Secondary Hypogammaglobulinemia

An Increasingly Recognized Complication of Treatment with Immunomodulators and After Solid Organ Transplantation

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KEYWORDS

• Secondary immunodeficiency • Hypogammaglobulinemia • Antibody deficiency
• Immunosuppressive therapy • Immunosuppressive biological therapies
• Hematologic malignancy • Infections • Rituximab

KEY POINTS

- Secondary hypogammaglobulinemia is an increasingly common development in patients treated with immunosuppressive therapy.
- Screening for an underlying immunodeficiency is crucial in people with a history of recurrent, severe, or unusual infections or hematologic malignancies and before transplantation and starting immunomodulatory agents, including biologics.
- Preexistent primary or secondary immunodeficiency is exponentially magnified by immunosuppressive therapy, which can lead to reactivation and acceleration of latent, residual, and opportunistic infections.
- Antibody deficiency is characterized by decreased serum immunoglobulin levels in combination with the inability to mount primary and anamnestic protective antibody responses to vaccinations and infectious antigens.
- Management of secondary hypogammaglobulinemia includes screening for infections before starting immunomodulatory agents as indicated, early vaccination, antiinfective prophylaxis, and replacement immunoglobulin when indicated.

Disclosure Statement: No disclosures (B. Kaplan). Primary Immunodeficiency Disease Advisory Board: CSL-Behring; lecturer on primary immunodeficiency disease: Shire; LINK Advisory Board: Grifols (V.R. Bonagura).
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Immunol Allergy Clin N Am 39 (2019) 31–47
https://doi.org/10.1016/j.iac.2018.08.005
immunology.theclinics.com

INTRODUCTION

Primary immunodeficiency disorders (PIDDs), defined as inherited conditions that impair the function of the immune system, are distinct from secondary immunodeficiencies (SIDs), which can occur as a consequence of underlying illness, immunosuppressive treatment, and environmental and personal factors. SIDs result from altered immune system function in association with immunosuppressive therapies, malnutrition, infiltrative diseases or malignancies, infectious diseases, protein-losing disorders, structural abnormalities or surgery, certain hereditary disorders, extremes of age, harsh climates, isolation, extreme stress, sleep deprivation, radiation, and idiosyncratic drug-induced adverse effects.[1,2] SIDs are more prevalent than PIDD and are frequently unrecognized by clinicians.

Multiple medications in therapeutic doses can cause hypogammaglobulinemia. Decreased serum immunoglobulin A (IgA) can be caused by various anticonvulsant[3] and psychotropic agents, such as phenytoin, carbamazepine, valproic acid, chlorpromazine,[4] lamotrigine, and zonisamide. There are also reports of lamotrigine and carbamazepine causing decreases in total immunoglobulin G (IgG) and IgG subclasses[5] and a common variable immunodeficiency–like disease.[6,7]

Immunosuppressive therapies (ISTs) are indispensable for treating autoimmune, connective tissue, and malignant diseases and before and after hematopoietic stem cell (HSC) and solid organ transplantation. They are used to induce or maintain clinical remission, to decrease flares, and as steroid-sparing agents. In HSC transplantation, medical ISTs are used for the prevention and treatment of graft-versus-host disease. As the use of immunomodulatory drugs, including biologics, continues to increase, clinicians should be aware of their potential adverse reactions. These reactions include significant effects on innate, cellular, and humoral immunity that in turn can lead to severe, even fatal infections and autoimmune and lymphoproliferative diseases.

Medication-induced immunosuppression can be especially detrimental in patients with underlying immunodeficiency diseases, both primary and secondary. Many immunodeficient patients have a higher risk for developing autoimmunity and malignancy; however, more than 50% of patients with PIDD are not diagnosed until 25 years of age.[8] Consequently, treatment of autoimmunity and malignancy with IST without recognizing the underlying PIDD can put these patients at higher risk for complications. Likewise, hypogammaglobinemia secondary to hematologic malignancy is likely to be aggravated by IST. Hence, screening for preexistent immunodeficiency is crucial to decrease infectious complications of medication-induced immunosuppression. This article reviews immunosuppressive medications that commonly cause hypogammaglobulinemia.

NONBIOLOGICAL IMMUNOSUPPRESSIVE DRUGS THAT CAUSE HYPOGAMMAGLOBULINEMIA

Many of the traditional (nonbiological) immunosuppressive medications are used for the treatment of various autoimmune, malignant, and transplant rejection. Glucocorticoids,[9–11] sulfasalazine, gold, mycophenolate mofetil, methotrexate, azathioprine, and alkylating agents affect various pathways of innate and acquired immunity and can cause cytopenias, lymphocyte dysfunction and decrease immunoglobulin production (**Table 1**). Combining immunosuppressive medications leads to more frequent and severe hypogammaglobulinemia.[12,13] Immunosuppression can be complicated by an increased risk and severity of bacterial, viral, fungal, and protozoan infections, including opportunistic.

