2016

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

Jolan E. Walter
University of South Florida St. Petersburg

Jocelyn R. Farmer
Massachusetts General Hospital

Zsofia Foldvari
University of Oslo

Troy R. Torgerson
University of Washington - Seattle Campus

Megan A. Cooper
Washington University School of Medicine in St. Louis

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

Jolan E. Walter, MD, PhD[a,b,c], Jocelyn R. Farmer, MD, PhD[d], Zsofia Foldvari, MD[e,f], Troy R. Torgerson, MD, PhD[g], and Megan A. Cooper, MD, PhD[h] *St Petersburg, Fla; Boston, Mass; Oslo, Norway; Seattle, Wash; and St Louis, Mo*

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)**

Key words: *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 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

[a]Department of Pediatrics & Medicine, University of South Florida at Johns Hopkins All Children's Hospital, St Petersburg, Fla
[b]Division of Pediatric Allergy & Immunology, Massachusetts General Hospital for Children, Boston, Mass
[c]Division of Immunology, Boston Children's Hospital, Boston, Mass
[d]Department of Allergy & Immunology, Massachusetts General Hospital, Boston, Mass
[e]Department of Cancer Immunology, Oslo University Hospital Radiumhospitalet, Oslo, Norway
[f]K. G. Jebsen Centers for Cancer Immunotherapy and for Inflammation Research, Institute for Clinical Medicine, University of Oslo, Oslo, Norway
[g]Department of Pediatrics, University of Washington School of Medicine, Seattle, Wash
[h]Department of Pediatrics, Division of Rheumatology, Washington University School of Medicine, St Louis, Mo

Conflicts of interest: J. E. Walter has been supported by grant number 5K08AI103035 and the Jeffrey Modell Foundation. J. R. Farmer is employed by Massachusetts General Hospital. T. R. Torgerson has consultancy arrangements with Baxalta Biosciences, CSL Behring, and ADMA Biologics; has received one or more grants from or has one or more grants pending with Baxalta Biosciences, CSL Behring, and the NIH; and has received one or more payments for the development of educational presentations for Baxalta Biosciences, CSL Behring, Questcor Pharmaceuticals, and Robert Wood Johnson Foundation. The rest of the authors declare that they have no relevant conflicts of interest.
Received for publication June 10, 2016; revised August 1, 2016; accepted for publication August 19, 2016.
Corresponding author: Jolan E. Walter, MD, PhD, University of South Florida at Johns Hopkins All Children's Hospital, 601 4th St South (CRI 4008), St Petersburg, FL 33701. E-mail: jolanwalter@health.usf.edu.
2213-2198

http://dx.doi.org/10.1016/j.jaip.2016.08.004

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

TABLE I. PIDs associated with autoimmune disease

PID	Immunologic defect	AI cytopenias prevalence (%)	Rheum disease prevalence (%)	GI disease prevalence (%)	Other noninfectious manifestations	References
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)	20-24
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	25-29
ALPS	*TNFRSF6* (*FAS*), *TNFSF6* (*FASL*), *CASP10* High DN T cells, IL-10, IL-18, vitamin B_{12}, 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)	30-35
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)	36-39
CTLA4	*CTLA4* (haploinsuficiency) Impaired FOXP3+ Treg cells, activated effector & decreased naive 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)	40-42
LRBA	*LRBA* Decreased/impaired FOXP3+ Treg cells, 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)	43-45
IPEX	*FOXP3* Impaired FOXP3+ Treg cells, high IgE, high eosinophils, low T_H1 cytokines, high T_H2 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)	46
STAT3-GOF	*STAT3* Decreased/impaired FOXP3+ Treg cells, 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)	47,48
STAT1-GOF	*STAT1* Augmented T_H1, decreased/impaired T_H17, low memory B cells, low IgG_2/IgG_4	AIHA or ITP (4)	SLE (2)	AIE (4)	Aneurysms, eczema, carcinomas Other autoimunity (thyroiditis, T1DM, alopecia, vitiligo, psoriasis, hepatitis)	49,50

(continued)

TABLE I. *(Continued)*

PID	Immunologic defect	AI cytopenias prevalence (%)	Rheum disease prevalence (%)	GI disease prevalence (%)	Other noninfectious manifestations	References
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	51
CGD	*CYBB* (x), *CYBA, NCF1, NCF2, NCF4* Dysfunctional NADPH oxidase, impaired phagocytosis, aseptic hyperinflammation	ITP (1.4)	DLE (2.7) Chorioretinitis (2.2) SLE, APLS, vasculitis, & arthritis (<1)	IBD (17-88)	Lymphoproliferative pathology with severe multiorgan granulomatous disease (GI tract, lungs, kidneys, eyes)	52-55

AI, Autoimmune; *AN*, autoimmune neutropenia; *APLS*, antiphospholipid syndrome; *DLE*, discoid lupus erythematosus; *DN*, double negative; *FTT*, failure to thrive; *GBS*, Guillain-Barre syndrome; *GLILD*, granulomatous and lymphocytic interstitial lung disease; *GN*, glomerulonephritis; *HSM*, hepatosplenomegaly; *LAD*, lymphadenopathy; *MG*, myasthenia gravis; *NADPH*, nicotinamide adenine dinucleotide phosphate; *NRH*, nodular regenerative hyperplasia; *PBC*, primary biliary cirrhosis; *pDGS*, partial DiGeorge syndrome; *PID*, primary immunodeficiency; *RA*, rheumatoid arthritis; *rheum*, rheumatologic; *sm*, switched memory; *T1DM*, type 1 diabetes mellitus; *Tfh*, follicular helper T cell; *WAS*, Wiskott-Aldrich syndrome; *XLA*, x-linked agammaglobulinemia.
*Patient self-reported.

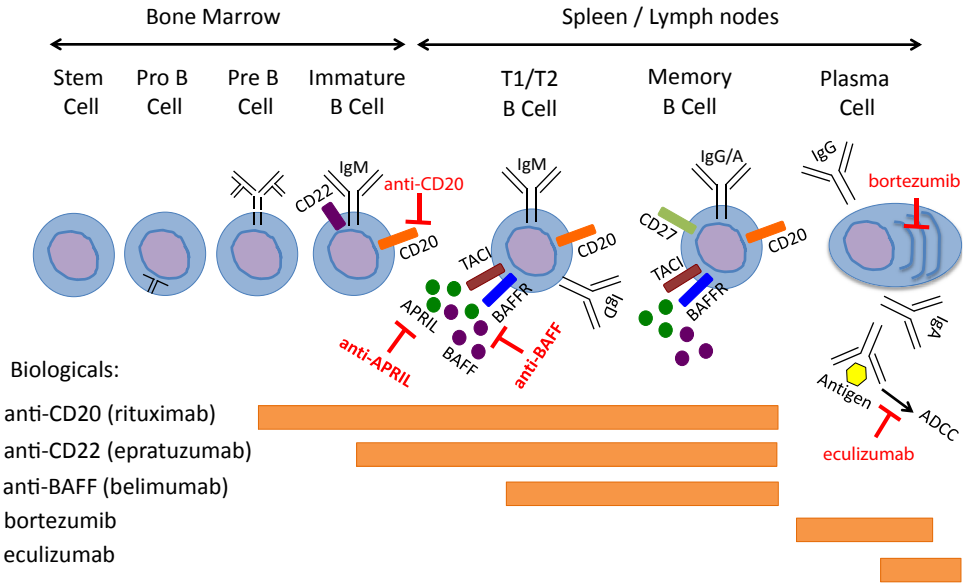

FIGURE 1. Mechanisms of targeting B-cell pathology in the treatment of autoimmune and inflammatory diseases associated with PID.

being used as primary therapy.[68,69] Sirolimus was first trialed in 4 corticosteroid-refractory patients with ALPS 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 most patients.[70] Treatment response in ALPS has been shown to coincide with a specific reduction in double-negative T cells, which are particularly dependent on an intact mTOR pathway.[70-73]

Autoimmune cytopenias have been associated with partial DiGeorge syndrome, occasionally preceding diagnosis of the underlying genetic defect (Table I).[74-76] Breaks in both central T-cell tolerance (eg, thymic aplasia/dysplasia) and peripheral T-cell tolerance (eg, T-cell proliferation to low-affinity self-antigens) have been proposed to induce autoimmunity.[36] 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.[75] Progression despite rituximab has been reported in 2 cases of severe autoimmune cytopenias associated with partial DiGeorge syndrome, one requiring HSCT for definitive treatment[77] and the other requiring plasmaphoresis in combination with splenectomy for stabilization.[78]

Autoimmune cytopenias can also occur in the setting of regulatory T-cell (Treg) dysfunction. Cytotoxic T-lymphocyte antigen 4 (CTLA4) haploinsufficiency is a novel autosomal-dominant immunodeficiency in which decreased CTLA4 cell surface expression results in impaired Treg-cell 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

