-molecule inhibitor of p110β            | n.a.                                | pts with APDS/PASLI                                  |
| **Complement**       |                       |                                             |                                      |                                                      |
| Complement C5        | Eculizumab            | recombinant humanized IgG2 anti-C5 mAb      | generalized MG, PNH                 |                                                      |
| **Cytokines and receptors** |               |                                             |                                      |                                                      |
| TNFα                 | Etanercept            | soluble TNFα receptor IgG Fc fusion protein | RA                                   | AlnD (pts with TRAPS)                                |
| Infliximab           |                      | human mouse chimeric anti-TNFα mAb         | RA, UC                              | CVID with GLILD                                      |
| Adalimumab           |                      | Fully human anti-TNFα mAb                  | RA, UC                              |                                                      |
| Golimumab            |                      | Fully human anti-TNFα mAb                  | RA, UC                              |                                                      |
| Certolizumab pegol   |                      | Humanized pegylated Fab’ fragment          | RA, CD                              |                                                      |
| **IL-1β pathway**    | Anakinra              | Recombinant IL-1R antagonist                | RA, CAPS                            | CGD and AlnD [pts with CAPS, FMF, TRAPS, HIDS, DIRA] |
| Rilonacept           | fusion of IL-1R and IL-1R accessory protein | CAPS                                     | AlnD [CAPS such as FCAS, MWS, less effective in NOMID] |
| Canakinumab          | mAb to IL-1β          |                                             | JIA, CAPS                           |                                                      |
| **IL-6R**            | Tocilizumab           | Humanized IL-6R antagonist                  | RA, JIA                             | pt with STAT3 GOF                                    |
| **IL-12/IL-23**      | Ustekinumab           | Fully human anti-IL-12/IL-23 mAb (anti-p40) | PsA                                 | CGD, LAD-1                                          |
| **IL-17**            | Secukinumab           | Fully human anti-IL-17 mAb                  | PsO                                 |                                                      |
Treatment of PID patients with autoimmunity is most successful when fine-tuned immune modulation is achieved using biologicals specifically targeting the imbalanced immune pathway. Definitive therapy with HSCT or gene therapy should be considered for treatment of refractory cases.

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REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest

1. Walter JE, Farmer JR, Foldvari Z, et al. Mechanism-based strategies for the management of autoimmunity and immune dysregulation in primary immunodeficiencies. J Allergy Clin Immunol Pract 2016; 4:1089–1100.
2. Nagamine K, Peterson P, Scott HS, et al. Positional cloning of the APECED gene. Nat Genet 1997; 17:393–398.
3. Finnish-German AC. An autoimmune disease, APECED, caused by mutations in a novel gene featuring two PHD-type zinc-finger domains. Nat Genet 1997; 17:399–403.
4. Bennett CL, Christie J, Ramsdell F, et al. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nat Genet 2001; 27:20–21.
5. Chatila TA, Blaeser F, Ho N, et al. JM2, encoding a fork head-related protein, is mutated in X-linked autoimmunity-allergic disregulation syndrome. J Clin Invest 2000; 106:R75–81; PMC387260.
6. Baud O, Goulet O, Canioni D, et al. Treatment of the immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) by allogeneic bone marrow transplantation. N Engl J Med 2001; 344:1758–1762.
7. Barzaghi F, Amaya Hernandez LC, Neven B, et al. Long-term follow-up of IPEX syndrome patients after different therapeutic strategies: an international multicenter retrospective study. J Allergy Clin Immunol 2018; 141: 1036–1049; e1035. PMC6050203.
8. Bride K, Teachey D. Autoimmune lymphoproliferative syndrome: more than a fascinating disease. F1000Res 2017; 6:1928; PMC5688920.
9. Cepika AM, Sato Y, Liu JM, et al. Tregopathies: monogenic diseases resulting in regulatory T-cell deficiency. J Allergy Clin Immunol 2018; 142: 1679–1695.
Autoimmunity as a continuum in primary immunodeficiency

Walter et al.

10. Bertincamp R, Gerard L, Bouboul D, et al. Exclusion of patients with a severe T-cell defect improves the definition of common variable immunodeficiency. J Allergy Clin Immunol Pract 2016; 4:1147–1157.

