Mechanism-Based Strategies for the Management of Autoimmunity and Immune Dysregulation in Primary Immunodeficiencies

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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. **(J Allergy Clin Immunol Pract 2016;4:1089-100)**

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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 on correcting the underlying immune dysregulation while minimizing nonspecific immune suppression. Herein, we will review the 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.

TREATMENT OF AUTOIMMUNE CYTOPENIAS IN PIDs

Although autoimmune cytopenias, including autoimmune hemolytic anemia (AIHA), immune thrombocytopenic purpura (ITP), and autoimmune neutropenia, 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 multilineage 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 multilineage cytopenias, AIHA with no response to first-line therapy, persistent/chronic ITP, and autoimmune neutropenia in a patient older than 2 years and/or persistent for more than 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 therapy.[16] In the fraction of patients who relapse after 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

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Abbreviations used
AIE- Autoimmune enteropathy
AIHA- Autoimmune hemolytic anemia
ALPS- Autoimmune lymphoproliferative syndrome
BAFF- B-cell—activating factor
CGD- Chronic granulomatous disease
CID- Combined immunodeficiency
CTLA4- Cytotoxic T-lymphocyte antigen 4
CID- Combined immunodeficiency
CVID- Common variable immunodeficiency
GI- Gastrointestinal
GOF- Gain-of-function
HSCT- Hematopoietic stem cell transplantation
IBD- Inflammatory bowel disease
IPEX- Immune dysregulation polyendocrinopathy enteropathy X-linked syndrome
ITP- Immune thrombocytopenic purpura
IVIG- Intravenous immunoglobulin
JIA- Juvenile idiopathic arthritis
LRBA- LPS-responsive vesicle trafficking, beach and anchor containing protein
PID- Primary immunodeficiency
RAG- Recombination activating gene
SCID- Severe combined immunodeficiency
SLE- Systemic lupus erythematosus
STAT- Signal transducer and activator of transcription
Treg- Regulatory T cell

biomarkers to direct care. In contrast, second-line treatment strategies for PID-associated autoimmune cytopenias are increasingly being targeted to the underlying mechanism of immunopathology.

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 immunoglobulin levels (low IgG level with low IgM and/or IgA level), 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[56] and 81% for AIHA[57]; however, prolonged use was often required, which increased the 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.[8,56,57] 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.[58] In a subsequent multicenter study of 33 patients with CVID with refractory autoimmune cytopenias, which included steroid dependence (56%), immunomodulatory therapy (44%), and previous splenectomy (21%), rituximab was demonstrated to have a durable response rate of 59%.[59] The authors proposed that rituximab be considered standard second-line therapy, before 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 immunoglobulin replacement therapy and/or had undergone splenectomy.[59] Although a matter of concern, the rate of severe bacterial infections was not significantly different than that observed in patients with CVID with ITP treated by the more traditional approach of corticosteroids with or without high-dose IVIG.[56] Therefore, the risk for infection with rituximab use needs to be considered primarily in patients with CVID 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.[60] Bortezomib has shown promising results in peritransplant cases of PID-associated refractory autoimmune cytopenias specifically (4 of 5 patients with PID responded to treatment and only 2 patients required transition to alternative therapy[61]). 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,[62-65] but are yet to be trialed in PID specifically. Finally, the terminal complement inhibitor eculizumab (anti-C5) has been used to rescue a patient from fatal complications related to treatment-refractory AIHA.[66] Because 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.

Targeting T-cell pathology

Patients with PID 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) T cells occurs secondary to defective apoptosis. Although 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 posttreatment.[67] Similarly, splenectomy is less preferred because it may result in unfavorable outcomes with recurrent cytopenias and high rates of sepsis (41%) in patients with ALPS.[30]

The conventional first-line therapy for ALPS-associated autoimmune cytopenias has been corticosteroids, but second-line therapies including mycophenolate mofetil (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 double-negative T cells are increasingly