TABLE II. CIDs 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	92,98,99
DCLRE1 (ARTEMIS)	Nonhomologous end joining, opening the hairpins	AIHA, ITP, AN	NA		100,101
ADA	Deamination of adenosine and 2′-deoxyadenosine	AIHA, ITP	PEG-ADA, HSCT	AI thyroiditis, T1DM	102
PNP	Conversion of inosine and guanosine to hypoxanthine	AIHA, ITP	Steroids, rituximab, azathioprine, cyclosporine, HSCT		103
RMRP	RNA component of the mitochondrial RNA processing (RMRP) endoribonuclease complex	AIHA, ITP post-HSCT	Steroids, IVIG, rituximab, HSCT	Granulomas	104
TRAC	Loss of TCR (transmembrane & intracytoplasmic domains)	AIHA	Treatment is not discussed, s/p HSCT	Vitiligo, alopecia areata, pityriasis rubra pilaris	105
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		106
CD3γ	TCR signal transduction	AIHA, ITP	Steroids	AI hepatitis & thyroiditis, minimal change disease	107
ZAP70	CD3ζ binding, T-cell activation	ITP	IVIG	Arthritis, nephritis in the mouse model	108
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	109
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		110-112
ORAI1 (CRACM1)	Store-operated calcium entry, interaction with STIM1, T-cell activation	ITP, AN	NA		113
STIM1	ER-resident calcium sensor, activates ORAI1 to promote store-operated calcium entry	AIHA, ITP	Steroids		114
MAGT1	Magnesium-specific transporter and immune regulator	Unspecified cytopenias	NA		115
PIK3CD (PI3K-D)	Akt-mTOR pathway activation, generation of short-lived effector CD8+ cells	AIHA, ITP	NA		116,117
TPP2	Cell proliferation and survival, antiapoptotic	AIHA, ITP	Steroids, IVIG, cyclosporine, MMF, rituximab, sirolimus, HSCT		118
DOCK8	Intracellular signal transduction	AIHA	NA	Thyroiditis	119-122
MHCII	Antigen presentation	Unspecified cytopenias	NA		7,123

AI, Autoimmune; *AN*, autoimmune neutropenia; *ER*, endoplasmic reticulum; *GBS*, Guillain-Barre syndrome; *MG*, myasthenia gravis; *MMF*, mycophenolate mofetil; *NA*, not annotated; *T1DM*, type 1 diabetes mellitus; *TCR*, T-cell receptor.

with CTLA4-immunoglobulin (abatacept) has been anecdotally reported to treat pancytopenia and associated life-threatening autoimmunity otherwise refractory to corticosteroids, tacrolimus, azathioprine, cyclophosphamide, and sirolimus.[40] LPS-responsive vesicle trafficking, beach and anchor containing protein (LRBA) deficiency is an associated autosomal-recessive

PID in which Treg-cell impairment occurs secondary to aberrant recycling of CTLA4 to the cell surface.[43] It is strongly associated with systemic autoimmunity including cytopenias (Table I). Major treatment modalities have included corticosteroids (39%), IVIG (39%), mycophenolate mofetil (22%), abatacept (15%), tacrolimus/sirolimus (11%), and HSCT (11%).[44] Interestingly, inhibition of lysosomal degradation via chloroquine/hydroxychloroquine rescued CTLA4 expression in LRBA-deficient cells *in vitro*[43] and improved lymphoproliferative lung pathology in a patient with *LRBA* mutation *in vivo*[79]; however, improvement in autoimmune cytopenias specifically is yet to be described.

Finally, patients with signal transducer and activator of transcription (*STAT*)*1*-gain-of-function (GOF) mutations develop chronic mucocutaneous candidiasis and autoimmunity including cytopenias in the background of prominent T-cell dysregulation (Table I). Specifically, naive CD4+ T cells are uniquely biased toward IFN-γ production irrespective of polarizing conditions and expansion of follicular helper T cells relative to Treg cells has been shown.[80] T-cell targeting with cyclosporine has been anecdotally used to treat AIHA in *STAT1*-GOF with benefit.[81] More recently, a janus kinase 1/2 inhibitor (ruxolitinib) was used to treat 2 distinct cases of *STAT1*-GOF with associated autoimmunity including autoimmune cytopenias[80] and refractory alopecia areata.[82] Ruxolitinib was shown to reduce hyperresponsiveness to IFN-γ, restore T_H17 and Treg-cell counts, induce long-lasting control of autoimmunity (up to 6 months posttreatment[82]), and had the unexpected benefit of reducing the occurrence of mucocutaneous candidiasis in both cases.

Immune reconstitution

Patients with severe immunodeficiency may require progression to HSCT for definitive treatment. Wiskott-Aldrich syndrome is a well-described PID in which autoimmune cytopenias occur beyond abnormal platelet number, size, and function.[83] AIHA is severe, early-onset, and poorly responsive to corticosteroids, and ITP mainly occurs postsplenectomy (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,[84-87] as demonstrated by the 55% of patients with Wiskott-Aldrich syndrome who developed autoimmune cytopenias in the posttransplant period.[88] Thrombopoietin receptor agonists such as romiplostim and eltrombopag are emerging therapies for ITP, mainly by promoting platelet production. Because these agents are not immunosuppressive, they could be particularly useful in the treatment of ITP on a background of PID going forward.[89-91]

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).[92] Specific *RAG* mutation, RAG activity, and ultimately the resultant B- and T-cell repertoire correlate well with these distinct phenotypes.[93] 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 Treg cells, impaired B-cell receptor editing in the bone marrow, and elevated B-cell–activating factor [BAFF] expression).[94-96] 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 patients with CID-AI/G with autoimmune cytopenias.[97]

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*)[91] (Table II). The largest review to date details 14 hypomorphic ARTEMIS cases, where 6 of 14 patients (45%) had autoimmune cytopenias.[100] For the other PIDs in this group, autoimmune cytopenias are more sporadically reported and treatment strategies have not been discussed in depth.

TREATMENT OF RHEUMATOLOGIC DISEASE IN PIDs

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 before 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.[98,124,125] Therefore, clinicians must consider the 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, which have been reviewed elsewhere.[126-128]

Targeting B-cell pathology

CVID has been associated with rheumatologic complications including inflammatory arthritis, vasculitis, and SLE (Table I). Most patients will require therapy beyond IVIG. Case reports have demonstrated successful use of rituximab to treat both CVID-associated SLE[129] and ANCA-positive vasculitis.[130] 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 Food and Drug Administration approval for the treatment of SLE.[131] 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.[132] In inflammatory conditions, BAFF levels may elevate and contribute to the survival of autoreactive cells.[133] Although promising, belimumab is 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).

Targeting T-cell pathology

The predominance of rheumatologic complications seen in patients with Treg-cell dysfunction including CTLA4 haploinsufficiency, LRBA deficiency, and *STAT3*-GOF (Table I) converges on the hypothesis that FOXP3+CD25+CD4+ Treg

cells play a critical role in host defense against the development of rheumatologic diseases including inflammatory arthritis.[134] Consistent with this hypothesis, CTLA4-immunoglobulin therapy (abatacept) is approved by the Food and Drug Administration for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis (JIA) in the general population. More recently, abatacept has shown benefit in PID. In LRBA deficiency, 2 children with inflammatory arthritis and uveitis (clinically consistent with JIA) demonstrated robust response to abatacept therapy.[43,135] Inflammatory arthritis can also complicate the course of CTLA4 haploinsufficiency,[41] and it is 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.[47,48] Immunophenotype is notable for decreased Treg-cell numbers and functional expression of FOXP3 and CD25, potentially mediated by increased STAT3-dependent SOCS3 expression driving decreased STAT5 phosphorylation.[47,48] Because Treg-cell inhibition in *STAT3*-GOF is indirect, clinicians hypothesized that the use of an anti-IL6R antibody (tocilizumab) might be beneficial via blocking upstream IL-6–induced STAT3 activation. To date, 1 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 1-year follow-up period.[47]

Inflammatory arthritis is also a known complication of x-linked agammaglobulinemia, a PID in which autoreactive B cells are effectively absent because of maturation arrest at the pre–B-cell stage. Although infectious joint inflammation resolving on immunoglobulin replacement therapy is frequently seen in x-linked agammaglobulinemia,[25] aseptic arthritis has also been described including presentations of rheumatoid arthritis,[136] JIA,[137,138] and enthesitis-related arthritis.[139] Infiltrating CD8+ T cells can be seen on joint cytology.[137] Underlying mechanisms of T-cell–driven autoimmunity[139] and/or innate immune hyperactivation[140,141] have been proposed. In these cases, IVIG alone can be insufficient management,[136,139] progression despite methotrexate has been described,[136] nonsteroidal anti-inflammatory drugs may provide some benefit,[138,139] and there is no systematic guidance for the use of T-cell– or innate immune-targeted strategies to date.