Table 1
Immunosuppressive (nonbiological) drugs that cause hypogammaglobulinemia

	Use	Mechanism of Action	Adverse Effects on Immune Cells and Immunoglobulin Levels	Associated Infections
GCs	Multiple antiinflammatory and autoimmune diseases	• Effect innate and acquired immunity via expression of multiple genes • Dose-dependent GS effects	• More significant effect on T cells compared with B cells • Hypogammaglobulinemia typically mild and not clinically significant • At high doses and chronic use: decrease number of peripheral B cells and decrease IgG and IgA levels • More significant hypogammaglobulinemia, caused by combination of glucocorticoids with other immunosuppressive medications	• Mild and severe bacterial, fungal, and viral infections • More common and more severe when GS are used with other immunosuppressive medications
Sulfasalazine	Rheumatoid arthritis, ulcerative colitis, other autoimmune diseases	• Exact mechanism of action unknown	• Inhibits neutrophil migration and reduces lymphocyte responses • Selective IgA deficiency • Reversible hypogammaglobulinemia, typically asymptomatic • Anemia, leukopenia	• Sepsis, pneumonia, no specific pathogens reported
Methotrexate	Acute lymphoid leukemia, juvenile idiopathic and rheumatoid arthritis, severe psoriasis	• Antimetabolite • Interferes with DNA synthesis, repair, and cellular replication by inhibiting dihydrofolate reductase	• Decreases immunoglobulin levels (rare) and antibody synthesis • Cytopenias • In high doses, causes profound bone marrow suppression	• Predominantly opportunistic infections, such as *Pneumocystis jiroveci* pneumonia, cryptococcosis, CMV disease (including pneumonia, sepsis), nocardiosis, herpes simplex and zoster infections, histoplasmosis • Bacterial infections, when used in combination with steroids

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Table 1
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	Use	Mechanism of Action	Adverse Effects on Immune Cells and Immunoglobulin Levels	Associated Infections
Azathioprine (active form: 6-mercaptopurin)	Rheumatoid arthritis, systemic lupus erythematosus, other autoimmune diseases, transplant rejection	• Purine analogue of guanine and hypoxanthine	• Decreases T- and B-cell numbers, B-cell proliferation, antibody formation, and NK cell activity • Myelosuppression, predominantly leukopenia, hepatitis, and lymphoproliferative disorders	• Bacterial, viral, fungal, protozoal, opportunistic infections • Rate of infections significantly higher in patients who had renal transplants compared with those with rheumatoid arthritis
Mycophenolate mofetil (active form: mycophenolic acid)	Autoimmune hepatitis, refractory autoimmune cytopenias, lupus nephritis, myasthenia gravis, transplant rejection	• Blocks the production of guanine nucleotides required for DNA synthesis	• Inhibits T- and B-cell proliferation, recruitment of lymphocytes into areas of inflammation and antibody production by B lymphocytes • Leukopenia, other cytopenias, increased risk of lymphoproliferative disorders and skin cancers • Hypogammaglobulinemia, especially in combination with other immunomodulators	• Predominantly opportunistic infections, such as CMV, *Pneumocystis jiroveci*, nocardiosis, histoplasmosis, cryptococcosis, reactivation of polyoma viruses, herpes zoster and simplex viruses • Bacterial infections, especially with concomitant GCs
Cyclophosphamide, chlorambucil, melphalan	Different types of leukemia and lymphoma, multiple myeloma, cancers, autoimmune diseases, minimal change disease	• Alkylating agents • Cross-link strands of DNA and RNA and inhibit protein synthesis • Inhibition cholinesterase activity	• T- and B-cell lymphopenia • Suppressed antibody responses • Cytopenias, myelodysplastic syndrome • Secondary malignancies	• Bacterial, fungal (*Pneumocystis jiroveci*), viral (herpes zoster), protozoal, parasitic (*Strongyloides*) infections • Reactivation of latent infections

Abbreviations: CMV, cytomegalovirus; GCs, glucocorticoids; NK, natural killer.

BIOLOGICAL THERAPIES THAT CAUSE HYPOGAMMAGLOBULINEMIA

Biologics are large molecule therapeutics, usually proteins, which are isolated from human (or sometimes other biological) material or produced by in vitro cell culture or cell lines and recombinant gene technology. They include vaccines, blood and blood components, cellular therapies, gene therapy, tissues, and recombinant therapeutic proteins.[14] Immunosuppressive biological agents selectively target specific cytokines and/or block their receptors, typically with high affinity. The therapeutic precision of these drugs is very useful in the treatment of specific underlying diseases; but it can cause a profound deficiency of the targeted immunologic mediator, mimicking the disease observed in patients with PIDDs with homozygous genetic deletions of these mediators (**Table 2**).

Anti-CD20 Monoclonal Antibodies

Rituximab is a chimeric antibody against CD20 that selectively targets B cells and induces complete depletion of circulating and tissue-based CD201 B lymphocytes. It is widely used to treat malignant and autoimmune diseases. Early clinical trials demonstrated mild, transient hypogammaglobulinemia during the treatment with rituximab,[15] with an average B-cell recovery of 6 to 9 months after completion of therapy, with no significant increase in infection rate.[16,17] However, with expanding use of rituximab, its use in maintenance drug regimens, in combination with other immunosuppressive medications, and the availability of longer follow-up data, it has become clear that some patients treated with rituximab develop long-lasting B-cell immunosuppression. T-cell lymphopenia, predominantly affecting $CD4^+$ T cells has been reported as well.[18] It can be persistent and more prominent with maintenance regimens.[19] Depending on the study, up to 56% of rituximab-treated patients are reported to develop hypogammaglobulinemia with predominantly decreased IgG and immunoglobulin M (IgM) serum levels.[20,21] For the most part, hypogammaglobulinemia is mild, but some of these patients develop severe infections that require temporary or long-term immunoglobulin replacement therapy (IGRT).[22–24] Severe cytomegalovirus (CMV) infection, reactivation of latent hepatitis B infection and fatal progressive multifocal leukoencephalopathy were described with rituximab. In a study of 211 patients with non–Hodgkin lymphoma, 39% developed new onset decreased serum IgG and 72% of patients with preexisting low serum IgG had worsening of their hypogammaglobinemia. Seven percent developed symptomatic hypogammaglobinemia, defined by recurrent non-neutropenic infections.[25] Similar findings of post–rituximab hypogammaglobulinemia and increased severe infections were also reported in patients with rheumatoid arthritis,[22,26,27] multisystem autoimmune disease,[27] antineutrophil cytoplasmic antibody-associated vasculitis,[28] systemic lupus erythematosus,[29] and multiple myeloma[30] and in patients with neuroinflammatory diseases.[31]

