HHS Public Access

Author manuscript

J Allergy Clin Immunol Pract. Author manuscript; available in PMC 2017 November 01.

Published in final edited form as:

J Allergy Clin Immunol Pract. 2016 ; 4(6): 1089–1100. doi:10.1016/j.jaip.2016.08.004.

Mechanism-based strategies for the management of autoimmunity and immune dysregulation in primary immunodeficiencies

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Abstract

A broad spectrum of autoimmunity is now well described in patients with primary immunodeficiencies (PIDs). Management of autoimmune disease in the background of PID is particularly challenging given the seemingly discordant goals of immune support and immune suppression. Our growing ability to define the molecular underpinnings of immune dysregulation has facilitated novel targeted therapeutics. This review focuses on mechanism-based treatment strategies for the most common autoimmune and inflammatory complications of PID including autoimmune cytopenias, rheumatologic disease, and gastrointestinal disease. We aim to provide guidance regarding the rational use of these agents in the complex PID patient population.

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Keywords

primary immunodeficiencies (PIDs); treatment; autoimmunity; cytopenias; arthritis; vasculitis; lupus; autoimmune enteropathy (AIE); inflammatory bowel disease (IBD)

Autoimmune and inflammatory diseases can complicate the course of primary immunodeficiency (PID) and the complex care of these patients (1). The clinical spectrum is broad and frequently includes autoimmune cytopenias, rheumatologic disease, and gastrointestinal (GI) disease (2, 3). The pathogenesis of immune dysregulation leading to autoimmunity in PIDs was recently comprehensively reviewed (4). In light of mechanistic understanding, it is timely to review management strategies.

Balancing immunosuppressive therapy in patients with susceptibility to infection is a clinical challenge. Treatment success hinges upon correcting the underlying immune dysregulation while minimizing nonspecific immune suppression. Herein we will review management of PID-associated autoimmunity by therapeutic mechanism: targeting B cell, T cell, or innate immune pathology or using hematopoietic stem cell transplantation (HSCT) to reconstitute the immune system.

1. Treatment of autoimmune cytopenias in primary immunodeficiencies

While autoimmune cytopenias, including autoimmune hemolytic anemia (AIHA), immune thrombocytopenic purpura (ITP), and autoimmune neutropenia (AN), occur in the general population, they are particularly common in patients with PID. As an example, PID was uncovered in 13% of children with AIHA (5) and up to 50% of children with multi-lineage cytopenias (Evans syndrome) (6). Autoimmune cytopenias have been described in both innate and adaptive immune deficiencies (3, 7) and may be the first sign of immune dysregulation that precedes the classical presentation of PID with recurrent or opportunistic infections (8, 9). Clinical warning signs that may prompt the clinician to consider PID at an earlier stage include: multi-lineage cytopenias, AIHA with no response to first-line therapy, persistent/chronic ITP, and AN in a patient > two years of age and/or persistent for > 24 months (10-14).

Corticosteroids are the mainstay of treatment for AIHA with a high response rate around 80% in the general population (15). For ITP, corticosteroids or high-dose intravenous immunoglobulin (IVIG) are considered first-line (16). In the fraction of patients who relapse following these therapies, splenectomy has been the traditional second-line approach. With the advance of biologics, anti-CD20 antibody (rituximab) is now considered an effective second-line approach although randomized clinical trials are lacking. In general, clinical approach in treatment-resistant cases is one of therapeutic trial and error in the absence of a guiding underlying immunophenotype or biomarkers to direct care. By contrast, second-line treatment strategies for PID-associated autoimmune cytopenias are increasingly being targeted to the underlying mechanism of immunopathology.

1.1 Targeting B cell pathology

Several studies address the approach to autoimmune cytopenias in the background of common variable immunodeficiency (CVID), a heterogeneous condition defined by decreased serum immunoglobulins (low IgG with low IgM and/or IgA), frequent infections, and poor antigen-specific antibody titers (17). Classical CVID is considered to be a primary disorder of B cells. However, improved genetic discovery and immunophenotyping has led to reclassification of a growing CVID subset as *de facto* combined immunodeficiency (CID) (18).

The link between CVID and autoimmunity was first established in the 1990s (19) and has been greatly expanded since that time (**Table I**) (20, 21). Initial treatment regimens for autoimmune cytopenias included combinations of corticosteroids, high-dose IVIG, and anti-Rho(D) in the case of ITP. These guidelines were extrapolated from the standard of care in the general population. Initial response rates to corticosteroids were reasonable, 85% for ITP (22) and 81% for AIHA (23); however, prolonged use was often required, which increased risk for infection as a secondary complication. Before the era of biologics, nearly half of these autoimmune cytopenia cases ultimately required second-line splenectomy (response rates of 60-80%), which was in contrast to the majority of first-line treatment responders seen in the general population (8, 22, 23). Other agents such as vinca-alkaloids, danazol, cyclophosphamide, azathioprine, and cyclosporine did not show long-term success and are now rarely used.

In 2004, rituximab was introduced as second-line therapy for CVID-associated AIHA (24). In a subsequent multicenter study of 33 CVID patients with refractory autoimmune cytopenias, which included steroid-dependence (56%), immunomodulatory therapy (44%), and prior splenectomy (21%), rituximab was demonstrated to have a durable response rate of 59% (25). The authors proposed that rituximab be considered standard second-line therapy, prior to splenectomy and/or other immunomodulatory therapy, in CVID-associated autoimmune cytopenias. Although 24% of patients developed severe bacterial infections after rituximab treatment, half of these cases were off of immunoglobulin replacement therapy and/or had undergone splenectomy (25). While concerning, the rate of severe bacterial infections was not significantly different than that observed in CVID patients with ITP treated by the more traditional approach of corticosteroids with or without high-dose IVIG (22). Therefore, risk for infection with rituximab use needs to be considered primarily in CVID patients not receiving immunoglobulin replacement therapy.