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 nicotinamide adenine dinucleotide phosphate (NADPH) oxidase results in defective phagocytosis. Profound aseptic hyperinflammatory responses are seen in CGD, characterized by loss of anti-inflammatory mediators,[142] impaired clearance of apoptotic cells,[143] and downstream CD4+ T-cell skewing, which can drive autoimmune arthritis in the mouse model.[144] In patients, CGD has been associated with cutaneous discoid lupus erythematosus, chorioretinitis, inflammatory arthritis, vasculitis, and SLE as well as discoid lupus erythematosus in female carriers of x-linked disease (Table I).[52,53,145,146] A single case series on treatment of rheumatologic manifestations in CGD recently demonstrated clinical stabilization with systemic corticosteroids (1 case of discoid lupus erythematosus), methotrexate (1 case of antiphospholipid syndrome), and etanercept (1 case of JIA).[52] Although 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 patients with PID with significant susceptibility to infection.

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 posttransplant. A total of 70% of patients with Wiskott-Aldrich syndrome have associated autoimmunity, which can include inflammatory arthritis and vasculitis (Table I). Although arthritis and vasculitis generally improve after HSCT or gene therapy, there are several cases where autoimmunity has persisted or even newly arisen.[85-87] RAG deficiency has also been associated with rheumatologic and autoimmune diseases including vitiligo, myasthenia gravis, and vasculitis (Table II).[92] Progression of vasculitis in RAG deficiency despite treatment with corticosteroids, IVIG, and rituximab has been described.[98] In contrast, HSCT in RAG deficiency has been case reported to be curative/preventative for polyautoimmunity.[98,147] Because fewer posttransplant autoinflammatory complications were observed in patients with RAG deficiency compared with patients with impaired ARTEMIS,[148] the 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 are yet to be determined.

TREATMENT OF GI DISEASE IN PIDs

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).[149] In the background of frequent infections (eg, *Giardia*, *Campylobacter*, *Salmonella*, rotavirus, enterovirus, and 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]

Targeting T-cell pathology

Gastritis, AIE, and IBD have all been described in CVID.[150] Small intestinal biopsy frequently demonstrates villous atrophy that resembles sprue apart from the absence of plasma cells.[151,152] Lymphocytic infiltrates and occasional granulomas can occur both in the small intestine and in the colon, consisting predominantly of CD8+ T cells.[151-153] Unfortunately, GI inflammatory disease in CVID has been notoriously difficult to treat. Despite benefit from combination rituximab/azathioprine therapy to manage granulomatous lung pathology,[154] a similar response has not been seen in the inflamed GI tract.[155] TNF-α inhibitors[156,157] as well as the anti-α4β7 integrin monoclonal vedolizumab, which may inhibit Treg-cell trafficking to the GI mucosa,[150] 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)

(J.E. Walter and J.R. Farmer, 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 Treg cells in host defense against autoinflammation in the GI tract. Immune dysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX) is a profound disorder of FOXP3+CD25+CD4+ Treg cells caused by mutations in *FOXP3*. The pathognomonic clinical features of IPEX are severe and early-onset dermatitis, type 1 diabetes mellitus, and failure to thrive secondary to refractory diarrhea starting in infancy.[158,159] A demonstrated break in peripheral B-cell tolerance leading to the production of autoantibodies to the brush border proteins villin and AIE-75 has been described.[160,161] However, the role of antivillin 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.[162] 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 pretransplant period.[163-165]

Beyond intrinsic Treg-cell defects secondary to abnormal FOXP3, CD25, or STAT5b, interestingly, AIE and IBD are shared complications of other Treg-cell disorders including CTLA4 haploinsufficiency,[41,42] LBRA deficiency,[166] *STAT1*-GOF,[167] *STAT3*-GOF,[47] as well as mutated *RAG1*,[168] *DOCK8*,[169] and *ITCH*.[170,171] Furthermore, autoimmune GI disease can be robustly induced (27%-54% symptomatic with watery diarrhea) on treatment with anti-CTLA4 biologics.[172] These data again converge on the hypothesis that Treg cells are critical in gut homeostasis.[173] To this end, infiltrating T cells have been demonstrated on intestinal biopsy in CTLA4 haploinsufficiency,[41] and lack of response to traditional therapeutics including TNF-α inhibitors has been demonstrated in LBRA deficiency.[166] In contrast, sirolimus has been reliably efficacious in CTLA4 haploinsufficient patients, and immune reconstitution with abatacept has been shown to markedly reduce AIE.[40]

Targeting innate immune pathology

Profound autoimmune GI disease can also occur in the setting of innate immune deficiency. Classic is CGD, where multiorgan granulomatous inflammatory pathology occurs, most prominently affecting the GI tract in up to 73% to 88% of patients (Table I).[54,174] 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 disease.[54,174-176] Despite the predisposition toward infection, no causative pathogens were identified in up to 93% of CGD-associated inflammatory GI disease cases,[54] suggesting an underlying mechanism of aseptic autoimmunity. Treatment outcomes to date demonstrate limited benefit from corticosteroids (63%-86% relapse rate) and/or nonsteroidal anti-inflammatory drugs (50%-100% relapse rate).[54] Immunomodulation with methotrexate, azathioprine, cyclosporine, and thalidomide has been case reported as successful.[54,174,177,178] Finally, despite efficacy in colitis management, TNF-α inhibitors should be avoided given the high rate of complicating deadly infections (2 deaths out of 5 infliximab-treated patients with CGD[179]).

Immune reconstitution

In CGD, HSCT has been shown to be curative in terms of both the recurrent infections and the multiorgan granulomatous pathology.[180] However, using full myeloablative conditioning, patients with peritransplant comorbidities including colitis had increased mortality,[180] 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[181]). Because this study included 33% of patients with active peritransplant colitis, the data suggest that this reduced-intensity conditioning HSCT can be considered in severe CGD cases complicated by IBD.

Finally, although directed immunosuppression in IPEX can help to reduce the burden of multiorgan 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.[182-188] Even in the case of partial donor chimerism, clinical disease remission has been reported, coinciding with the presence of full donor Treg cells.[184,186] The selective advantage of wild-type Treg cells is consistent with the underlying pathophysiology of IPEX and may dictate Treg-cell sparing therapies for graft-versus-host disease in the posttransplant period.[159]

CONCLUSIONS

Autoimmune and inflammatory diseases can greatly complicate the care of patients with PID. Treatment strategies in PID should be targeted not only to the clinical spectrum of autoimmunity (cytopenias, rheumatologic disease, and/or GI disease) but also 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 patients with PID and broaden our basic understanding of autoimmune and inflammatory disease.

Acknowledgment

We would like to acknowledge Dr Maurizio Miano from Hematology Unit, IRCCS Istituto Giannini Gaslini, Genoa, Italy for thoughtful comments on the section of autoimmune cytopenias in autoimmune lymphoproliferative syndrome and related diseases.

REFERENCES

1. Picard C, Al-Herz W, Bousfiha A, Casanova JL, Chatila T, Conley ME, et al. Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency 2015. J Clin Immunol 2015;35:696-726.
2. Allenspach E, Torgerson TR. Autoimmunity and primary immunodeficiency disorders. J Clin Immunol 2016;36:57-67.
3. Maggadottir SM, Sullivan KE. The intersection of immune deficiency and autoimmunity. Curr Opin Rheumatol 2014;26:570-8.
4. Grimbacher B, Warnatz K, Yong PF, Korganow AS, Peter HH. The crossroads of autoimmunity and immunodeficiency: lessons from polygenic traits and monogenic defects. J Allergy Clin Immunol 2016;137:3-17. quiz 8.