Retrospective studies of patients with recurrent or severe infections and hypogammaglobulinemia requiring IGRT after rituximab treatment found persistent B-cell abnormalities.[32,33] Makatsori and colleagues[32] found that all 19 patients had reduced or absent B cells, reduced specific antibody levels, no response to *Haemophilus influenza B* (HIB), tetanus, and pneumococcal vaccinations, and needed IGRT for a mean of 36 months (range 7 months to 7 years) after the last rituximab dose. In the other study, 45% (5 of 11) of patients had persistently undetectable $CD19^+$ B cells (<3 cells) 9 to 31 months after receiving rituximab.[33] B-cell recovery in the rest of the patients was delayed with an average reconstitution time of 23 months after the last dose of rituximab. Furthermore, B-cell subpopulations after rituximab treatment were skewed toward naive B cells; there was a significant decrease in switched and memory B cells

Table 2
Biological agents that cause secondary hypogammaglobulinemia

Medication	Target	Selected Indications	Immunologic Effects	Infectious Complications
Rituximab	• Anti-CD20 chimeric monoclonal antibody	CLL NHL AAV RA	• B-cell depletion • Hypogammaglobulinemia • Decreased antibody responses to vaccinations	• Potentially fatal bacterial, fungal, and viral infections (CMV, herpes simplex, varicella zoster, parvovirus B19, West Nile, hepatitis B and C); PML due to JC virus infection • Reactivation of hepatitis B several months after completion of therapy
Ofatumumab	• Second-generation anti-CD20 human monoclonal antibody • Binds to a unique, more membrane proximal epitope of the CD20 and has been shown to be more potent than rituximab in preclinical models	Initial treatment as well as relapsed and refractory CLL	• B-cell depletion • Hypogammaglobulinemia (5%) in clinical trials	• 65%–70% incidence of bacterial, viral, and fungal infections, including sepsis (8%–10%) • Reactivation of hepatitis B several months after completion of therapy
Obinutuzumab	• Third-generation humanized anti-CD20 monoclonal antibody • More potent activity through antibody-dependent cellular cytotoxicity and direct B-cell apoptosis than rituximab	CLL, follicular lymphoma	• Limited data • B-cell depletion	• Limited data • Incidence of infection: 38%, including fatal and serious bacterial, fungal, and viral (herpes virus) infections

Alemtuzumab	• Recombinant monoclonal antibody specific for CD52 (Campath-1 antigen), which is present on many mature immune cells (T and B cells, NK cells, eosinophils, neutrophils, monocytes/macrophages, and dendritic cells) • Causes antibody-dependent cellular and complement-mediated lysis	Relapsing remitting multiple sclerosis, CLL, renal transplant rejection	• Reduction in B, T, NK cells and neutropenia early in treatment, persists for 4 to 9 mo after stopping therapy	• Bacterial, viral, fungal, and protozoal (*Listeria*) infections • CMV reactivation and infection • Reactivation of hepatitis B or hepatitis C, herpes, human papilloma virus, and tuberculosis • Also, increased risk of secondary autoimmune disease (30%–40%) and infections, including bacterial, fungal, *Listeria monocytogenes*
Belimumab	Anti-BLys humanized monoclonal antibody	SLE	• Alters B cells' survival and reduces the differentiation of B cells into immunoglobulin-producing plasma cells	Pneumonia, urinary tract infection, cellulitis, and bronchitis
Atacicept	Humanized fusion protein that binds BLys and APRIL	—	• Decreased numbers of mature and total circulating B cells and serum IgG, IgM, and IgA	Phase II/III trial in lupus nephritis stopped because of low immunoglobulin levels and pneumonias in some patients

Abbreviations: AAV, ANCA-associated vasculitis; BLys, B-lymphocyte stimulator; CLL, chronic lymphoid leukemia; CMV, cytomegalovirus; NHL, non-Hodgkin lymphoma; NK, natural killer; PML, progressive multifocal leukoencephalopathy; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

in all of the patients. All patients had persistently low serum IgG levels with associated low IgA and IgM in 78% and 89% of these patients, respectively. None of these patients achieved an adequate response to *Streptococcus pneumoniae* polysaccharide vaccination (PPSV23). At 3.4 years after rituximab treatment (range, 1.0–6.5 years), 82% of patients were still requiring IGRT.[33]

Several factors associated with significant, symptomatic, persistent hypogammaglobinemia after rituximab have been described (see **Table 3**).[22–24,26–31,34–36] These include low baseline immunoglobulin levels, low CD19 count, more rituximab doses administered, use of other immunosuppressive drugs, older age, underlying disease treated with rituximab and concomitant medical conditions, or a combination of these risk factors.

The impact of rituximab on vaccination responses has been evaluated as well. Significantly decreased antibody responses were found to PPSV23, HIB,[37] and influenza A[38] vaccines within 6 months after CD20-depleting therapy. In patients with rheumatoid arthritis, antibody responses to influenza vaccination, administered 4 to 8 weeks after rituximab therapy, were significantly reduced compared with methotrexate-treated patients and healthy controls.[39] Humoral response improved, although it was still partial, when immunization was given 6 to 10 months after rituximab therapy, even in the absence of the repopulation of B cells. Another study of patients with rheumatoid arthritis measured vaccine responses after rituximab and methotrexate therapy for 36 weeks, compared with receiving methotrexate alone for 12 weeks. The investigators found similar tetanus toxoid responses in both groups but significantly decreased responses to PPSV23 and keyhole limpet hemocyanin (KLH, protein neoantigen) vaccines in the rituximab-treated group.[40] Antibody responses in 46 patients with newly diagnosed type 1 diabetes mellitus who completed 4 doses of rituximab and received no other IST showed protective, although significantly blunted, responses to tetanus, diphtheria. and hepatitis A immunizations 12 months after rituximab treatment compared with the placebo group.[41]