Response to B cell depletion therapy in most cases of CVID-associated autoimmune cytopenias localized the immunopathology to the B cell compartment and suggested that other therapies targeting this compartment may also be efficacious. It should be emphasized that rituximab depletes only maturing B cells and does not target long-lived plasma cells that can sustain autoantibody production in lymphoid niches for some time (months) after treatment. Alternative B cell-directed therapy may include bortezomib, a proteasome inhibitor that is approved for the treatment of multiple myeloma and preferentially causes apoptosis of antibody-producing plasma cells through activation of the unfolded protein response (UPR) (26). Bortezomib has shown promising results in peri-transplant cases of

PID-associated refractory autoimmune cytopenias specifically (four of five patients with PID responded to treatment and only two patients required transition to alternative therapy (27)). Additional B cell-directed therapies currently in clinical trial include an anti-CD22 antibody (epratuzumab) and an anti-APRIL antibody. Both show promise in severe refractory autoimmune diseases including cytopenias (28-31), but have yet to be trialed in PID specifically. Finally, the terminal complement inhibitor eculizumab (anti-C5) has been utilized to rescue a patient from fatal complications related to treatment-refractory AIHA (32). Since it acts distal to the B cell in autoantibody mediated diseases, it could in theory be applied in combination with B cell depleting therapies to more completely control disease. The mechanism of action for these biologics is reviewed in **Figure 1**.

1.2 Targeting T cell pathology

PID patients with prominent T cell dysfunction may not fully benefit from the removal of autoreactive B cells. In autoimmune lymphoproliferative syndrome (ALPS), the accumulation of pathognomonic TCR$\alpha\beta^{+}CD4^{-}CD8^{-}$ (double negative, DN) T cells occurs secondary to defective apoptosis. While autoimmune cytopenias are a key feature of the disease (**Table I**), rituximab is a therapy of last resort given the associated finding of profound and prolonged hypogammaglobulinemia up to 4 years post-treatment (33). Similarly, splenectomy is less preferred as it may result in unfavorable outcomes with recurrent cytopenias and high rates of sepsis (41%) in ALPS patients (34).

The conventional first-line therapy for ALPS-associated autoimmune cytopenias has been corticosteroids, but second-line therapies including mycophenolate mofetil (MMF, a prodrug of mycophenolic acid that inhibits inosine monophosphate dehydrogenase and suppresses T and B cells) and sirolimus (an mTOR inhibitor) that more effectively target DN T cells are increasingly being used as primary therapy (35, 36). Sirolimus was first trialed in four corticosteroid-refractory ALPS patients in 2009 and resulted in marked improvements in both autoimmune cytopenias and associated systemic inflammatory features (arthritis, colitis, lymphadenopathy, and splenomegaly) (10). In a subsequent trial of 30 patients with refractory autoimmune cytopenias across multiple PIDs (CVID and ALPS), sirolimus resulted in a complete and durable remission in the majority of patients (37). Treatment response in ALPS has been shown to coincide with a specific reduction in DN T cells, which are particularly dependent on an intact mTOR pathway (37-40).

Autoimmune cytopenias have been associated with partial DiGeorge syndrome (pDGS), occasionally preceding diagnosis of the underlying genetic defect (**Table I**) (41-43). Breaks in both central T cell tolerance (e.g., thymic aplasia/dysplasia) and peripheral T cell tolerance (e.g., T cell proliferation to low-affinity self antigens) have been proposed to induce autoimmunity (44). To date, large studies do not exist as to the optimal therapeutic approach. Steroids and azathioprine have been anecdotally used to treat ITP with benefit (42). Progression despite rituximab has been reported in two cases of severe autoimmune cytopenias associated with pDGS, one requiring HSCT for definitive treatment (45), the other requiring plasmaphoresis in combination with splenectomy for stabilization (46).

Autoimmune cytopenias can also occur in the setting of regulatory T cell (Treg) dysfunction. CTLA4 haploinsufficiency is a novel autosomal-dominant immunodeficiency where

decreased CTLA4 cell surface expression results in impaired Treg suppressor function. It has been associated with a broad clinical spectrum of autoimmunity including high rates of ITP and AIHA (**Table I**). Here, direct complementation of the underlying immunoregulatory defect with CTLA4-Ig (abatacept) has been anecdotally reported to treat pancytopenia and associated life-threatening autoimmunity otherwise refractory to corticosteroids, tacrolimus, azathioprine, cyclophosphamide, and sirolimus (47). LRBA deficiency is an associated autosomal-recessive PID where Treg impairment occurs secondary to aberrant recycling of CTLA4 to the cell surface (48). It is strongly associated with systemic autoimmunity including cytopenias (**Table I**). Major treatment modalities have included corticosteroids (39%), IVIG (39%), MMF (22%), abatacept (15%), tacrolimus/sirolimus (11%), and HSCT (11%) (49). Interestingly, inhibition of lysosomal degradation via chloroquine/hydroxychloroquine rescued CTLA4 expression in LRBA deficient cells *in vitro* (48) and improved lymphoproliferative lung pathology in a patient with *LRBA* mutation *in vivo* (50), however, improvement in autoimmune cytopenias specifically has yet to be described.