5. Aladjidi N, Leverger G, Leblanc T, Picat MQ, Michel G, Bertrand Y, et al. New insights into childhood autoimmune hemolytic anemia: a French national observational study of 265 children. Haematologica 2011;96:655-63.
6. Teachey DT, Manno CS, Axsom KM, Andrews T, Choi JK, Greenbaum BH, et al. Unmasking Evans syndrome: T-cell phenotype and apoptotic response reveal autoimmune lymphoproliferative syndrome (ALPS). Blood 2005;105:2443-8.
7. Arkwright PD, Abinun M, Cant AJ. Autoimmunity in human primary immunodeficiency diseases. Blood 2002;99:2694-702.
8. Wang J, Cunningham-Rundles C. Treatment and outcome of autoimmune hematologic disease in common variable immunodeficiency (CVID). J Autoimmun 2005;25:57-62.
9. Savasan S, Warrier I, Buck S, Kaplan J, Ravindranath Y. Increased lymphocyte Fas expression and high incidence of common variable immunodeficiency disorder in childhood Evans' syndrome. Clin Immunol 2007;125:224-9.
10. Teachey DT, Greiner R, Seif A, Attiyeh E, Bleesing J, Choi J, et al. Treatment with sirolimus results in complete responses in patients with autoimmune lymphoproliferative syndrome. Br J Haematol 2009;145:101-6.
11. Heitink-Polle KM, Nijsten J, Boonacker CW, de Haas M, Bruin MC. Clinical and laboratory predictors of chronic immune thrombocytopenia in children: a systematic review and meta-analysis. Blood 2014;124:3295-307.
12. Teachey DT, Lambert MP. Diagnosis and management of autoimmune cytopenias in childhood. Pediatr Clin North Am 2013;60:1489-511.
13. Miano M. How I manage Evans syndrome and AIHA cases in children. Br J Haematol 2016;172:524-34.
14. Farruggia P, Fioredda F, Puccio G, Porretti L, Lanza T, Ramenghi U, et al. Autoimmune neutropenia of infancy: data from the Italian neutropenia registry. Am J Hematol 2015;90:E221-2.
15. Lechner K, Jager U. How I treat autoimmune hemolytic anemias in adults. Blood 2010;116:1831-8.
16. Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011;117:4190-207.
17. Bonilla FA, Barlan I, Chapel H, Costa-Carvalho BT, Cunningham-Rundles C, de la Morena MT, et al. International Consensus Document (ICON): common variable immunodeficiency disorders. J Allergy Clin Immunol Pract 2016;4:38-59.
18. Buchbinder D, Baker R, Lee YN, Ravell J, Zhang Y, McElwee J, et al. Identification of patients with RAG mutations previously diagnosed with common variable immunodeficiency disorders. J Clin Immunol 2015;35:119-24.
19. Sneller MC, Strober W, Eisenstein E, Jaffe JS, Cunningham-Rundles C. NIH conference: new insights into common variable immunodeficiency. Ann Intern Med 1993;118:720-30.
20. Resnick ES, Moshier EL, Godbold JH, Cunningham-Rundles C. Morbidity and mortality in common variable immune deficiency over 4 decades. Blood 2012;119:1650-7.
21. Gathmann B, Mahlaoui N, CEREDIH, Gerard L, Oksenhendler E, Warnatz K, et al. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. J Allergy Clin Immunol 2014;134:116-26.
22. Chapel H, Lucas M, Lee M, Bjorkander J, Webster D, Grimbacher B, et al. Common variable immunodeficiency disorders: division into distinct clinical phenotypes. Blood 2008;112:277-86.
23. Quinti I, Soresina A, Spadaro G, Martino S, Donnanno S, Agostini C, et al. Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. J Clin Immunol 2007;27:308-16.
24. Atarod L, Raissi A, Aghamohammadi A, Farhoudi A, Khodadad A, Moin M, et al. A review of gastrointestinal disorders in patients with primary antibody immunodeficiencies during a 10-year period (1990-2000), in children hospital medical center. Iran J Allergy Asthma Immunol 2003;2:75-9.
25. Lee PP, Chen TX, Jiang LP, Chan KW, Yang W, Lee BW, et al. Clinical characteristics and genotype-phenotype correlation in 62 patients with X-linked agammaglobulinemia. J Clin Immunol 2010;30:121-31.
26. Chun JK, Lee TJ, Song JW, Linton JA, Kim DS. Analysis of clinical presentations of Bruton disease: a review of 20 years of accumulated data from pediatric patients at Severance Hospital. Yonsei Med J 2008;49:28-36.
27. Garcia-Garcia E, Staines-Boone AT, Vargas-Hernandez A, Gonzalez-Serrano ME, Carrillo-Tapia E, Mogica-Martinez D, et al. Clinical and mutational features of X-linked agammaglobulinemia in Mexico. Clin Immunol 2016;165:38-44.
28. Bateman EA, Ayers L, Sadler R, Lucas M, Roberts C, Woods A, et al. T cell phenotypes in patients with common variable immunodeficiency disorders: associations with clinical phenotypes in comparison with other groups with recurrent infections. Clin Exp Immunol 2012;170:202-11.
29. Hernandez-Trujillo VP, Scalchunes C, Cunningham-Rundles C, Ochs HD, Bonilla FA, Paris K, et al. Autoimmunity and inflammation in X-linked agammaglobulinemia. J Clin Immunol 2014;34:627-32.
30. Price S, Shaw PA, Seitz A, Joshi G, Davis J, Niemela JE, et al. Natural history of autoimmune lymphoproliferative syndrome associated with FAS gene mutations. Blood 2014;123:1989-99.
31. Neven B, Magerus-Chatinet A, Florkin B, Gobert D, Lambotte O, De Somer L, et al. A survey of 90 patients with autoimmune lymphoproliferative syndrome related to TNFRSF6 mutation. Blood 2011;118:4798-807.
32. Sneller MC, Dale JK, Straus SE. Autoimmune lymphoproliferative syndrome. Curr Opin Rheumatol 2003;15:417-21.
33. Ucar D, Kim JS, Bishop RJ, Nussenblatt RB, Rao VK, Sen HN. Ocular Inflammatory Disorders in Autoimmune Lymphoproliferative Syndrome (ALPS) [e-pub ahead of print]. Ocul Immunol Inflamm 2016. http://dx.doi.org/10.1080/09273948.2016.1175637.
34. Rieux-Laucat F, Blachere S, Danielan S, De Villartay JP, Oleastro M, Solary E, et al. Lymphoproliferative syndrome with autoimmunity: a possible genetic basis for dominant expression of the clinical manifestations. Blood 1999;94:2575-82.
35. Jackson CE, Fischer RE, Hsu AP, Anderson SM, Choi Y, Wang J, et al. Autoimmune lymphoproliferative syndrome with defective Fas: genotype influences penetrance. Am J Hum Genet 1999;64:1002-14.
36. McLean-Tooke A, Spickett GP, Gennery AR. Immunodeficiency and autoimmunity in 22q11.2 deletion syndrome. Scand J Immunol 2007;66:1-7.
37. Gennery AR, Barge D, O'Sullivan JJ, Flood TJ, Abinun M, Cant AJ. Antibody deficiency and autoimmunity in 22q11.2 deletion syndrome. Arch Dis Child 2002;86:422-5.
38. Jawad AF, McDonald-Mcginn DM, Zackai E, Sullivan KE. Immunologic features of chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). J Pediatr 2001;139:715-23.
39. Tison BE, Nicholas SK, Abramson SL, Hanson IC, Paul ME, Seeborg FO, et al. Autoimmunity in a cohort of 130 pediatric patients with partial DiGeorge syndrome. J Allergy Clin Immunol 2011;128:1115-1117.e1-3.
40. Lee S, Moon JS, Lee CR, Kim HE, Baek SM, Hwang S, et al. Abatacept alleviates severe autoimmune symptoms in a patient carrying a de novo variant in CTLA-4. J Allergy Clin Immunol 2016;137:327-30.
41. Schubert D, Bode C, Kenefeck R, Hou TZ, Wing JB, Kennedy A, et al. Autosomal dominant immune dysregulation syndrome in humans with CTLA4 mutations. Nat Med 2014;20:1410-6.
42. Kuehn HS, Ouyang W, Lo B, Deenick EK, Niemela JE, Avery DT, et al. Immune dysregulation in human subjects with heterozygous germline mutations in CTLA4. Science 2014;345:1623-7.
43. Lo B, Zhang K, Lu W, Zheng L, Zhang Q, Kanellopoulou C, et al. AUTOIMMUNE DISEASE. Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy. Science 2015;349:436-40.
44. Gamez-Diaz L, August D, Stepensky P, Revel-Vilk S, Seidel MG, Noriko M, et al. The extended phenotype of LPS-responsive beige-like anchor protein (LRBA) deficiency. J Allergy Clin Immunol 2016;137:223-30.
45. Alkhairy OK, Abolhassani H, Rezaei N, Fang M, Andersen KK, Chavoshzadeh Z, et al. Spectrum of phenotypes associated with mutations in LRBA. J Clin Immunol 2016;36:33-45.
46. Barzaghi F, Passerini L, Bacchetta R. Immune dysregulation, polyendocrinopathy, enteropathy, x-linked syndrome: a paradigm of immunodeficiency with autoimmunity. Front Immunol 2012;3:211.
47. Milner JD, Vogel TP, Forbes L, Ma CA, Stray-Pedersen A, Niemela JE, et al. Early-onset lymphoproliferation and autoimmunity caused by germline STAT3 gain-of-function mutations. Blood 2015;125:591-9.
48. Flanagan SE, Haapaniemi E, Russell MA, Caswell R, Lango Allen H, De Franco E, et al. Activating germline mutations in STAT3 cause early-onset multi-organ autoimmune disease. Nat Genet 2014;46:812-4.
49. Baris S, Alroqi F, Kiykim A, Karakoc-Aydiner E, Ogulur I, Ozen A, et al. Severe early-onset combined immunodeficiency due to heterozygous gain-of-function mutations in STAT1. J Clin Immunol 2016;36:641-8.
50. Toubiana J, Okada S, Hiller J, Oleastro M, Lagos Gomez M, Aldave Becerra JC, et al. Heterozygous STAT1 gain-of-function mutations underlie an unexpectedly broad clinical phenotype. Blood 2016;127:3154-64.
51. Sullivan KE, Mullen CA, Blaese RM, Winkelstein JA. A multiinstitutional survey of the Wiskott-Aldrich syndrome. J Pediatr 1994;125:876-85.
52. De Ravin SS, Naumann N, Cowen EW, Friend J, Hilligoss D, Marquesen M, et al. Chronic granulomatous disease as a risk factor for autoimmune disease. J Allergy Clin Immunol 2008;122:1097-103.
53. Winkelstein JA, Marino MC, Johnston RB Jr, Boyle J, Curnutte J, Gallin JI, et al. Chronic granulomatous disease: report on a national registry of 368 patients. Medicine (Baltimore) 2000;79:155-69.