In an effort to further improve the therapeutic efficacy of rituximab, newer anti-CD20 monoclonal antibodies have been developed, such as ofatumumab, ocrelizumab, and obinutuzumab. Reactivation of hepatitis B has also been reported following anti-CD20 monoclonal antibody therapy. The Food and Drug Administration recommends screening all patients for hepatitis B virus (HBV) infection before starting treatment with ofatumumab and rituximab and monitoring patients who had prior HBV infection for clinical and laboratory signs of hepatitis B or HBV reactivation during and several months after treatment.[41]

Other Immunomodulatory Biologics

Other immunomodulatory biologics, such as monoclonal antibodies to cytokines that inhibit B-cell function (belimumab) and T-cell antigens (alemtuzumab),[42,43] are used in the setting of inflammatory disorders and have a potential of causing hypogammaglobulinemia (see **Table 2**). Abatacept downregulates T-cell activation by binding to CD80 and CD86 receptors on antigen-presenting cells and disrupts CD28 costimulation of T cells. It has not been associated with hypogammaglobulinemia; however, abatacept-treated patients with rheumatoid arthritis demonstrated significantly decreased serotype-specific IgG responses to PPSV23 compared with controls, while preserving opsonization responses, measured by multiplexed opsonophagocytic killing assay.[44] Belatacept is a second-generation CTLA-4-Ig fusion protein that has superior binding to CD80 and CD86 compared with abatacept, used in patients with renal transplants. Antithymocyte globulin

Table 3
Risk factors for postrituximab hypogammaglobulinemia and severe infections

Postrituximab Complications	Risk Factors	Underlying Disease	Notes	References
Hypogammaglobulinemia	• Low baseline IgG levels[a]	MAID	Weak association with cyclophosphamide exposure, but not cumulative rituximab dose	Roberts et al,[21] 2015
		RA	—	De La Torre et al,[27] 2012
			IgG levels <8 g/L	Boleto et al,[26] 2018
		Lymphoma	—	Filanovsky et al,[34] 2016
	• Low IgG levels at the time of rituximab	MAID	—	Roberts et al,[21] 2015
	• + Methotrexate	RA	—	Boleto et al,[26] 2018
	• Rituximab >8 doses	Lymphoma	—	Filanovsky et al,[34] 2016
	• + Fludarabine	Lymphoma	—	Filanovsky et al,[34] 2016
	• Prior purine exposure • Heavily pretreated patients	Non-Hodgkin lymphoma	—	Casulo et al,[25] 2013
Low IgM	• Baseline serum IgM $\leq$0.8 g/L • +Mycophenolate mofetil	Systemic lupus erythematosus	—	Reddy et al,[23] 2017

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Table 3
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Postrituximab Complications	Risk Factors	Underlying Disease	Notes	References
Infections	• Lower IgG levels[a] • Lower CD19 counts • Creatinine clearance ≤45 mL/min[a] • Older age • Diabetes mellitus • Prednisone dosage >15 mg/d	Systemic autoimmune disease (RA excluded)	History of pneumococcal vaccination significantly *decreased* the risk of serious bacterial infections events	Heusele et al,[24] 2014
	• Baseline IgG level <6 g/L[a] • Chronic lung disease and/or cardiac insufficiency • Extra-articular involvement	RA	—	Gottenberg et al,[35] 2010
	• Low IgG	RA	Infection rates higher in low-IgG patients even before they developed low IgG	van Vollenhoven et al,[22] 2013
	• Reduction in IgM after rituximab • Duration of rituximab • G-CSF administration	Hematology patients	—	Kanbayashi et al,[36] 2009
	• IgG ≤375 • Low IgA	Granulomatosis with polyangiitis	IgG ≤375 associated with 23 times higher odds of infection, requiring hospitalization	Shah et al,[28] 2017
	• +Fludarabine • Female sex	Lymphoma	—	Cabanillas et al,[20] 2006
	• +Fludarabine • Secondary prolonged hypogammaglobulinemia	Lymphoma	—	Filanovsky et al,[34] 2016
	• Secondary hypogammaglobulinemia	RA	—	Boleto et al,[26] 2018

Abbreviations: G-CSF, granulocyte-colony stimulating factor; MAID, multisystem autoimmune disease; RA, rheumatoid arthritis.
[a] Baseline levels refer to levels before rituximab treatment.

(ATG) causes depletion of both T and B cells and is associated with increased herpes virus infections. There are no reports of ATG-induced hypogammaglobulinemia.

MALIGNANCIES AND HYPOGAMMAGLOBULINEMIA

While evaluating patients with suspected medication-induced hypogammaglobulinemia, it is important to remember that underlying illnesses like malignancies, particularly lymphoproliferative disorders, such as chronic lymphoid leukemia (CLL) and multiple myeloma (MM), are causes of SID. The incidence of hypogammaglobulinemia in CLL increases with disease duration and is present in up to 85% of patients at some point in their disease course, and severe infections are the major cause of death in 25% to 50% of patients with CLL.[45,46] Infection is also a major cause of morbidity and mortality in MM.[47] Malignancy-associated immunodeficiency with hypogammaglobulinemia is multifactorial. It involves various pathways of the immune system and is compounded by the treatment modalities used to manage these diseases. Splenectomy, immunosuppressive, antiinflammatory, and biological drugs, as well as underlying medical conditions/complications associated with malignancies, such as cytopenias, cardiac and pulmonary pathology, protein-losing nephropathy and gastroenteropathy, metabolic diseases, such as diabetes and uremia, all exponentially magnify SID in these patients. Identifying patients at risk for serious or recurrent infections secondary to hypogammaglobulinemia and treating them appropriately and prophylactically play a key role in preventing serious infections, which is a major cause of poor outcomes in patients with hematologic malignancies. Early vaccination, antiinfection prophylaxis, and replacement immunoglobulin are important preventative components.[48]