Finally, patients with *STAT1*-GOF mutations develop chronic mucocutaneous candidiasis and autoimmunity including cytopenias in the background of prominent T cell dysregulation (**Table I**). Specifically, naïve CD4+ T cells are uniquely biased towards IFN-γ production irrespective of polarizing conditions and expansion of follicular helper T cells relative to Tregs has been shown (51). T cell targeting with cyclosporine has been anecdotally used to treat AIHA in *STAT1*-GOF with benefit (52). More recently, a janus kinase (JAK) 1/2 inhibitor (ruxolitinib) was used to treat two distinct cases of *STAT1*-GOF with associated autoimmunity including autoimmune cytopenias (51) and refractory alopecia areata (53). Ruxolitinib was shown to reduce hyper-responsiveness to IFN-γ, restore Th17 and Treg counts, induce long-lasting control of autoimmunity (up to 6 months post-treatment (53)), and had the unexpected benefit of reducing occurrence of mucocutaneous candidiasis in both cases.

1.3 Immune Reconstitution

Patients with severe immunodeficiency may require progression to HSCT for definitive treatment. Wiskott-Aldrich syndrome (WAS) is a well-described PID where autoimmune cytopenias occur beyond abnormal platelet number, size, and function (54). AIHA is severe, early-onset, and poorly responsive to corticosteroids, and ITP mainly occurs post-splenectomy (**Table I**). The presence of autoimmunity increases disease severity and contributes to the indication for HSCT. Unfortunately, even after HSCT and/or gene therapy autoimmune cytopenias may resurface and become refractory (55-58), as demonstrated by the 55% of WAS patients who developed autoimmune cytopenias in the post-transplant period (59). Thrombopoietin receptor agonists such as romiplostim and eltrombopag are emerging therapies for ITP, mainly by promoting platelet production. Since these agents are not immunosuppressive, they could be particularly useful in the treatment of ITP on a background of PID going forward (60-62).

Finally, autoimmunity is increasingly recognized among patients with CIDs secondary to classical severe combined immunodeficiency (SCID)-related gene defects. Patients with recombination activating gene (*RAG*) mutations can have broad clinical heterogeneity

ranging from early-onset severe infections (SCID phenotype) to delayed-onset autoimmune and inflammatory complications such as cytopenias, vasculitis and granulomas (CID-AI/G phenotype) (63). Specific *RAG* mutation, RAG activity, and ultimately the resultant B and T cell repertoire correlate well with these distinct phenotypes (64). Several checkpoints of B and T cell tolerance are impaired in RAG deficiency, which results in impaired removal of autoreactive cells (abnormal thymic selection, dysfunctional Tregs, impaired B cell receptor editing in the bone marrow, and elevated B cell activating factor (BAFF) expression) (65-67). However the relative contribution of these mechanisms in driving autoimmunity is still unclear. Treatment outcomes data in our RAG deficient cohort suggest that second-line therapy with biologics is not standardized and often ineffective. Progression to HSCT for definitive treatment was ultimately required in 20% of CID-AI/G patients with autoimmune cytopenias (68).

Autoimmune cytopenias have been anecdotally reported in other CIDs (*PIK3CD* (PI3K-D), *TPP2*, and *DOCK8*) as well as in hypomorphic SCID variants (*DCLRE1 (*ARTEMIS), *ADA*, *PNP*, *RMRP*, and *ORAI1*) (62) (**Table II**). The largest review to date details 14 hypomorphic ARTEMIS cases, where 6 of 14 patients (45%) had autoimmune cytopenias (69). For the other PIDs in this group, autoimmune cytopenias are more sporadically reported, and treatment strategies have not been discussed in depth.

2. Treatment of rheumatologic disease in primary immunodeficiencies

PIDs are now known to be associated with a spectrum of rheumatologic disease including inflammatory arthritis, vasculitis, systemic lupus erythematosus (SLE), and SLE-like disorders (**Table I**). It is not uncommon that rheumatologic disease is treated prior to the discovery of an underlying PID, which can result in substantial infectious complications. Indeed, delay in immunophenotyping and definitive treatment has resulted in increased morbidity and/or fatal outcomes in cases recently reported (70-72). Therefore, clinicians must consider risk for infection when approaching therapeutic options for rheumatologic disease in PID. Here, we discuss PID-associated rheumatologic diseases with polyautoimmunity. There are a significant number of important PIDs that cause primarily rheumatologic disease, for example complement deficiencies and monogenic disorders of dysregulated IL-1 production, that have been reviewed elsewhere (73-75).

2.1 Targeting B cell pathology

CVID has been associated with rheumatologic complications including inflammatory arthritis, vasculitis, and SLE (**Table I**). The majority of patients will require therapy beyond IVIG. Case reports have demonstrated successful use of rituximab to treat both CVID-associated SLE (76) and ANCA-positive vasculitis (77). These data localize pathology to the B cell compartment and suggest that other B cell targeting strategies may be efficacious. Belimumab is a novel therapeutic uniquely targeting BAFF that just gained FDA approval for the treatment of SLE (78). Rationale for its use originated in the notion that autoreactive B cells have less BAFF-R on their surface and reside in an anergic state when BAFF levels are normal (79). In inflammatory conditions, BAFF levels may elevate and contribute to the survival of autoreactive cells (80). While promising, belimumab has yet to be trialed in

CVID specifically and may need special consideration in patients with BAFF receptor deficiencies (TACI and BAFF-R). Other potential mechanisms of targeting B cell pathology that may prove efficacious in CVID-associated rheumatologic disease have already been reviewed (**Figure 1**).