54. Magnani A, Brosselin P, Beaute J, de Vergnes N, Mouy R, Debre M, et al. Inflammatory manifestations in a single-center cohort of patients with chronic granulomatous disease. J Allergy Clin Immunol 2014;134:655-662.e8.
55. Song E, Jaishankar GB, Saleh H, Jithpratuck W, Sahni R, Krishnaswamy G. Chronic granulomatous disease: a review of the infectious and inflammatory complications. Clin Mol Allergy 2011;9:10.
56. Michel M, Chanet V, Galicier L, Ruivard M, Levy Y, Hermine O, et al. Autoimmune thrombocytopenic purpura and common variable immunodeficiency: analysis of 21 cases and review of the literature. Medicine (Baltimore) 2004;83:254-63.
57. Seve P, Bourdillon L, Sarrot-Reynauld F, Ruivard M, Jaussaud R, Bouhour D, et al. Autoimmune hemolytic anemia and common variable immunodeficiency: a case-control study of 18 patients. Medicine (Baltimore) 2008;87:177-84.
58. Wakim M, Shah A, Arndt PA, Garratty G, Weinberg K, Hofstra T, et al. Successful anti-CD20 monoclonal antibody treatment of severe autoimmune hemolytic anemia due to warm reactive IgM autoantibody in a child with common variable immunodeficiency. Am J Hematol 2004;76:152-5.
59. Gobert D, Bussel JB, Cunningham-Rundles C, Galicier L, Dechartres A, Berezne A, et al. Efficacy and safety of rituximab in common variable immunodeficiency-associated immune cytopenias: a retrospective multicentre study on 33 patients. Br J Haematol 2011;155:498-508.
60. Raedler L. Velcade (Bortezomib) receives 2 new FDA indications: for retreatment of patients with multiple myeloma and for first-line treatment of patients with mantle-cell lymphoma. Am Health Drug Benefits 2015;8:135-40.
61. Khandelwal P, Davies SM, Grimley MS, Jordan MB, Curtis BR, Jodele S, et al. Bortezomib for refractory autoimmunity in pediatrics. Biol Blood Marrow Transplant 2014;20:1654-9.
62. Lee WJ, Lee ST, Moon J, Sunwoo JS, Byun JI, Lim JA, et al. Tocilizumab in autoimmune encephalitis refractory to rituximab: an institutional cohort study [e-pub ahead of print]. Neurotherapeutics 2016. http://dx.doi.org/10.1007/s13311-016-0442-6.
63. Wallace DJ, Hobbs K, Clowse ME, Petri M, Strand V, Pike M, et al. Long-term safety and efficacy of epratuzumab in the treatment of moderate-to-severe systemic lupus erythematosus: results from an open-label extension study. Arthritis Care Res (Hoboken) 2016;68:534-43.
64. Gao Q, Li Q, Xue Z, Wu P, Yang X. In vitro and in vivo evaluation of a humanized anti-APRIL antibody. Curr Mol Med 2013;13:464-5.
65. Liu XG, Hou M. Immune thrombocytopenia and B-cell-activating factor/a proliferation-inducing ligand. Semin Hematol 2013;50:S89-99.
66. Ma K, Caplan S. Refractory IgG warm autoimmune hemolytic anemia treated with eculizumab: a novel application of anticomplement therapy. Case Rep Hematol 2016;2016:9181698.
67. Rao VK, Price S, Perkins K, Aldridge P, Tretler J, Davis J, et al. Use of rituximab for refractory cytopenias associated with autoimmune lymphoproliferative syndrome (ALPS). Pediatr Blood Cancer 2009;52:847-52.
68. Miano M, Scalzone M, Perri K, Palmisani E, Caviglia I, Micalizzi C, et al. Mycophenolate mofetil and Sirolimus as second or further line treatment in children with chronic refractory primitive or secondary autoimmune cytopenias: a single centre experience [e-pub ahead of print]. Br J Haematol 2015. http://dx.doi.org/10.1111/bjh.13533.
69. Rao VK, Oliveira JB. How I treat autoimmune lymphoproliferative syndrome. Blood 2011;118:5741-51.
70. Bride KL, Vincent T, Smith-Whitley K, Lambert MP, Bleesing JJ, Seif AE, et al. Sirolimus is effective in relapsed/refractory autoimmune cytopenias: results of a prospective multi-institutional trial. Blood 2016;127:17-28.
71. Kato H, Perl A. Mechanistic target of rapamycin complex 1 expands Th17 and IL-4+ CD4−CD8− double-negative T cells and contracts regulatory T cells in systemic lupus erythematosus. J Immunol 2014;192:4134-44.
72. Volkl S, Rensing-Ehl A, Allgauer A, Schreiner E, Lorenz MR, Rohr J, et al. Hyperactive mTOR pathway promotes lymphoproliferation and abnormal differentiation in autoimmune lymphoproliferative syndrome. Blood 2016;128:227-38.
73. Teachey DT. New advances in the diagnosis and treatment of autoimmune lymphoproliferative syndrome. Curr Opin Pediatr 2012;24:1-8.
74. Akar NA, Adekile AD. Chromosome 22q11.2 deletion presenting with immune-mediated cytopenias, macrothrombocytopenia and platelet dysfunction. Med Princ Pract 2007;16:318-20.
75. Hernandez-Nieto L, Yamazaki-Nakashimada MA, Lieberman-Hernandez E, Espinosa-Padilla SE. Autoimmune thrombocytopenic purpura in partial DiGeorge syndrome: case presentation. J Pediatr Hematol Oncol 2011;33:465-6.
76. DePiero AD, Lourie EM, Berman BW, Robin NH, Zinn AB, Hostoffer RW. Recurrent immune cytopenias in two patients with DiGeorge/velocardiofacial syndrome. J Pediatr 1997;131:484-6.