AFTER SOLID ORGAN TRANSPLANTATION

The risk of infection in organ transplant patients is governed by the "the net state of immunosuppression" and the epidemiologic exposures of the individual.[49] Many factors influence the "net state of immunosuppression," including type, dose, duration, and timeline of IST; host factors, such as underlying diseases and comorbidities, cytopenias, hypogammaglobulinemia and metabolic problems; the presence of devitalized tissues or fluid collections in the transplanted organ; and the presence of invasive devices and concomitant infection with immunomodulating viruses.[50–53] Transplant-associated IST increases the risk of nosocomial, community-acquired, and donor-derived infections and leads to reactivation and acceleration of latent, residual, and opportunistic infections. Hypogammaglobulinemia is one of numerous immunologic manifestations of transplant-associated immunosuppression. Hypogammaglobulinemia and low specific titers to PPSV23 and CMV were demonstrated to be risk factors for severe bacterial infections and CMV disease in heart transplant patients.[54] As rituximab is increasingly used for prevention and treatment of posttransplant lymphoproliferative disorders[55–57] and ABO blood group incompatibility,[58,59] the incidence of hypogammaglobulinemia is likely to increase. Identifying and addressing pretransplant and IST-related hypogammaglobulinemia along with widely used antimicrobial prophylaxis may decrease the rate of infections and improve outcomes.

EVALUATION AND MANAGEMENT OF HUMORAL DEFECT IN SECONDARY IMMUNODEFICIENCIES

Antibody deficiency is characterized not solely by abnormal immunoglobulin levels but also by the inability to mount primary and/or amnestic protective antibody responses to vaccinations and infectious antigens. Vaccines typically used by immunologists to

identify antibody responses are tetanus toxoid and diphtheria toxin, HIB, and polysaccharide and conjugated pneumococcal (PCV13) vaccines as well as viral (measles, mumps, rubella, varicella) and neoantigen vaccines, such as φX174 and KLH. Although the administration of live viral vaccines is not appropriate in many immunodeficient patients, and neoantigen vaccines are not widely available, responses to tetanus toxoid, HIB, PPSV23, and PCV13 provide useful information in the management of patients with SID. B-cell phenotyping may be helpful in identifying patients with persistent humoral immune dysfunction caused by anti-CD20 therapies alone or compounded by preexistent immune defect of an underlying disease, such as PIDD, malignancy, and autoimmune disease.[32,60]

When evaluating patients with SID, it is also important to remember that autoimmune and some monoclonal proliferative diseases often are associated with hypergammaglobulinemia. The normal pretreatment and posttreatment immunoglobulin levels may be inadequately low for some of these patients, in line with the concept of the biological trough,[61] as characterized in PIDD. Additionally, patients treated with rituximab usually maintain protective specific antibody levels to the antigens they were exposed to before the treatment with a B-cell depleting drug, as immunoglobulin-producing plasma cells lose the CD20 cell surface marker during differentiation. However, these patients may not be able to mount appropriate responses to new infectious antigens or vaccines not received before B-cell depleting therapy and are at risk for infectious complications.

Management of SID includes screening for infections before starting immunomodulatory agents (for example, hepatitis B, CMV), early vaccinations, antiinfective prophylaxis, and replacement immunoglobulin when indicated. Reducing IST and treatment interruption in patients receiving immunosuppressive biologics should be considered if new infection develops. Patients with a history of recurrent and/or severe bacterial infections in the setting of hypogammaglobulinemia, poor responses to vaccinations, or failure to maintain vaccine titers should have a trial of IGRT to prevent further infections. Although optimal doses of IGRT in SID have not been established, the typical starting dosage is 350 to 400 mg/kg/mo (up to 600 mg/kg/mo in patients with bronchiectasis). The dose of intravenous or subcutaneous immunoglobulin should be adjusted to the lowest effective dose depending on the clinical response. The authors have adapted suggested protocols for the investigation, monitoring, and management of antibody failure in patients with CLL for use in patients with SID[62] (**Fig. 1**).

DISCUSSION AND FUTURE DIRECTIONS

SID, specifically hypogammaglobulinemia, is complex and multifactorial, involving multiple immune pathways. The use of immunomodulatory therapies and HSC or organ transplantation transformed the lives of countless patients, allowing the significant chance of a sustainable remission or total cure of a wide variety of diseases that, otherwise, had grave or fatal prognoses. As we accumulate knowledge and develop a clearer understanding of the immune mechanisms of the diseases themselves and the medical interventions that lead to SID, we must be continuously mindful that we should suspect, recognize, and treat early the underlying components of SID that can lead to serious, life-threatening, or fatal infections. It is important to remember that the immunosuppressive effects of medications may occur not only during or immediately after their use but can also manifest months or years after completion of this therapy. Drug-induced immunosuppression may be persistent and require long-term treatment with IGRT. Although not every patient with hypogammaglobulinemia will develop recurrent or serious infections, our role as clinicians is to identify patients at risk, as well as symptomatic patients with antibody deficiencies, and then institute appropriate, timely treatment.