2.2 Targeting T cell pathology

The predominance of rheumatologic complications seen in patients with Treg dysfunction including CTLA4haploinsufficiency, LRBA deficiency, and *STAT3*-GOF (**Table I**) converges on the hypothesis that FOXP3+CD25+CD4+ Tregs play a critical role in host defense against the development of rheumatologic diseases including inflammatory arthritis (81). Consistent with this hypothesis, CTLA4-Ig therapy (abatacept) is FDA approved for the treatment of rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) in the general population. More recently, abatacept has shown benefit in PID. In LRBA deficiency, two children with inflammatory arthritis and uveitis (clinically consistent with JIA) demonstrated robust response to abatacept therapy (48, 82). Inflammatory arthritis can also complicate the course of CTLA4 haploinsufficiency (83), and it has yet to be determined whether abatacept will be additionally beneficial in these cases. Finally, inflammatory arthritis has been reported in several patients with *STAT3*-GOF (84, 85). Immunophenotype is notable for decreased Treg numbers and functional expression of FOXP3 and CD25, potentially mediated by increased STAT3-dependent SOCS3 expression driving decreased STAT5 phosphorylation (84, 85). As Treg inhibition in *STAT3*-GOF is indirect, clinicians hypothesized that use of an anti-IL6R antibody (tocilizumab) might be beneficial via blocking upstream IL-6-induced STAT3 activation. To date, one patient with *STAT3*-GOF complicated by arthritis and scleroderma-like skin changes refractory to treatment with TNF-α inhibitors, anti-IL-1 therapy, and rituximab demonstrated sustained response to tocilizumab over a one year follow-up period (84).

Inflammatory arthritis is also a known complication of x-linked agammaglobulinemia (XLA), a PID where autoreactive B cells are effectively absent due to maturation arrest at the pre-B cell stage. While infectious joint inflammation resolving on immunoglobulin replacement therapy is frequently seen in XLA (86), aseptic arthritis has also been described including presentations of RA (87), JIA (88, 89), and enthesitis-related arthritis (ERA) (90). Infiltrating CD8+ T cells can be seen on joint cytology (87). Underlying mechanisms of T cell-driven autoimmunity (90) and/or innate immune hyperactivation (91, 92) have been proposed. In these cases, IVIG alone can be insufficient management (87, 90), progression despite methotrexate has been described (87), nonsteroidal anti-inflammatories (NSAIDs) may provide some benefit (89, 90), and there is no systematic guidance for the use of T cell or innate immune targeted strategies to date.

2.3 Targeting innate immune pathology

In contrast to the PIDs previously presented, patients with chronic granulomatous disease (CGD) develop systemic autoimmunity in the background of a primary innate immune deficiency. Here decreased NADPH oxidase results in defective phagocytosis. Profound aseptic hyper-inflammatory responses are seen in CGD, characterized by loss of anti-inflammatory mediators (93), impaired clearance of apoptotic cells (94), and downstream

CD4+ T cell skewing that can drive autoimmune arthritis in the mouse model (95). In patients, CGD has been associated with cutaneous discoid lupus erythematosus (DLE), chorioretinitis, inflammatory arthritis, vasculitis, and SLE as well as DLE in female carriers of x-linked disease (**Table I**) (96-99). A single case series on treatment of rheumatologic manifestations in CGD recently demonstrated clinical stabilization with systemic corticosteroids (one case of DLE), methotrexate (one case of antiphospholipid syndrome (APLS)), and etanercept (one case of JIA) (96). While these anecdotal data are promising, anti-TNF-α therapies have been associated with invasive fungal disease even in immunocompetent hosts and should be used cautiously in these and other PID patients with significant susceptibility to infection.

2.4 Immune Reconstitution

HSCT has the potential to be curative for PID with autoimmunity in terms of reconstitution of the immune system and reduced susceptibility to infection. However, autoimmune disease can sometimes persist or even broaden post-transplant. 70% of WAS patients have associated autoimmunity that can include inflammatory arthritis and vasculitis (**Table I**). Although arthritis and vasculitis generally improve following HSCT or gene therapy, there are several cases where autoimmunity has persisted or even newly arisen (56-58). RAG deficiency has also been associated with rheumatologic and autoimmune diseases including vitiligo, myasthenia gravis (MG), and vasculitis (**Table II**) (63). Progression of vasculitis in RAG deficiency despite treatment with corticosteroids, IVIG, and rituximab has been described (70). In contrast, HSCT in RAG deficiency has been case reported to be curative/preventative for polyautoimmunity (70, 100). As fewer post-transplant auto-inflammatory complications were observed in patients with RAG deficiency compared to patients with impaired ARTEMIS (101), benefit of HSCT may be PID-specific. However, additional clinical evidence is required to determine whether HSCT is truly curative for rheumatologic disease in PID. Optimal timing for transplantation, regimen for conditioning, and goal for donor chimerism have yet to be determined.

3. Treatment of GI disease in primary immunodeficiencies

PIDs have been associated with a broad clinical spectrum of autoimmune GI disorders including gastritis (pernicious anemia), celiac disease, autoimmune enteropathy (AIE), and inflammatory bowel disease (IBD) (**Table I**) (102). In the background of frequent infections (e.g., *Giardia, Campylobacter, Salmonella,* rotavirus, enterovirus, norovirus) diagnosis of nonspecific GI symptoms such as nausea, vomiting, diarrhea, and weight loss becomes particularly challenging. However, elucidating the underlying pathophysiology is critical given the associated finding of increased mortality in the PID subgroup with GI complications specifically (20).