11. Speckmann C, Doerken S, Aiuti A, et al. A prospective study on the natural history of patients with profound combined immunodeficiency: an interim analysis. J Allergy Clin Immunol 2017; 139:1302–1310; e1304. PMC6311415.

12. Chandrakasan S, Chandra S, Davila Saldana BJ, et al. Primary immune regulatory disorders for the pediatric hematologist and oncologist: a case-based review. Pediatr Blood Cancer 2019; 66:2766–2778.

13. Tsucher A, Provot J, Jais JP, et al., members of the CFDN. Autoimmune and inflammatory manifestations occur frequently in patients with primary immune deficiencies. J Allergy Clin Immunol 2017; 140:1388–1393; e1388.

14. This is a large French national study on autoimmune and inflammatory manifestations, and clinical outcome in various groups of patients with primary immune deficiencies. They conclude that 26% of patients had at least one autoimmune or inflammatory manifestation that negatively impacts treatment outcome.

15. Goda V, Malik A, Kalmar T, et al. Autoimmune and/or inflammatory complications. HSCT is the preferred treatment for immunodeficiency patients. J Allergy Clin Immunol 2018; 141:2546–2553; e2542.

16. This mechanistic study highlights that CTLA4-Ig is an effective treatment for LRBA deficiency. Immunodeficiency patients. J Clin Immunol 2018; 38:120–129; e120.

17. The heterogeneity of autoimmunity in CVID is silenced by nonrandom X-chromosome inactivation. J Clin Invest 2019; 143:258–265; PMC6400323.

18. The major presentations are autoimmunity, chronic diarrhea, hypogammaglobulinemia, and recurrent infections. Although it is a monogenic immune dysregulation syndrome, in this cohort, the genotype-phenotype correlation is poor. HSCT is discussed.

19. The large study of 109 patients examined clinical phenotype of LRBA deficiency. The major presentations are autoimmunity, chronic diarrhea, hypogammaglobulinemia, and recurrent infections. Although it is a monogenic immune dysregulation syndrome, in this cohort, the genotype-phenotype correlation is poor. HSCT is discussed.

20. The large study of 243 patients with APDS highlights the most common disease manifestations including recurrent respiratory infections, lymphoproliferation, autoimmunity, and enteropathy. The main immune phenotype is hyper-IgM syndrome, and B and CD4+ T-cell lymphopenia. HSCT is discussed as a promising treatment for severe or recalcitrant cases.

21. The large study of a European CVID cohort identified NFKB1 deficiency by whole-exome sequencing. The study claims that NFKB1 is the most common monogenic cause of common variable immunodeficiency in Europeans. J Allergy Clin Immunol 2018; 141:995–1002; e996.

22. This large study of a European CVID cohort identified NFKB1 deficiency by whole-exome sequencing. The study claims that NFKB1 is the most common monogenic cause of common variable immunodeficiency in Europeans. J Allergy Clin Immunol 2018; 141:995–1002; e996.

23. The large study of a European CVID cohort identified NFKB1 deficiency by whole-exome sequencing. The study claims that NFKB1 is the most common monogenic cause of common variable immunodeficiency in Europeans. J Allergy Clin Immunol 2018; 141:995–1002; e996.

24. Weiler FG, Peterson P, Costa-Carvalho BT, et al. Clinical aspects of STAT3 gain-of-function germline mutations: a systematic review. J Allergy Clin Immunol Pract 2019; 7:1968.e9–1969.e9.

25. This is a large study of a European CVID cohort identified NFKB1 deficiency by whole-exome sequencing. The study claims that NFKB1 is the most common monogenic cause of common variable immunodeficiency in Europeans. J Allergy Clin Immunol 2018; 141:995–1002; e996.

26. The large study of a European CVID cohort identified NFKB1 deficiency by whole-exome sequencing. The study claims that NFKB1 is the most common monogenic cause of common variable immunodeficiency in Europeans. J Allergy Clin Immunol 2018; 141:995–1002; e996.