77. Soldatou A, Anastassiou T, Vougiouka O, Goussetis E, Kossiva L. Transient effect of anti-CD20 therapy in a child with 22q11.2 deletion syndrome and severe steroid refractory cytopenias: a case report. J Pediatr Hematol Oncol 2013;35:311-4.
78. Damlaj M, Seguin C. Refractory autoimmune hemolytic anemia in a patient with DiGeorge syndrome treated successfully with plasma exchange: a case report and review of the literature. Int J Hematol 2014;100:494-7.
79. Mustillo PJ, editor. Response to hydroxychloroquine in CVID with granulomatous interstitial lung disease (GL-ILD). Clinical Immunology Society (CIS) Annual Meeting; April 14-17, 2016; Boston, Mass.
80. Weinacht KG, Charbonnier LM, Plant A, Torgerson T, Rosenzweig S, Fleisher T, et al, editors. Successful therapy of a patient with a novel STAT1 gain of function mutation and life-threatening cytopenias with Janus kinase inhibitor ruxolitinib. American Society of Hematology (ASH) Annual Meeting; December 5-8, 2015; Orlando, Fla.
81. Mizoguchi Y, Tsumura M, Okada S, Hirata O, Minegishi S, Imai K, et al. Simple diagnosis of STAT1 gain-of-function alleles in patients with chronic mucocutaneous candidiasis. J Leukoc Biol 2014;95:667-76.
82. Higgins E, Al Shehri T, McAleer MA, Conlon N, Feighery C, Lilic D, et al. Use of ruxolitinib to successfully treat chronic mucocutaneous candidiasis caused by gain-of-function signal transducer and activator of transcription 1 (STAT1) mutation. J Allergy Clin Immunol 2015;135:551-3.
83. Dupuis-Girod S, Medioni J, Haddad E, Quartier P, Cavazzana-Calvo M, Le Deist F, et al. Autoimmunity in Wiskott-Aldrich syndrome: risk factors, clinical features, and outcome in a single-center cohort of 55 patients. Pediatrics 2003;111:e622-7.
84. Moratto D, Giliani S, Bonfim C, Mazzolari E, Fischer A, Ochs HD, et al. Long-term outcome and lineage-specific chimerism in 194 patients with Wiskott-Aldrich syndrome treated by hematopoietic cell transplantation in the period 1980-2009: an international collaborative study. Blood 2011;118:1675-84.
85. Ozsahin H, Cavazzana-Calvo M, Notarangelo LD, Schulz A, Thrasher AJ, Mazzolari E, et al. Long-term outcome following hematopoietic stem-cell transplantation in Wiskott-Aldrich syndrome: collaborative study of the European Society for Immunodeficiencies and European Group for Blood and Marrow Transplantation. Blood 2008;111:439-45.
86. Conyers RK, Cole TS. Successful second bone marrow transplantation in a Wiskott-Aldrich syndrome patient with systemic vasculitis. J Allergy Clin Immunol 2016;137:1615-6.
87. Hacein-Bey Abina S, Gaspar HB, Blondeau J, Caccavelli L, Charrier S, Buckland K, et al. Outcomes following gene therapy in patients with severe Wiskott-Aldrich syndrome. JAMA 2015;313:1550-63.
88. Shin CR, Kim MO, Li D, Bleesing JJ, Harris R, Mehta P, et al. Outcomes following hematopoietic cell transplantation for Wiskott-Aldrich syndrome. Bone Marrow Transplant 2012;47:1428-35.
89. Seidel MG, Urban C, Sipurzynski J, Beham-Schmid C, Lackner H, Benesch M. High response rate but short-term effect of romiplostim in paediatric refractory chronic immune thrombocytopenia. Br J Haematol 2014;165:419-21.
90. Gerrits AJ, Leven EA, Frelinger AL III, Brigstocke SL, Berny-Lang MA, Mitchell WB, et al. Effects of eltrombopag on platelet count and platelet activation in Wiskott-Aldrich syndrome/X-linked thrombocytopenia. Blood 2015;126:1367-78.
91. Seidel MG. Autoimmune and other cytopenias in primary immunodeficiencies: pathomechanisms, novel differential diagnoses, and treatment. Blood 2014;124:2337-44.
92. Walter JE, Rosen LB, Csomos K, Rosenberg JM, Mathew D, Keszei M, et al. Broad-spectrum antibodies against self-antigens and cytokines in RAG deficiency. J Clin Invest 2015;125:4135-48.
93. Notarangelo LD, Kim MS, Walter JE, Lee YN. Human RAG mutations: biochemistry and clinical implications. Nat Rev Immunol 2016;16:234-46.
94. Villa A, Marrella V, Rucci F, Notarangelo LD. Genetically determined lymphopenia and autoimmune manifestations. Curr Opin Immunol 2008;20:318-24.
95. Walter JE, Rucci F, Patrizi L, Recher M, Regenass S, Paganini T, et al. Expansion of immunoglobulin-secreting cells and defects in B cell tolerance in Rag-dependent immunodeficiency. J Exp Med 2010;207:1541-54.
96. Kreuzaler M, Rauch M, Salzer U, Birmelin J, Rizzi M, Grimbacher B, et al. Soluble BAFF levels inversely correlate with peripheral B cell numbers and the expression of BAFF receptors. J Immunol 2012;188:497-503.
97. Foldvari Z, Walter JE, editors. Clinical spectrum and outcome of treatment for autoimmune cytopenias in RAG deficiency. Clinical Immunology Society Annual Meeting; April 14-17, 2016; Boston, Mass.
98. Henderson LA, Frugoni F, Hopkins G, de Boer H, Pai SY, Lee YN, et al. Expanding the spectrum of recombination-activating gene 1 deficiency: a