3.1 Targeting T cell pathology

Gastritis, AIE, and IBD have all been described in CVID (103). Small intestinal biopsy frequently demonstrates villous atrophy that resembles sprue apart from the absence of plasma cells (104, 105). Lymphocytic infiltrates and occasional granulomas can occur both in the small intestine and the colon, consisting predominantly of CD 8+ T cells (104-106).

Unfortunately, GI inflammatory disease in CVID has been notoriously difficult to treat. Despite benefit from combination rituximab/azathioprine therapy to manage granulomatous lung pathology (107), a similar response has not been seen in the inflamed GI tract (108). TNF-α inhibitors (109, 110) as well as the anti-α4β7 integrin monoclonal vedolizumab, which may inhibit Treg trafficking to the GI mucosa (103), have been anecdotally reported as successful. We have a case of severe CVID-associated AIE with negative genetic testing for *CTLA4* and *LRBA* mutations currently improving after 4 months of treatment with abatacept (weight gain, decreased stool output, decreased infiltrating T cells on biopsy) (Walter, JE and Farmer, JR; unpublished data). Therefore, GI inflammatory disease may be a unique complication of CVID where B cell targeting is insufficient and directed T cell targeting is required to effectively manage this often life-threatening complication.

Mounting data are converging on the importance of Tregs in host defense against auto-inflammation in the GI tract. Immune dysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX) is a profound disorder of FOXP3+CD25+CD4+ Tregs caused by mutations in *FOXP3*. The pathognomonic clinical features of IPEX are severe and early-onset dermatitis, type I diabetes mellitus, and failure to thrive secondary to refractory diarrhea starting in infancy (111, 112). A demonstrated break in peripheral B cell tolerance leading to the production of auto-antibodies to the brush border proteins villin and AIE-75 has been described (113, 114). However, the role of anti-villin and anti-AIE-75 in disease pathogenesis is entirely unclear. AIE on biopsy is characterized by villous atrophy with infiltrating lymphocytes and eosinophils. Histopathologic patterns of “graft-versus-host disease-like,” “celiac disease-like,” and “depletion of the intestinal goblet cells” have all been described (115). Most single targeted immunosuppressive agents have been disappointing in the management of the profound autoimmunity and failure to thrive. However, T cell targeted therapeutics including tacrolimus, cyclosporine, and sirolimus have shown benefit in reducing the burden of IPEX-related autoimmune disease in the pre-transplant period (116-118).

Beyond intrinsic Treg defects secondary to abnormal FOXP3, CD25 or STAT5b; interestingly, AIE and IBD are shared complications of other Treg disorders including CTLA4 haploinsufficiency (83, 119), LBRA deficiency (120), *STAT1*-GOF (121) *STAT3*-GOF (84), mutated *RAG1* (122) or *DOCK8* (123), and ITCH deficiency (124, 125). Furthermore, autoimmune GI disease can be robustly induced (27-54% symptomatic with watery diarrhea) upon treatment with anti-CTLA4 biologics (126). These data again converge on the hypothesis that Tregs are critical in gut homeostasis (127). To this end, infiltrating T cells have been demonstrated on intestinal biopsy in CTLA4 haploinsufficiency (83), and lack of response to traditional therapeutics including TNF-α inhibitors has been demonstrated in LBRA deficiency (120). By contrast, sirolimus has been reliably efficacious in CTLA-4 haploinsufficient patients, and immune reconstitution with abatacept has been shown to markedly reduce AIE (47).

3.2 Targeting innate immune pathology

Profound autoimmune GI disease can also occur in the setting of innate immune deficiency. Classic is CGD, where multi-organ granulomatous inflammatory pathology occurs, most

prominently affecting the GI tract in up to 73-88% of patients (**Table I**) (128, 129). Biopsy demonstrates skip lesions most frequently affecting the ano-rectum and consisting of crypt abscesses, large pigment-containing macrophages, and noncaseating granulomas, which can be indistinguishable from Crohn's disease (128-131). Despite the predisposition towards infection, no causative pathogens were identified in up to 93% of CGD-associated inflammatory GI disease cases (128), suggesting an underlying mechanism of aseptic autoimmunity. Treatment outcomes to date demonstrate limited benefit from corticosteroids (63-86% relapse rate) and/or NSAIDs (50-100% relapse rate) (128). Immunomodulation with methotrexate, azathioprine, cyclosporine, and thalidomide have been case reported as successful (128, 129, 132, 133). Finally, despite efficacy in colitis management, TNF-α inhibitors should be avoided given the high rate of complicating deadly infections (two deaths out of five infliximab-treated CGD patients (134)).

3.3 Immune Reconstitution

In CGD, HSCT has been shown to be curative both in terms of the recurrent infections and the multi-organ granulomatous pathology (135). However, using full myeloablative conditioning, patients with peri-transplant comorbidities including colitis had increased mortality (135), bringing up controversy as to the optimal timing and conditioning for transplant. More recently, reduced-intensity conditioning using high-dose fludarabine, serotherapy, and low-dose busulfan in high-risk CGD was shown to be both safe and effective (89% event-free survival at 21 month follow-up (136)). As this study included 33% of patients with active peri-transplant colitis, the data suggest that this reduced-intensity conditioning HSCT can be considered in severe CGD cases complicated by IBD.