27. This is a large study of a European CVID cohort identified NFKB1 deficiency by whole-exome sequencing. The study claims that NFKB1 is the most common monogenic cause of common variable immunodeficiency in Europeans. J Allergy Clin Immunol 2018; 141:995–1002; e996.

28. This is a large study of a European CVID cohort identified NFKB1 deficiency by whole-exome sequencing. The study claims that NFKB1 is the most common monogenic cause of common variable immunodeficiency in Europeans. J Allergy Clin Immunol 2018; 141:995–1002; e996.

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30. The large study of a European CVID cohort identified NFKB1 deficiency by whole-exome sequencing. The study claims that NFKB1 is the most common monogenic cause of common variable immunodeficiency in Europeans. J Allergy Clin Immunol 2018; 141:995–1002; e996.

31. The large study of a European CVID cohort identified NFKB1 deficiency by whole-exome sequencing. The study claims that NFKB1 is the most common monogenic cause of common variable immunodeficiency in Europeans. J Allergy Clin Immunol 2018; 141:995–1002; e996.

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45. Preite S, Huang B, Cannons JL, et al. PI3K orchestrates T follicular helper cell differentiation in a context dependent manner: implications for autoimmunity. Front Immunol 2018; 9:3079; PMC6330320.

46. Chao G, Li X, JI Y, et al. CTLA-4 regulates T follicular regulatory cell differentiation and participates in intestinal damage caused by spontaneous autoimmunity. Biochem Biophys Res Commun 2018; 505:865–871.

47. Thauland TJ, Pellerin L, Ohgami RS, et al. Case study: mechanism for increased follicular helper T cell development in activated PI3K delta syndrome. Front Immunol 2019; 10:753; PMC6473200.

48. Resnick ES, Mosher EL, Godbold JH, Cunningham-Rundles C. Morbidity and mortality in common variable immune deficiency over 4 decades. Blood 2012; 119:1650–1657; 3286343.

49. Farmer JR, Ong MS, Barmettler S, et al. Common variable immunodeficiency non-infectious disease endotypes redefined using unbiased network clustering in large electronic datasets. Front Immunol 2017; 8:1740; PMC5767273.

50. Her M, Kavanaugh A. Alterations in immune function with biologic therapies for autoimmune disease. J Allergy Clin Immunol 2016; 137:19–27.

51. Notarangelo LD, Fleisher TA. Targeted strategies directed at the molecular defect: toward precision medicine for select primary immunodeficiency disorders. J Allergy Clin Immunol 2017; 139:715–723; PMC5692414.

52. Marciano BE, Holland SM. Primary immunodeficiency diseases: current and emerging therapeutics. Front Immunol 2017; 8:937; PMC5552668.

53. Leiding JW, Ballow M. Precision medicine in the treatment of primary immunodeficiency diseases. Curr Opin Allergy Clin Immunol 2018; 18:159–166.

54. Amaya-Unbe L, Rojas M, Aizzi G, et al. Primary immunodeficiency and autoimmunity: a comprehensive review. J Autoimmun 2019; 99:52–72.

55. Rao VK, Webster S, Dalm V, et al. Effective ‘activated PI3Kdelta syndrome’-targeted therapy with the PI3Kdelta inhibitor leniolisib. Blood 2017; 130:2307–2316; PMC5701526.

This study highlights that leniolisib trial improved immune dysregulation and decreased lymphoproliferation without significant adverse effects in six patients with activated PI3Kδ syndrome. The study demonstrates the effectiveness of therapy that targets the biochemical cause of a rare PID.

56. Westermann-Clark E, Grossi A, Fioredda F, et al. RAG deficiency with ALPS features successfully treated with TCRalphabeta/CD19 cell depleted haploidentical stem cell transplant. Clin Immunol 2018; 187:102–103; PMC5941922.

57. Barzaghi F, Minniti F, Mauro M, et al. ALPS-like phenotype caused by ADA2 deficiency rescued by allogeneic hematopoietic stem cell transplantation. Front Immunol 2018; 9:2767; PMC6359227.

58. MF Silva S, Ladomenou F, Carpenter B, et al. Allogeneic hematopoietic stem cell transplantation for severe, refractory juvenile idiopathic arthritis. Blood Adv 2018; 2:777–786; PMC5894259.