



A Canadian perspective on the use of immunoglobulin therapy to reduce infectious complications in chronic lymphocytic leukemia

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ABSTRACT

Infections are a major cause of morbidity and mortality in patients with chronic lymphocytic leukemia (CLL), who typically have increased susceptibility because of hypogammaglobulinemia (HGG) related to their disease and its treatment. Immunoglobulin replacement therapy (IGRT) has been shown to reduce the frequency of bacterial infections and associated hospitalizations in patients with HGG or a history of infection, or both. However, use of IGRT in CLL is contentious. Studies examining such treatment were conducted largely before the use of newer chemoimmunotherapies, which can extend lifespan, but do not correct the HGG inherent to the disease. Thus, the utility of IGRT has to be re-evaluated in the current setting. Here, we discuss the evidence for the use of IGRT in CLL and provide a practical approach to its use in the prevention and management of infections.

Key Words Chronic lymphocytic leukemia, hypogammaglobulinemia, immunoglobulins, immunoglobulin replacement therapy, infection, IVIG, SCIG, immunodeficiency

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BACKGROUND

Chronic lymphocytic leukemia (CLL) is a hematopoietic neoplasia, marked by the proliferation and accumulation of small, mature-appearing, immunologically incompetent B lymphocytes in blood, bone marrow, lymph nodes, and spleen¹. Chronic lymphocytic leukemia is the most common leukemia in adults in North America, with a median age at diagnosis ranging between 67 and 72 years¹. In Canada, 2165 individuals were diagnosed with CLL in 2010, and another report based on data collected during 1998–2003 suggested that as many as 7.99 people are diagnosed per 100,000 population per year^{2,3}.

The prognosis of patients with CLL depends on a number of factors (for example, immunophenotype, molecular genetics, stage of disease, etc.), and survival ranges from 1–2 years to more than 15 years⁴.

INFECTIONS AND HYPOGAMMAGLOBULINEMIA

Infection is a frequent cause of morbidity and mortality in patients with CLL. The germinal description of the natural history of CLL published by Wintrobe and Hasenbush⁵ in 1939 established that point, estimating that 38.2% of CLL patients develop infections (usually more than one type of infection over the course of their disease), with an attributable mortality rate of 66.7%. Subsequent studies have estimated that approximately one third to one half of all CLL patients develop at least 1 infectious complication during the course of their disease⁶. Those infections have traditionally been classified as moderate (that is, requiring oral antibiotics and no hospitalization) or severe (that is, requiring parenteral antibiotics or hospitalization, or both). Before the advent of novel therapeutics, mortality

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rates of 25%–50% were found to be directly attributable to such infections^{7,8}.

Infections in patients with CLL are paradigmatically bacterial in origin and tend to occur in the respiratory tract; however, they can also affect the skin, gastrointestinal tract, and bloodstream⁷. Before the use of purine analogues, the most frequent bacterial infections included *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Escherichia coli*⁸. Infections with opportunistic organisms such as *Listeria*, *Nocardia*, *Candida*, *Aspergillus*, *Pneumocystis jiroveci*, *Histoplasmosis*, *Cryptococcus*, and non-tuberculous (“atypical”) mycobacteria can also occur in these patients if they are sufficiently immunosuppressed from specific chemotherapeutic regimens⁸.

Although no clinical trials have examined the use of prophylactic antibiotics in patients with CLL, guidelines for their use in preventing opportunistic infections are associated with certain treatments^{8–15}. In addition, certain antineoplastic agents (for example, purine analogues, alkylating agents, alemtuzumab, and combination chemotherapy) can also increase the risk of select viral diseases (herpes simplex, cytomegalovirus, Epstein–Barr virus, and human herpesvirus 8, for instance)^{7,8}. Furthermore, novel therapies have recently changed the landscape of CLL treatment. Among them, Bruton kinase inhibitors such as ibrutinib and idelalisib have shown promising efficacy in the treatment of CLL. A recent review of prolonged therapy with ibrutinib suggested a decline in the infection rate during treatment¹⁶. Two mechanisms are proposed: first, inhibition of the interleukin-associated T-cell kinase, which can promote T-helper cell type 1 CD4 T-cell outgrowth, leading to a reduction of morbidity from infection in animal models; and second, some return of the humoral immunity function (mainly the level of immunoglobulin A), although the exact mechanisms of immunoglobulin (Ig) stabilization or improvement remain unknown¹⁷. Thus, the spectrum of infections in patients with CLL varies according to disease stage (early vs. late) and treatment history, with a core susceptibility to bacterial respiratory tract infections, but potentially extending to other organisms as a result of CLL-directed therapy.