Finally, while directed immunosuppression in IPEX can help to reduce the burden of multi-organ inflammatory pathology, HSCT is the only definitive treatment. Improved outcomes are seen with earlier age and fewer comorbidities at time of transplant and with the use of reduced-toxicity conditioning regimens (137-143). Even in the case of partial donor chimerism, clinical disease remission has been reported, coinciding with the presence of full donor Tregs (139, 141). The selective advantage of wild-type Tregs is consistent with the underlying pathophysiology of IPEX and may dictate Treg-sparing therapies for graft-versus-host disease in the post-transplant period (112).

Summary—Autoimmune and inflammatory diseases can greatly complicate the care of PID patients. Treatment strategies in PID should be targeted not only to the clinical spectrum of autoimmunity (cytopenias, rheumatologic disease, and/or GI disease) but to the underlying molecular cause of immune dysregulation (B cell, T cell, and/or innate immune pathology). As we advance our understanding of mechanisms that mediate autoimmunity in PID, we inherently improve the care of our PID patients and broaden our basic understanding of autoimmune and inflammatory disease.

Abbreviations

PIDs	primary immunodeficiencies
GI	gastrointestinal

HSCT	hematopoietic stem cell transplantation
AIHA	autoimmune hemolytic anemia
ITP	immune thrombocytopenic purpura
AN	autoimmune neutropenia
IVIG	intravenous immunoglobulin
CVID	common variable immunodeficiency
CID	combined immunodeficiency
SCID	severe combined immunodeficiency
ALPS	autoimmune lymphoproliferative syndrome
WAS	Wiskott-Aldrich syndrome
CGD	chronic granulomatous disease
pDGS	partial DiGeorge syndrome
XLA	x-linked agammaglobulinemia
IPEX	immune dysregulation polyendocrinopathy enteropathy X-linked syndrome
SLE	systemic lupus erythematosus
DLE	discoid lupus erythematosus
RA	rheumatoid arthritis
JIA	juvenile idiopathic arthritis
ERA	enthesitis-related arthritis
MG	myasthenia gravis
APLS	antiphospholipid syndrome
AIE	autoimmune enteropathy
IBD	inflammatory bowel disease
BAFF	B cell activating factor
CTLA4	cytotoxic T-lymphocyte antigen 4
LRBA	LPS-responsive vesicle trafficking, beach and anchor containing protein
RAG	recombination activating gene
STAT	signal transducer and activator of transcription
GOF	gain-of-function

Treg	regulatory T cell
DN	double negative
UPR	unfolded protein response
JAK	janus kinase
MMF	mycophenolate mofetil
NSAID	nonsteroidal anti-inflammatory

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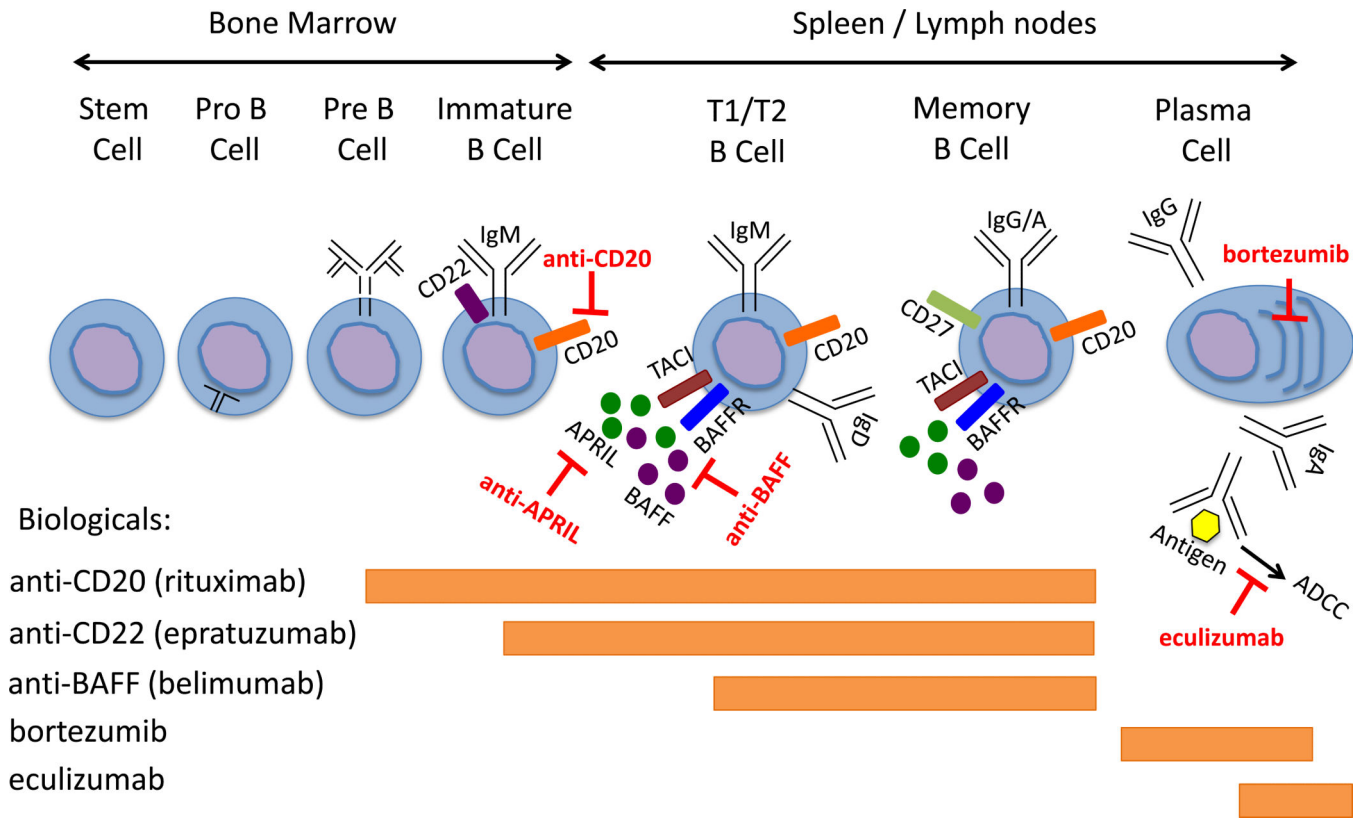

Figure 1.
Mechanisms of targeting B cell pathology in the treatment of autoimmune and inflammatory diseases associated with PID.