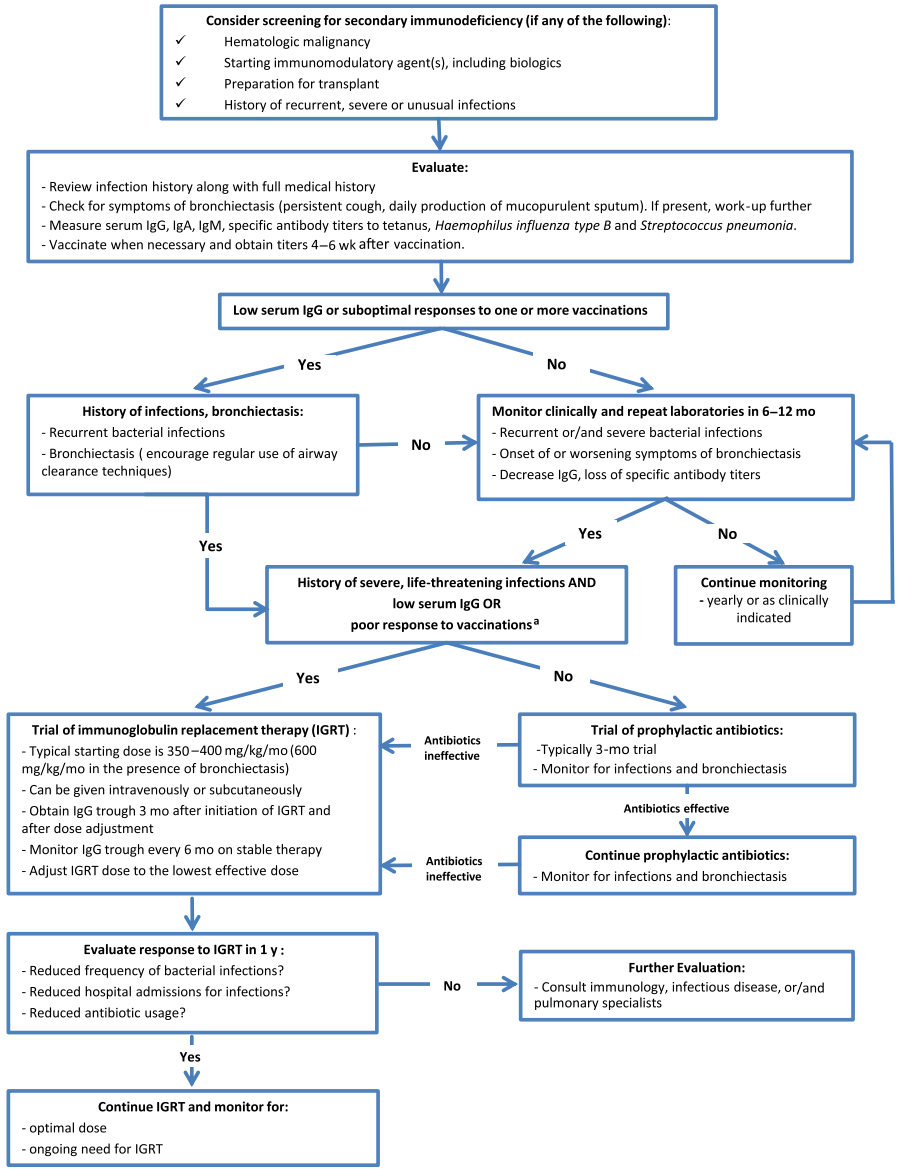

Fig. 1. Suggested protocol for work-up and management of humoral defect in SID. [a] It is a clinical decision whether or not to try antibiotic prophylaxis first or to go directly to IGRT. Patients treated with anti-CD20 agents may have protective preexisting-specific antibody titers but fail to generate new vaccine responses. (*Adapted from* Dhalla F, Lucas M, Schuh A, et al. Antibody deficiency secondary to chronic lymphocytic leukemia: should patients be treated with prophylactic replacement immunoglobulin? J Clin Immunol 2014;34(3):280; with permission.)

The natural history and management of SID vary depending on the causes of SID, thus, underscoring the need for further studies. For example, the characteristics and prognosis of SID secondary to lymphoma is different from that of chronic ITP treated with pulse steroids and rituximab. To differentiate between SID secondary

to underlying illness and medication-induced immunodeficiency, the authors proposed the term *persistent immunodeficiency after treatment with immunomodulatory drugs*.[33] Obtaining baseline immunologic studies, such as serum IgG, IgA, IgM levels, selected specific antibody titers, and, when appropriate, immunophenotyping of peripheral blood lymphocytes in patients with hematologic malignancies, or before starting immunomodulatory agents and transplant therapy, is critical to identify a previously undiagnosed PIDD and help predict whether a given patient is at a higher risk of developing SID. It will allow clinicians to treat patients promptly, avoid recurrent and serious infectious complications, and help the development of an accurate prognosis. New controlled trials are needed to identify risk factors for patients who are likely to develop symptomatic SID and the efficacy, safety, and cost-effectiveness of the treatment of these patients with prophylactic antimicrobials and IGRT.

ACKNOWLEDGMENTS

The authors thank Galina Marder for critical reading of the article.