The primary factor contributing to core susceptibility is impaired antibody production, which most commonly manifests as hypogammaglobulinemia (HGG)⁷. Over the course of the disease, HGG occurs in approximately 85% of patients, becoming more prevalent in advanced CLL⁷. The mechanisms contributing to the development of HGG in CLL are multifactorial. Because CLL is a malignant clonal disorder of B cells, the resulting dysfunctional B lymphocytes have an impaired ability to produce Ig, at least *in vitro*¹⁸. Additionally, the malignant B cells have the capacity to directly induce apoptosis of healthy Ig-producing plasma cells¹⁹. Lastly, CLL appears to be associated with dysfunctional T-helper cells, which are normally involved in the generation of antibody responses²⁰. Thus, an impaired capacity to produce functionally diverse Igs appears to be an intrinsic general feature of CLL.

Although not all patients with HGG will necessarily develop problematic infections, studies to date have demonstrated that such infections more frequently occur when IgG levels fall below 6 g/L^{7,21}. Conversely, not

all patients with CLL and quantitatively normal levels of serum IgG are free of infection. The basis for the discordance is probably multifactorial and relates to the disease-induced immune dysfunction. Monoclonal Igs are produced in some patients with CLL and might contribute to a false “normal” level^{22–24}. In CLL, HGG is progressive, typically worsening as the disease evolves, and HGG is associated with a reduced probability of survival^{16,25}. Compounding that issue is the knowledge that certain treatments for CLL (for example, fludarabine, rituximab, stem-cell transplantation, radiation, glucocorticoids) also appear to reduce Ig levels²⁶.

Primary immunodeficiency disorders (PIDs) marked by HGG are caused by inborn errors of B-cell development or maturation and are associated with increased susceptibility to the same types of infections associated with HGG in CLL²⁷. Decades of experience have established Ig replacement therapy (IGRT) as the standard of care for the prevention of such infections in PIDs with HGG. There is no reason to believe that CLL patients with HGG would not similarly benefit from the same approach. Although this topic has historically been contentious, CLL therapies are improving control of the disease, and accordingly, the use of IGRT to mitigate the risk of infection in patients with CLL has to be revisited.

Assessing the Risk of Infection

Given that patients with CLL are at increased risk of infection, particularly bacterial respiratory tract infections, their risk should be routinely evaluated. Evaluation should consist of regular clinical assessments that include a detailed history of recent infections, focusing particularly on frequency, severity, required treatment, and sequelae. Infections requiring hospitalization or prolonged or repeated courses of antimicrobial therapy are obviously concerning.

In episodes of infection, microbiologic confirmation provides insight into whether the infection is likely to be related to HGG (for example, encapsulated bacteria, viruses) or to the chemotherapies being used (for example, *Pneumocystis jiroveci* with steroids); such confirmation should be pursued^{7,26}. The clinical evaluation should be performed concomitantly with monitoring of serum Ig levels. Given that HGG worsens with disease duration, clinical (infection history) and laboratory (Ig level) evaluations should be performed at least every 6–12 months, although the timing should be tailored to each patient. Because treatment for CLL can itself worsen HGG and lead to infections, it is also advisable to measure serum Ig levels and circulating CD19+ B cells before treatment with immunomodulatory agents is started²⁸. For some agents (rituximab, for instance), delayed B-cell recovery (>9 months) and treatment-induced neutropenia could be associated with an increased risk of serious infections^{28,29}. Thus, periodic measurement of Ig levels and CD19+ B cells could aid in identifying patients at risk.

In the investigation of suspected PIDs, antibody responses to protein and polysaccharide antigens are routinely used to characterize the integrity of B-cell immunity (Table 1)⁷. Whether, based on residual B-cell function, those responses can similarly be used to stratify CLL patients into low-risk and high-risk categories for infection is not clear. Older studies assessing vaccine responses in patients with

TABLE 1 Immunologic characteristics of the major diagnostically applied vaccines^a

Vaccine	T cell-independent or –dependent	Timing of peak antibody level	Protective level
Hib conjugate	Dependent	6 Months (3–4 weeks after 3rd dose)	1.0 µg/mL
Meningococcal conjugate	Dependent	2–4 Weeks	2.0 µg/mL
Meningococcal polysaccharide	Independent	2–4 Weeks	2.0 µg/mL
Pneumococcal conjugate	Dependent	4 Weeks	1.3 µg/mL
Pneumococcal polysaccharide	Independent	4 Weeks	1.3 µg/mL
Rabies	Dependent	21 Days after 3rd dose for pre-exposure prophylaxis	0.5 IU
Tetanus	Dependent	2–3 Weeks after initial series	0.15 IU/mL

^a Adapted from Orange *et al.*, 2012³⁰.
Hib = *Haemophilus influenzae* type b.