Table I

Primary immunodeficiencies associated with autoimmune disease.

PID	Immunologic Defect	AI Cytopenias Prevalence (%)	Rheum Disease Prevalence (%)	GI Disease Prevalence (%)	Other Noninfectious Manifestations	Refs.
CVID	Polygenic low IgG (low IgA or IgM), low vaccine titers, low sm B cells, high $CD19^{hi}21^{lo}$ B cells	ITP (5.6-14.2) AIHA (2.7-7) AN (<1-2.7) Evans (4.2)	RA (3.2) vasculitis & SLE (<1-2.7)	diarrhea (14-23) malabsorption/AIE (6-9) IBD (4.2)	Lymphoproliferative pathology (LAD, HSM, GLILD, NRH, leukemia, lymphoma) Other autoimmunity (hepatitis, alopecia, thyroiditis, vitiligo)	(20, 21, 144-146)
XLA	*BTK* Low/absent circulating B cells, loss of germinal centers, pan low immunoglobulins, impaired innate immune signaling, decreased Tfh cells	ITP (2.7*) AIHA (9.8*)	RA/JIA (1.8*-16)	diarrhea (8*-29) IBD (3.6*-3.8)	Neutropenia in the setting of overwhelming infection	(86, 147-150)
ALPS	*TNFRSF6* (*FAS*), *TNFSF6* (*FASL*), *CASP10* high DN T cells, IL-10, IL-18, vit B12, FAS; decreased FAS-mediated apoptosis	ITP (26-39) AIHA (29-36) AN (8-37) Evans (10-23)	uveitis (1-10) vasculitis (4) arthritis (case reported)	IBD (case reported)	Lymphoproliferative pathology (LAD, HSM, lymphoma) Other autoimmunity (hepatitis, PBC, GBS, GN)	(34, 151-155)
pDGS	22q11.2 impaired thymic development, decreased T cell number & function, variably decreased IgG/A/M & sm B cells	ITP (3.1-6.3) AIHA (0.5-3.1) Evans (0.5-3.1)	vasculitis (3.1) arthritis (2.5-3.1)	IBD (0.5)	Craniofacial anomalies, hypoplastic thymus, conotruncal cardiac anomalies, hypocalcemia Other autoimmunity (thyroiditis)	(44, 156-158)
CTLA4	*CTLA4* (haploinsuficiency) impaired FOXP3+ Tregs, activated effector & decreased naïve T cells, low IgG, low B cells, high $CD21^{lo}$ B cells	ITP (35) AIHA (28)	arthritis (14)	Diarrhea/AIE (78)	Lymphoproliferative pathology (LAD, HSM, GLILD) Other autoimmunity (thyroiditis)	(47, 83, 119)
LRBA	*LRBA* decreased/impaired FOXP3+ Tregs, activated T effector cells, low IgG, low B cells (sm B cells and plasmablasts)	ITP (29-52) AIHA (39-57) AN (24)	arthritis (26) uveitis (10)	Diarrhea/AIE (61-62)	Growth retardation, eczema Lymphoproliferative pathology (LAD, HSM, GLILD, lymphoma) Other autoimmunity (T1DM, thyroiditis, hepatitis, alopecia)	(48, 49, 159)
IPEX	*FOXP3* impaired FOXP3+ Tregs, high IgE, high eosinophils, low Th1 cytokines, high Th2 cytokines	AIHA or ITP or AN (31)	arthritis (1)	Diarrhea/AIE (92)	FTT, severe dermatitis Lymphoproliferative pathology (LAD, HSM) Other autoimmunity (early-onset T1DM, thyroiditis, hepatitis)	(160)
***STAT3*-GOF**	*STAT3* decreased/impaired FOXP3+ Tregs, increased DN T cells, variably low IgG	ITP (62) AIHA (69) AN (46) Evans (46)	arthritis (15-20)	AIE (38-60)	Short stature, eczema Lymphoproliferative pathology (LAD, HSM, GLILD, lymphoma) Other autoimmunity (T1DM, thyroiditis, alopecia, scleroderma, hepatitis)	(84, 85)

PID	Immunologic Defect	AI Cytopenias Prevalence (%)	Rheum Disease Prevalence (%)	GI Disease Prevalence (%)	Other Noninfectious Manifestations	Refs.
***STAT1*-GOF**	*STAT1* augmented Th1, decreased/impaired Th17, low memory B cells, low IgG2/IgG4	AIHA or ITP (4)	SLE (2)	AIE (4)	Aneurysms, eczema, carcinomas Other autoimunity (thyroiditis, T1DM, alopecia, vitiligo, psoriasis, hepatitis)	(161, 162)
WAS	*WAS* decreased T cell number & function, low IgG/A/M, high IgE, low vaccine titers	ITP (32) AIHA (14-36) Evans (20)	vasculitis (13) arthritis (10)	IBD (3)	Microthrombocytes with low count & poor function, eczema, mucosal bleeding, lymphoma, renal disease	(163)
CGD	*CYBB* (x), *CYBA, NCF1, NCF2, NCF4* dysfunctional NADPH oxidase, impaired phagocytosis, aseptic hyper-inflammation	ITP (1.4)	DLE (2.7) chorioretinitis (2.2) SLE, APLS, vasculitis, & arthritis (<1)	IBD (17-88)	Lymphoproliferative pathology with severe multi-organ granulomatous disease (GI tract, lungs, kidneys, eyes)	(96, 99, 128, 164)