family with early-onset autoimmunity. J Allergy Clin Immunol 2013;132:969-971.e1-2.
99. Dutmer CM, Asturias EJ, Smith C, Dishop MK, Schmid DS, Bellini WJ, et al. Late onset hypomorphic RAG2 deficiency presentation with fatal vaccine-strain VZV infection. J Clin Immunol 2015;35:754-60.
100. Lee PP, Woodbine L, Gilmour KC, Bibi S, Cale CM, Amrolia PJ, et al. The many faces of Artemis-deficient combined immunodeficiency—two patients with DCLRE1C mutations and a systematic literature review of genotype-phenotype correlation. Clin Immunol 2013;149:464-74.
101. Moshous D, Pannetier C, Chasseval Rd R, Deist Fl F, Cavazzana-Calvo M, Romana S, et al. Partial T and B lymphocyte immunodeficiency and predisposition to lymphoma in patients with hypomorphic mutations in Artemis. J Clin Invest 2003;111:381-7.
102. Sauer AV, Brigida I, Carriglio N, Aiuti A. Autoimmune dysregulation and purine metabolism in adenosine deaminase deficiency. Front Immunol 2012;3:265.
103. Delicou S, Kitra-Roussou V, Peristeri J, Goussetis E, Vessalas G, Rigatou E, et al. Successful HLA-identical hematopoietic stem cell transplantation in a patient with purine nucleoside phosphorylase deficiency. Pediatr Transplant 2007;11:799-803.
104. McCann LJ, McPartland J, Barge D, Strain L, Bourn D, Calonje E, et al. Phenotypic variations of cartilage hair hypoplasia: granulomatous skin inflammation and severe T cell immunodeficiency as initial clinical presentation in otherwise well child with short stature. J Clin Immunol 2014;34:42-8.
105. Morgan NV, Goddard S, Cardno TS, McDonald D, Rahman F, Barge D, et al. Mutation in the TCRalpha subunit constant gene (TRAC) leads to a human immunodeficiency disorder characterized by a lack of TCRalphabeta+ T cells. J Clin Invest 2011;121:695-702.
106. Yu GP, Nadeau KC, Berk DR, de Saint Basile G, Lambert N, Knapnougel P, et al. Genotype, phenotype, and outcomes of nine patients with T-B+NK+ SCID. Pediatr Transplant 2011;15:733-41.
107. Tokgoz H, Caliskan U, Keles S, Reisli I, Guiu IS, Morgan NV. Variable presentation of primary immune deficiency: two cases with CD3 gamma deficiency presenting with only autoimmunity. Pediatr Allergy Immunol 2013;24:257-62.
108. Fischer A, Picard C, Chemin K, Dogniaux S, le Deist F, Hivroz C. ZAP70: a master regulator of adaptive immunity. Semin Immunopathol 2010;32:107-16.
109. Hauck F, Randriamampita C, Martin E, Gerart S, Lambert N, Lim A, et al. Primary T-cell immunodeficiency with immunodysregulation caused by autosomal recessive LCK deficiency. J Allergy Clin Immunol 2012;130:1144-1152.e11.
110. Nehme NT, Pachlopnik Schmid J, Debeurme F, Andre-Schmutz I, Lim A, Nitschke P, et al. MST1 mutations in autosomal recessive primary immunodeficiency characterized by defective naive T-cell survival. Blood 2012;119:3458-68.
111. Abdollahpour H, Appaswamy G, Kotlarz D, Diestelhorst J, Beier R, Schaffer AA, et al. The phenotype of human STK4 deficiency. Blood 2012;119:3450-7.
112. Halacli SO, Ayvaz DC, Sun-Tan C, Erman B, Uz E, Yilmaz DY, et al. STK4 (MST1) deficiency in two siblings with autoimmune cytopenias: a novel mutation. Clin Immunol 2015;161:316-23.
113. McCarl CA, Picard C, Khalil S, Kawasaki T, Rother J, Papolos A, et al. ORAI1 deficiency and lack of store-operated Ca2+ entry cause immunodeficiency, myopathy, and ectodermal dysplasia. J Allergy Clin Immunol 2009;124:1311-1318.e7.
114. Picard C, McCarl CA, Papolos A, Khalil S, Luthy K, Hivroz C, et al. STIM1 mutation associated with a syndrome of immunodeficiency and autoimmunity. N Engl J Med 2009;360:1971-80.
115. Li FY, Chaigne-Delalande B, Su H, Uzel G, Matthews H, Lenardo MJ. XMEN disease: a new primary immunodeficiency affecting Mg2+ regulation of immunity against Epstein-Barr virus. Blood 2014;123:2148-52.
116. Crank MC, Grossman JK, Moir S, Pittaluga S, Buckner CM, Kardava L, et al. Mutations in PIK3CD can cause hyper IgM syndrome (HIGM) associated with increased cancer susceptibility. J Clin Immunol 2014;34:272-6.
117. Lucas CL, Kuehn HS, Zhao F, Niemela JE, Deenick EK, Palendira U, et al. Dominant-activating germline mutations in the gene encoding the PI(3)K catalytic subunit p110delta result in T cell senescence and human immunodeficiency. Nat Immunol 2014;15:88-97.
118. Stepensky P, Rensing-Ehl A, Gather R, Revel-Vilk S, Fischer U, Nabhani S, et al. Early-onset Evans syndrome, immunodeficiency, and premature immunosenescence associated with tripeptidyl-peptidase II deficiency. Blood 2015;125:753-61.
119. Su HC, Jing H, Zhang Q. DOCK8 deficiency. Ann N Y Acad Sci 2011;1246:26-33.
120. Zhang Q, Davis JC, Lamborn IT, Freeman AF, Jing H, Favreau AJ, et al. Combined immunodeficiency associated with DOCK8 mutations. N Engl J Med 2009;361:2046-55.
121. Alsum Z, Hawwari A, Alsmadi O, Al-Hissi S, Borrero E, Abu-Staiteh A, et al. Clinical, immunological and molecular characterization of DOCK8 and DOCK8-like deficient patients: single center experience of twenty-five patients. J Clin Immunol 2013;33:55-67.
122. Engelhardt KR, Gertz ME, Keles S, Schaffer AA, Sigmund EC, Glocker C, et al. The extended clinical phenotype of 64 patients with dedicator of cytokinesis 8 deficiency. J Allergy Clin Immunol 2015;136:402-12.
123. Griscelli C, Lisowska-Grospierre B, Mach B. Combined immunodeficiency with defective expression in MHC class II genes. Immunodefic Rev 1989;1:135-53.
124. De Ravin SS, Cowen EW, Zarember KA, Whiting-Theobald NL, Kuhns DB, Sandler NG, et al. Hypomorphic Rag mutations can cause destructive midline granulomatous disease. Blood 2010;116:1263-71.
125. Mathieu AL, Verronese E, Rice GI, Fouyssac F, Bertrand Y, Picard C, et al. PRKDC mutations associated with immunodeficiency, granuloma, and autoimmune regulator-dependent autoimmunity. J Allergy Clin Immunol 2015;135:1578-1588.e5.
126. Aksentijevich I, Kastner DL. Genetics of monogenic autoinflammatory diseases: past successes, future challenges. Nat Rev Rheumatol 2011;7:469-78.
127. ter Haar NM, Oswald M, Jeyaratnam J, Anton J, Barron KS, Brogan PA, et al. Recommendations for the management of autoinflammatory diseases. Ann Rheum Dis 2015;74:1636-44.
128. Sturfelt G, Truedsson L. Complement in the immunopathogenesis of rheumatic disease. Nat Rev Rheumatol 2012;8:458-68.
129. Al Hamzi H, Al Shaikh A, Arnaout RK. Poor specific antibody response immunodeficiency (dysgammaglobulinemia) predates systemic lupus erythematosus. Lupus 2013;22:961-6.
130. Hill F, Yonkof J, Chaitanya Arudra SK, Thomas J, Altorok N. Successful treatment of ANCA-associated vasculitis in the setting of common variable immunodeficiency using rituximab. Am J Ther 2016;23:e1239-45.
131. Lutalo PM, D'Cruz DP. Update on belimumab for the management of systemic lupus erythematosus. Expert Opin Biol Ther 2014;14:1701-8.
132. Liu Z, Davidson A. BAFF and selection of autoreactive B cells. Trends Immunol 2011;32:388-94.
133. Mackay F, Woodcock SA, Lawton P, Ambrose C, Baetscher M, Schneider P, et al. Mice transgenic for BAFF develop lymphocytic disorders along with autoimmune manifestations. J Exp Med 1999;190:1697-710.
134. Miyara M, Ito Y, Sakaguchi S. TREG-cell therapies for autoimmune rheumatic diseases. Nat Rev Rheumatol 2014;10:543-51.
135. Levy E, Stolzenberg MC, Bruneau J, Breton S, Neven B, Sauvion S, et al. LRBA deficiency with autoimmunity and early onset chronic erosive polyarthritis. Clin Immunol 2016;168:88-93.
136. Verbruggen G, De Backer S, Deforce D, Demetter P, Cuvelier C, Veys E, et al. X linked agammaglobulinaemia and rheumatoid arthritis. Ann Rheum Dis 2005;64:1075-8.
137. Zhu Z, Kang Y, Lin Z, Huang Y, Lv H, Li Y. X-linked agammaglobulinemia combined with juvenile idiopathic arthritis and invasive *Klebsiella pneumoniae* polyarticular septic arthritis. Clin Rheumatol 2015;34:397-401.
138. Vancsa A, Toth B, Szekanecz Z. BTK gene mutation in two non-identical twins with X-linked agammaglobulinemia associated with polyarticular juvenile idiopathic arthritis. Isr Med Assoc J 2011;13:579-80.
139. Sukumaran S, Marzan K, Shaham B, Church JA. A child with x-linked agammaglobulinemia and enthesitis-related arthritis. Int J Rheumatol 2011;2011:175973.
140. Lopez-Herrera G, Vargas-Hernandez A, Gonzalez-Serrano ME, Berron-Ruiz L, Rodriguez-Alba JC, Espinosa-Rosales F, et al. Bruton's tyrosine kinase—an integral protein of B cell development that also has an essential role in the innate immune system. J Leukoc Biol 2014;95:243-50.
141. Nyhoff LE, Barron BL, Johnson EM, Bonami RH, Maseda D, Fensterheim BA, et al. Bruton's tyrosine kinase deficiency inhibits autoimmune arthritis in mice but fails to block immune complex-mediated inflammatory arthritis. Arthritis Rheumatol 2016;68:1856-68.
142. Brown JR, Goldblatt D, Buddle J, Morton L, Thrasher AJ. Diminished production of anti-inflammatory mediators during neutrophil apoptosis and macrophage phagocytosis in chronic granulomatous disease (CGD). J Leukoc Biol 2003;73:591-9.
143. Fernandez-Boyanapalli RF, Frasch SC, McPhillips K, Vandivier RW, Harry BL, Riches DW, et al. Impaired apoptotic cell clearance in CGD due to altered macrophage programming is reversed by phosphatidylserine-dependent production of IL-4. Blood 2009;113:2047-55.
144. George-Chandy A, Nordstrom I, Nygren E, Jonsson IM, Postigo J, Collins LV, et al. Th17 development and autoimmune arthritis in the absence of reactive oxygen species. Eur J Immunol 2008;38:1118-26.