REFERENCES

1. Bonilla F. Practice parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol 2015;136(5):1186–205.
2. Chinen J, Shearer W. Secondary immunodeficiencies, including HIV infection. J Allergy Clin Immunol 2008;121(2S):S388–92.
3. Ashrafi M, Hosseini SA, Abolmaali S, et al. Effect of anti-epileptic drugs on serum immunoglobulin levels in children. Acta Neurol Belg 2010;110(1):65–70.
4. Abe S, Suzuki T, Hori T, et al. Hypogammaglobulinemia during antipsychotic therapy. Psychiatry Clin Neurosci 1998;52(1):115–7.
5. Svalheim S, Mushtaq U, Mochol M, et al. Reduced immunoglobulin levels in epilepsy patients treated with levetiracetam, lamotrigine, or carbamazepine. Acta Neurol Scand Suppl 2013;(196):11–5.
6. Maruyama S, Okamoto Y, Toyoshima M, et al. Immunoglobulin A deficiency following treatment with lamotrigine. Brain Dev 2016;38(10):947–9.
7. Smith J, Fernando T, McGrath N, et al. Lamotrigine-induced common variable immune deficiency. Neurology 2004;62(5):833–4.
8. Bousfiha AA, Jeddane L, Ailal F, et al. Primary immunodeficiency diseases worldwide: more common than generally thought. J Clin Immunol 2013;33(1):1–7.
9. Dixon WG, Abrahamowicz M, Beauchamp ME, et al. Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in older patients with rheumatoid arthritis: a nested case-control analysis. Ann Rheum Dis 2012;71(7):1128.
10. Berger W, Pollock J, Kiechel F, et al. Immunoglobulin levels in children with chronic severe asthma. Ann Allergy 1978;41(2):67–74.
11. Lack G, Ochs HD, Gelfand EW. Humoral immunity in steroid-dependent children with asthma and hypogammaglobulinemia. J Pediatr 1996;129(6):898.
12. Chen JY, Wang LK, Feng PH, et al. Risk of shingles in adults with primary Sjogren's syndrome and treatments: a nationwide population-based cohort study. PLoS One 2015;10(8):e0134930.
13. Yap DY, Yung S, Ma MK, et al. Serum immunoglobulin G level in patients with lupus nephritis and the effect of treatment with corticosteroids and mycophenolate mofetil. Lupus 2014;23(7):678–83.

14. What are "biologics" questions and answers. Available at: https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133077.htm. Accessed April 21, 2018.
15. Maloney DG, Grillo-Lopez AJ, Bodkin DJ, et al. IDEC-C2B8: results of a phase I multiple-dose trial in patients with relapsed non-Hodgkin's lymphoma. J Clin Oncol 1997;15:3266–74.
16. David TA, White CA, Grillo-Lopez AJ, et al. Single-agent monoclonal antibody efficacy in bulky non-Hodgkin's lymphoma: results of a phase II trial of rituximab. J Clin Oncol 1999;17:1851–7.
17. Piro LT, White CA, Grillo-Lopez AJ, et al. Extended rituximab (anti CD20 monoclonal antibody) therapy for relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma. Ann Oncol 1999;10:655–61.
18. Mélet J, Mulleman D, Goupille P, et al. Rituximab-induced T cell depletion in patients with rheumatoid arthritis: association with clinical response. Arthritis Rheum 2013;65(11):2783–90.
19. Yutaka T, Ito S, Ohigashi H, et al. Sustained CD4 and CD8 lymphopenia after rituximab maintenance therapy following bendamustine and rituximab combination therapy for lymphoma. Leuk Lymphoma 2015;56(11):3216–8.
20. Cabanillas F, Liboy I, Pavia O, et al. High incidence of non-neutropenic infections induced by rituximab plus fludarabine and associated with hypogammaglobulinemia: a frequently unrecognized and easily treatable complication. Ann Oncol 2006;17(9):1424–7.
21. Roberts DM, Jones RB, Smith RM, et al. Rituximab-associated hypogammaglobulinemia: incidence, predictors and outcomes in patients with multi-system autoimmune disease. J Autoimmun 2015;57:60–5.
22. van Vollenhoven RF, Emery P, Bingham CO, et al. Long term safety of rituximab in rheumatoid arthritis: 9.5-year follow-up of the global clinical trial programme with a focus on adverse events of interest in RA patients. Ann Rheum Dis 2013;72(9):1496–502.
23. Reddy V, Martinez L, Isenberg DA, et al. Pragmatic treatment of patients with systemic lupus erythematosus with rituximab: long-term effects on serum immunoglobulins. Arthritis Care Res (Hoboken) 2017;69(6):857–66.
24. Heusele M, Clerson P, Guery B, et al. Risk factors for severe bacterial infections in patients with systemic autoimmune diseases receiving rituximab. Clin Rheumatol 2014;33(6):799–805.
25. Casulo C, Maragulia J, Zelenetz AD. Incidence of hypogammaglobulinemia in patients receiving rituximab and the use of intravenous immunoglobulin for recurrent infections. Clin Lymphoma Myeloma Leuk 2013;13:106–11.
26. Boleto G, Avouac J, Wipff J, et al. Predictors of hypogammaglobulinemia during rituximab maintenance therapy in rheumatoid arthritis: a 12-year longitudinal multi-center study. Semin Arthritis Rheum 2018. https://doi.org/10.1016/j.semarthrit.2018.02.010.
27. De La Torre I, Leandro MJ, Valor L, et al. Total serum immunoglobulin levels in patients with RA after multiple B-cell depletion cycles based on rituximab: repletion with B-cell kinetics. Rheumatology 2012;51:833–40.
28. Shah S, Jaggi K, Greenberg K, et al. Immunoglobulin levels and infection risk with rituximab induction for anti-neutrophil cytoplasmic antibody-associated vasculitis. Clin Kidney J 2017;10(4):470–4.
29. Aguiar R, Araújo C, Martins-Coelho G, et al. Use of rituximab in systemic lupus erythematosus: a single center experience over 14 years. Arthritis Care Res 2017;69(2):257–62.