Abbreviations: patient self-reported (*), primary immunodeficiency (PID), autoimmune (AI), rheumatologic (rheum), gastrointestinal (GI), common variable immunodeficiency (CVID), autoimmune lymphoproliferative syndrome (ALPS), partial DiGeorge syndrome (pDGS), cytotoxic T-lymphocyte antigen 4 (CTLA4), LPS-responsive vesicle trafficking, beach and anchor containing protein (LRBA), immune dysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX), signal transducer and activator of transcription (STAT), gain-of-function (GOF), Wiskott-Aldrich syndrome (WAS), chronic granulomatous disease (CGD), regulatory T cell (Treg), helper T cell (Th), follicular helper T cell (Tfh), double negative (DN), switched memory (sm), autoimmune hemolytic anemia (AIHA), immune thrombocytopenic purpura (ITP), autoimmune neutropenia (AN), rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), discoid lupus erythematosus (DLE), anti-phospholipid syndrome (APLS), myasthenia gravis (MG), glomerulonephritis (GN), primary biliary cirrhosis (PBC), type I diabetes mellitus (T1DM), Guillain-Barre syndrome (GBS), autoimmune enteropathy (AIE), inflammatory bowel disease (IBD), lymphadenopathy (LAD), hepatosplenomegaly (HSM), granulomatous and lymphocytic interstitial lung disease (GLILD), nodular regenerative hyperplasia (NRH), failure to thrive (FTT)

Table II

Combined immunodeficiencies associated with autoimmune cytopenias.

Gene	Function	Autoimmune Cytopenias	Treatment Strategies	Associated Autoimmunity	References
RAG1, RAG2	dsDNA cleavage during V(D)J recombination	AIHA, ITP, AN	steroids, IVIG, rituximab, HSCT	vasculitis, GBS, MG, psoriasis, vitiligo	(63, 70, 165)
DCLRE1 (ARTEMIS)	non-homologous end joining, opening the hairpins	AIHA, ITP, AN	n.a.		(69, 166)
ADA	deamination of adenosine and 2′-deoxyadenosine	AIHA, ITP	PEG-ADA, HSCT	AI thyroiditis, T1DM	(167)
PNP	conversion of inosine and guanosine to hypoxanthine	AIHA, ITP	steroids, rituximab, azathioprine, cyclosporine, HSCT		(168)
RMRP	RNA component of the mitochondrial RNA processing (RMRP) endoribonuclease complex	AIHA, ITP post-HSCT	steroids, IVIG, rituximab, HSCT	granulomas	(169)
TRAC	loss of TCR (transmembrane & intra-cytoplasmic domains)	AIHA	treatment is not discussed, s/p HSCT	vitiligo, alopecia areata, pityriasis rubra pilaris	(170)
IL-7R	signaling through the IL-7 receptor ensures the development of mature B cells & T cells	AIHA, ITP	treatment is not discussed, s/p HSCT		(171)
CD3γ	TCR signal transduction	AIHA, ITP	steroids	AI hepatitis & thyroiditis, minimal change disease	(172)
ZAP70	CD3ζ binding, T cell activation	ITP	IVIG	arthritis, nephritis in the mouse model	(173)
LCK/p56	TCR signaling, associated with CD4 and CD8, upon activation mediates phosphorylation of CD3 and ZAP70	ITP	steroids, HSCT	retinal vasculitis, sterile septal and lobular neutrophillic panniculitis, sterile arthritis	(174)
MST1/STK4	interacts with Foxo1 that controls IL-7Ra expression in naive T cells and T cell homeostasis	AIHA, ITP, AN	steroids, IVIG, rituximab, cyclosporine, azathioprine		(175-177)
ORAI1 (CRACM1)	store operated calcium entry, interaction with STIM1, T cell activation	ITP, AN	n.a.		(178)
STIM1	ER-resident calcium sensor, activates ORAI1 to promote store operated calcium entry	AIHA, ITP	steroids		(179)
MAGT1	magnesium-specific transporter and immune regulator	unspecified cytopenias	n.a.		(180)
PIK3CD (PI3K-D)	Akt-mTOR pathway activation, generation of short lived effector CD8+ cells	AIHA, ITP	n.a.		(181, 182)
TPP2	cell proliferation and survival, anti-apoptotic	AIHA, ITP	steroids, IVIG, cyclosporine, MMF, rituximab, sirolimus, HSCT		(183)
DOCK8	intracellular signal transduction	AIHA	n.a.	thyroiditis	(184-187)
MHCII	antigen presentation	unspecified cytopenias	n.a.		(7, 188)

Abbreviations: not annotated (n.a.), autoimmune (AI), autoimmune hemolytic anemia (AIHA), immune thrombocytopenic purpura (ITP), autoimmune neutropenia (AN), intravenous immunoglobulin (IVIG), hematopoietic stem cell transplantation (HSCT), T cell receptor (TCR), endoplasmic reticulum (ER), myasthenia gravis (MG), type I diabetes mellitus (T1DM), Guillain-Barre syndrome (GBS), mycophenolate mofetil (MMF)