145. Manzi S, Urbach AH, McCune AB, Altman HA, Kaplan SS, Medsger TA Jr, et al. Systemic lupus erythematosus in a boy with chronic granulomatous disease: case report and review of the literature. Arthritis Rheum 1991;34:101-5.
146. Battersby AC, Cale AM, Goldblatt D, Gennery AR. Clinical manifestations of disease in X-linked carriers of chronic granulomatous disease. J Clin Immunol 2013;33:1276-84.
147. Chen K, Wu W, Mathew D, Zhang Y, Browne SK, Rosen LB, et al. Autoimmunity due to RAG deficiency and estimated disease incidence in RAG1/2 mutations. J Allergy Clin Immunol 2014;133:880-882.e10.
148. Schuetz C, Neven B, Dvorak CC, Leroy S, Ege MJ, Pannicke U, et al. SCID patients with ARTEMIS vs RAG deficiencies following HCT: increased risk of late toxicity in ARTEMIS-deficient SCID. Blood 2014;123:281-9.
149. Agarwal S, Mayer L. Diagnosis and treatment of gastrointestinal disorders in patients with primary immunodeficiency. Clin Gastroenterol Hepatol 2013;11:1050-63.
150. Uzzan M, Ko HM, Mehandru S, Cunningham-Rundles C. Gastrointestinal disorders associated with common variable immune deficiency (CVID) and chronic granulomatous disease (CGD). Curr Gastroenterol Rep 2016;18:17.
151. Malamut G, Verkarre V, Suarez F, Viallard JF, Lascaux AS, Cosnes J, et al. The enteropathy associated with common variable immunodeficiency: the delineated frontiers with celiac disease. Am J Gastroenterol 2010;105:2262-75.
152. Agarwal S, Smereka P, Harpaz N, Cunningham-Rundles C, Mayer L. Characterization of immunologic defects in patients with common variable immunodeficiency (CVID) with intestinal disease. Inflamm Bowel Dis 2011;17:251-9.
153. Daniels JA, Lederman HM, Maitra A, Montgomery EA. Gastrointestinal tract pathology in patients with common variable immunodeficiency (CVID): a clinicopathologic study and review. Am J Surg Pathol 2007;31:1800-12.
154. Chase NM, Verbsky JW, Hintermeyer MK, Waukau JK, Tomita-Mitchell A, Casper JT, et al. Use of combination chemotherapy for treatment of granulomatous and lymphocytic interstitial lung disease (GLILD) in patients with common variable immunodeficiency (CVID). J Clin Immunol 2013;33:30-9.
155. Boursiquot JN, Gerard L, Malphettes M, Fieschi C, Galicier L, Boutboul D, et al. Granulomatous disease in CVID: retrospective analysis of clinical characteristics and treatment efficacy in a cohort of 59 patients. J Clin Immunol 2013;33:84-95.
156. Chua I, Standish R, Lear S, Harbord M, Eren E, Raeiszadeh M, et al. Anti-tumour necrosis factor-alpha therapy for severe enteropathy in patients with common variable immunodeficiency (CVID). Clin Exp Immunol 2007;150:306-11.
157. Vazquez-Moron JM, Pallares-Manrique H, Martin-Suarez IJ, Benitez-Rodriguez B, Ramos-Lora M. Crohn's-like disease in a patient with common variable immunodeficiency treated with azathioprine and adalimumab. Rev Esp Enferm Dig 2013;105:299-302.
158. Bennett CL, Ochs HD. IPEX is a unique X-linked syndrome characterized by immune dysfunction, polyendocrinopathy, enteropathy, and a variety of autoimmune phenomena. Curr Opin Pediatr 2001;13:533-8.
159. Bacchetta R, Barzaghi F, Roncarolo MG. From IPEX syndrome to FOXP3 mutation: a lesson on immune dysregulation [e-pub ahead of print]. Ann N Y Acad Sci 2016. http://dx.doi.org/10.1111/nyas.13011.
160. Kinnunen T, Chamberlain N, Morbach H, Choi J, Kim S, Craft J, et al. Accumulation of peripheral autoreactive B cells in the absence of functional human regulatory T cells. Blood 2013;121:1595-603.
161. Kobayashi I, Kubota M, Yamada M, Tanaka H, Itoh S, Sasahara Y, et al. Autoantibodies to villin occur frequently in IPEX, a severe immune dysregulation, syndrome caused by mutation of FOXP3. Clin Immunol 2011;141:83-9.
162. Patey-Mariaud de Serre N, Canioni D, Ganousse S, Rieux-Laucat F, Goulet O, Ruemmele F, et al. Digestive histopathological presentation of IPEX syndrome. Mod Pathol 2009;22:95-102.
163. Bindl L, Torgerson T, Perroni L, Youssef N, Ochs HD, Goulet O, et al. Successful use of the new immune-suppressor sirolimus in IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome). J Pediatr 2005;147:256-9.
164. Yong PL, Russo P, Sullivan KE. Use of sirolimus in IPEX and IPEX-like children. J Clin Immunol 2008;28:581-7.
165. Gambineri E, Perroni L, Passerini L, Bianchi L, Doglioni C, Meschi F, et al. Clinical and molecular profile of a new series of patients with immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome: inconsistent correlation between forkhead box protein 3 expression and disease severity. J Allergy Clin Immunol 2008;122:1105-1112.e1.
166. Lopez-Herrera G, Tampella G, Pan-Hammarstrom Q, Herholz P, Trujillo-Vargas CM, Phadwal K, et al. Deleterious mutations in LRBA are associated with a syndrome of immune deficiency and autoimmunity. Am J Hum Genet 2012;90:986-1001.
167. Uzel G, Sampaio EP, Lawrence MG, Hsu AP, Hackett M, Dorsey MJ, et al. Dominant gain-of-function STAT1 mutations in FOXP3 wild-type immune dysregulation-polyendocrinopathy-enteropathy-X-linked-like syndrome. J Allergy Clin Immunol 2013;131:1611-23.
168. Schuetz C, Pannicke U, Jacobsen EM, Burggraf S, Albert MH, Honig M, et al. Lesson from hypomorphic recombination-activating gene (RAG) mutations: why asymptomatic siblings should also be tested. J Allergy Clin Immunol 2014;133:1211-5.
169. Sanal O, Jing H, Ozgur T, Ayvaz D, Strauss-Albee DM, Ersoy-Evans S, et al. Additional diverse findings expand the clinical presentation of DOCK8 deficiency. J Clin Immunol 2012;32:698-708.
170. Lohr NJ, Molleston JP, Strauss KA, Torres-Martinez W, Sherman EA, Squires RH, et al. Human ITCH E3 ubiquitin ligase deficiency causes syndromic multisystem autoimmune disease. Am J Hum Genet 2010;86:447-53.
171. Jin HS, Park Y, Elly C, Liu YC. Itch expression by Treg cells controls Th2 inflammatory responses. J Clin Invest 2013;123:4923-34.
172. Bertrand A, Kostine M, Barnetche T, Truchetet ME, Schaeverbeke T. Immune related adverse events associated with anti-CTLA-4 antibodies: systematic review and meta-analysis. BMC Med 2015;13:211.
173. Pedros C, Duguet F, Saoudi A, Chabod M. Disrupted regulatory T cell homeostasis in inflammatory bowel diseases. World J Gastroenterol 2016;22:974-95.
174. Marks DJ, Miyagi K, Rahman FZ, Novelli M, Bloom SL, Segal AW. Inflammatory bowel disease in CGD reproduces the clinicopathological features of Crohn's disease. Am J Gastroenterol 2009;104:117-24.
175. Alimchandani M, Lai JP, Aung PP, Khangura S, Kamal N, Gallin JI, et al. Gastrointestinal histopathology in chronic granulomatous disease: a study of 87 patients. Am J Surg Pathol 2013;37:1365-72.
176. Khangura SK, Kamal N, Ho N, Quezado M, Zhao X, Marciano B, et al. Gastrointestinal features of chronic granulomatous disease found during endoscopy. Clin Gastroenterol Hepatol 2016;14:395-402.e5.
177. Noel N, Mahlaoui N, Blanche S, Suarez F, Coignard-Biehler H, Durieu I, et al. Efficacy and safety of thalidomide in patients with inflammatory manifestations of chronic granulomatous disease: a retrospective case series. J Allergy Clin Immunol 2013;132:997-1000.e1-4.
178. Rosh JR, Tang HB, Mayer L, Groisman G, Abraham SK, Prince A. Treatment of intractable gastrointestinal manifestations of chronic granulomatous disease with cyclosporine. J Pediatr 1995;126:143-5.
179. Uzel G, Orange JS, Poliak N, Marciano BE, Heller T, Holland SM. Complications of tumor necrosis factor-alpha blockade in chronic granulomatous disease-related colitis. Clin Infect Dis 2010;51:1429-34.
180. Seger RA, Gungor T, Belohradsky BH, Blanche S, Bordigoni P, Di Bartolomeo P, et al. Treatment of chronic granulomatous disease with myeloablative conditioning and an unmodified hemopoietic allograft: a survey of the European experience, 1985-2000. Blood 2002;100:4344-50.
181. Gungor T, Teira P, Slatter M, Stussi G, Stepensky P, Moshous D, et al. Reduced-intensity conditioning and HLA-matched haemopoietic stem-cell transplantation in patients with chronic granulomatous disease: a prospective multicentre study. Lancet 2014;383:436-48.
182. Burroughs LM, Torgerson TR, Storb R, Carpenter PA, Rawlings DJ, Sanders J, et al. Stable hematopoietic cell engraftment after low-intensity nonmyeloablative conditioning in patients with immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome. J Allergy Clin Immunol 2010;126:1000-5.
183. Kucuk ZY, Bleesing JJ, Marsh R, Zhang K, Davies S, Filipovich AH. A challenging undertaking: stem cell transplantation for immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome. J Allergy Clin Immunol 2016;137:953-955.e4.
184. Horino S, Sasahara Y, Sato M, Niizuma H, Kumaki S, Abukawa D, et al. Selective expansion of donor-derived regulatory T cells after allogeneic bone marrow transplantation in a patient with IPEX syndrome. Pediatr Transplant 2014;18:E25-30.
185. Kasow KA, Morales-Tirado VM, Wichlan D, Shurtleff SA, Abraham A, Persons DA, et al. Therapeutic in vivo selection of thymic-derived natural T regulatory cells following non-myeloablative hematopoietic stem cell transplant for IPEX. Clin Immunol 2011;141:169-76.
186. Seidel MG, Fritsch G, Lion T, Jurgens B, Heitger A, Bacchetta R, et al. Selective engraftment of donor CD4+25high FOXP3-positive T cells in IPEX syndrome after nonmyeloablative hematopoietic stem cell transplantation. Blood 2009;113:5689-91.
187. Zhan H, Sinclair J, Adams S, Cale CM, Murch S, Perroni L, et al. Immune reconstitution and recovery of FOXP3 (forkhead box P3)-expressing T cells after transplantation for IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome. Pediatrics 2008;121:e998-1002.
188. Mazzolari E, Forino C, Fontana M, D'Ippolito C, Lanfranchi A, Gambineri E, et al. A new case of IPEX receiving bone marrow transplantation. Bone Marrow Transplant 2005;35:1033-4.