30. Vacca A, Melaccio A, Sportelli A, et al. Clin Immunol Subcutaneous immunoglobulins in patients with multiple myeloma and secondary hypogammaglobulinemia: a randomized trial. Clin Immunol 2018;191:110–5.
31. Tallantyre EC, Whittam DH, Jolles S, et al. Secondary antibody deficiency: a complication of anti-CD20 therapy for neuroinflammation. J Neurol 2018. https://doi.org/10.1007/s00415-018-8812-0.
32. Makatsori M, Kiani-Alikhan S, Manson AL, et al. Hypogammaglobulinaemia after rituximab treatment-incidence and outcomes. QJM 2014;107(10):821–8.
33. Kaplan B, Kopyltsova Y, Khokhar A, et al. Rituximab and immune deficiency: case series and review of the literature. J Allergy Clin Immunol Pract 2014;2(5):594–600.
34. Filanovsky K, Miller EB, Sigler E, et al. Incidence of profound hypogammaglobulinemia and infection rate in lymphoma patients following the combination of chemotherapy and rituximab. Recent Pat Anticancer Drug Discov 2016;11(2):228–35.
35. Gottenberg JE, Ravaud P, Bardin T, et al. Risk factors for severe infections in patients with rheumatoid arthritis treated with rituximab in the autoimmunity and rituximab registry. Arthritis Rheum 2010;62(9):2625–32.
36. Kanbayashi Y, Nomura K, Fujimoto Y, et al. Risk factors for infection in haematology patients treated with rituximab. Eur J Haematol 2009;82(1):26–30.
37. Nazi I, Kelton JG, Larché M, et al. The effect of rituximab on vaccine responses in patients with immune thrombocytopenia. Blood 2013;122:1946–53.
38. Yri OE, Torfoss D, Hungnes O, et al. Rituximab blocks protective serologic response to influenza A (H1N1) 2009 vaccination in lymphoma patients during or within 6 months after treatment. Blood 2011;118(26):6769–71.
39. van Assen S, Holvast A, Benne CA, et al. Humoral responses after influenza vaccination are severely reduced in patients with rheumatoid arthritis treated with rituximab. Arthritis Rheum 2010;62(1):75–81.
40. Bingham CO 3rd, Looney RJ, Deodhar A, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial. Arthritis Rheum 2010;62(1):64–74.
41. FDA Drug Safety Communication: boxed warning and new recommendations to decrease risk of hepatitis B reactivation with the immune-suppressing and anti-cancer drugs Arzerra (ofatumumab) and Rituxan (rituximab). Available at: https://www.fda.gov/drugs/drugsafety/ucm366406.htm. Accessed April 28, 2018.
42. Ruck T, Bittner S, Wiendl H, et al. Alemtuzumab in multiple sclerosis: mechanism of action and beyond. Int J Mol Sci 2015;16(7):16414–39.
43. O'Brien SM, Keating MJ, Mocarski ES. Updated guidelines on the management of cytomegalovirus reactivation in patients with chronic lymphocytic leukemia treated with alemtuzumab. Clin Lymphoma Myeloma 2006;7(2):125.
44. Migita K, Akeda Y, Akazawa M, et al. Effect of abatacept on the immunogenicity of 23-valent pneumococcal polysaccharide vaccination (PPSV23) in rheumatoid arthritis patients. Arthritis Res Ther 2015;17:357.
45. Hamblin TJ. Chronic lymphocytic leukaemia. Baillieres Clin Haematol 1987;1:449–91.
46. Hamblin AD, Hamblin TJ. The immunodeficiency of chronic lymphocytic leukaemia. Br Med Bull 2008;87:49–62.
47. Perri RT, Hebbel RP, Oken MM. Influence of treatment and response status on infection risk in multiple myeloma. Am J Med 1981;71(6):935–40.

48. Friman V, Winqvist O, Blimark C, et al. Secondary immunodeficiency in lymphoproliferative malignancies. Hematol Oncol 2016;34(3):121–32.
49. Fishman JA, Issa NC. Infection in organ transplantation: risk factors and evolving patterns of infection. Infect Dis Clin North Am 2010;24(2):273–83.
50. Collins LA, Samore MH, Roberts MS, et al. Risk factors for invasive fungal infections complicating orthotopic liver transplantation. J Infect Dis 1994;170:644.
51. Hadley S, Karchmer AW. Fungal infections in solid organ transplant recipients. Infect Dis Clin North Am 1995;9:1045.
52. van den Berg AP, Klompmaker IJ, Haagsma EB, et al. Evidence for an increased rate of bacterial infections in liver transplant patients with cytomegalovirus infection. Clin Transplant 1996;10:224.
53. Issa NC, Fishman JA. Infectious complications of antilymphocyte therapies in solid organ transplantation. Clin Infect Dis 2009;48:772.
54. Sarmiento E, Jaramillo M, Calahorra L, et al. Evaluation of humoral immunity profiles to identify heart recipients at risk for development of severe infections: a multicenter prospective study. J Heart Lung Transplant 2017;36(5):529–39.
55. Elstrom RL, Andreadis C, Aqui NA, et al. Treatment of PTLD with rituximab or chemotherapy. Am J Transplant 2006;6(3):569.
56. Choquet S, Leblond V, Herbrecht R, et al. Efficacy and safety of rituximab in B-cell post-transplantation lymphoproliferative disorders: results of a prospective multicenter phase 2 study. Blood 2006;107(8):3053.
57. Trappe R, Oertel S, Leblond V, et al. Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicentre phase 2 PTLD-1 trial. Lancet Oncol 2012;13(2):196–206.
58. Vo AA, Choi J, Cisneros K, et al. Benefits of rituximab combined with intravenous immunoglobulin for desensitization in kidney transplant recipients. Transplantation 2014;98(3):312–9.
59. Lee EC, Kim SH, Shim JR, et al. A comparison of desensitization methods: rituximab with/without plasmapheresis in ABO-incompatible living donor liver transplantation. Hepatobiliary Pancreat Dis Int 2018;17(2):119–25.
60. Anolik JH, Friedberg JW, Zheng B, et al. B-cell reconstitution after rituximab treatment of lymphoma recapitulates B-cell ontogeny. Clin Immunol 2007;122:139–45.
61. Bonagura VR. Dose and outcomes in primary immunodeficiency disorders. Clin Exp Immunol 2014;178(S1):7–9.
62. Dhalla F, Lucas M, Schuh A, et al. Antibody deficiency secondary to chronic lymphocytic leukemia: should patients be treated with prophylactic replacement immunoglobulin? J Clin Immunol 2014;34:277–82.