CLL have demonstrated that bacterial polysaccharides are generally ineffective in antibody formation: It is thought that HGG reflects impaired antibody responses to both primary immunization and re-immunization and likely reflects a similar phenomenon in response to primary infection or re-infection^{6,25,31}. An additional pragmatic hurdle in evaluating vaccine response is the time required for seroconversion, which encompasses both the time required for the body to generate a peak antibody response to the vaccine challenge and the time for the diagnostic laboratory to perform the tests; the resulting delays can be prohibitive. Further, the interpretation of serologic results can be straightforward for some vaccines (tetanus and *Haemophilus influenzae* type b, for instance), but perhaps less so for others (for example, *Pneumococcus* serotypes). Lastly, vaccines have evolved since the original studies, and vaccine immunogenicity in patients with CLL is not well defined. In discerning which patients with CLL would benefit from IGRT, further research is therefore needed to determine the utility of vaccine responses.

Ig PROPHYLAXIS

In patients who have an impaired ability to produce antibodies and who require prophylaxis, IGRT is the standard of care. Preparations for IGRT are derived by pooling normal polyvalent IgG antibodies from large numbers of healthy donors^{32,33}. Antibodies to foreign antigens (microbes, for example), to self-antigens (natural autoantibodies, for instance), and to other antibodies (for example, anti-idiotypic antibodies) are also included in the preparation. Immunoglobulin replacement therapy is available either as an intravenous infusion (IVIg) or as a subcutaneous injection (SCIG).

Current Indications for IGRT

In Canada, IVIg is currently indicated for the treatment of patients with PID and secondary immunodeficiency disorders³³. Those disorders include, but are not limited to, common variable immunodeficiency, X-linked agammaglobulinemia, congenital agammaglobulinemia, secondary HGG, Wiskott–Aldrich syndrome, and severe combined immunodeficiencies. Treatment with IVIg is also indicated for patients with immune thrombocytopenic purpura (to rapidly raise platelet counts for the prevention

of bleeding) and for patients with chronic inflammatory demyelinating polyneuropathy (to provide immunomodulation). Treatment with SCIG is currently indicated for adult and pediatric patients with PID who require IGRT. It is considered equivalent in efficacy to IVIg^{34,35}. Examples of currently approved IVIg preparations include Privigen (CSL Behring AG, King of Prussia, PA, U.S.A.), Gamunex (Bayer HealthCare, Leverkusen, Germany), IGIVnex (Grifols Therapeutics, Research Triangle Park, NC, U.S.A.), and Gammagard S/D (Baxter International, Deerfield, IL, U.S.A.). Current SCIG preparations include Hizentra (CSL Behring AG) and IGIVnex^{33–37}.

Evidence for IGRT in CLL

The compelling association between HGG and risk of infection prompted Fairley and Scott³⁸ to pioneer IGRT in 3 CLL patients in 1961. One patient remained free of severe infection on replacement; the second could not tolerate the intramuscular injections and died of infection upon stopping replacement; and in the third, the sentinel CLL-related infection was fatal (and did not improve when replacement was started during the infection). Admittedly, the cases were anecdotal, and other studies of intramuscular replacement suggested no benefit; however, that lack of benefit might have been a result of the difficulties associated with administering sufficient quantities of Ig intramuscularly.

The beneficial effect of IVIg was later demonstrated in 1988 in a randomized controlled double-blind clinical trial conducted by the Cooperative Group for the Study of Immunoglobulin in CLL³⁹, whereby, compared with placebo, use of IVIg was associated with fewer bacterial infections ($p = 0.01$, Table 1). The effect on serious infections was seen early, with segregation of the Kaplan–Meier curves at approximately 25 days after IVIg initiation. Additionally, compared with the control group, patients who received IGRT remained free of serious bacterial infection for a longer period after entering the study. Not unexpectedly, IVIg had no effect on viral (that is, herpes simplex virus or varicella zoster virus) or fungal infections; the same lack of effect is also seen in PID patients with HGG. A subsequent double-blind crossover follow-up study in a cohort of the same patients confirmed the earlier findings⁴⁰. Other studies have consistently demonstrated the beneficial effect of IGRT in CLL patients with respect to a decreased incidence

TABLE II Key studies investigating immunoglobulin (Ig) replacement therapy in chronic lymphocytic leukemia (CLL)^a

Reference	Patient characteristics	Intervention	Results
Cooperative Group, ^b 1988 ³⁹	81 with CLL who had HGG or infections, or both	400 mg/kg IV Ig every 3 weeks for 1 year vs. placebo (saline)	<ul style="list-style-type: none"> ■ Fewer bacterial infections overall in IV Ig group: 23 vs. 42, $p=0.01$ ■ Fewer moderate bacterial infections in IV Ig group: 10 vs. 21, $p=0.026$ ■ Longer time to 1st serious bacterial infection in IV Ig group: $p=0.026$ ■ No difference between groups in nonbacterial infections ■ No difference between groups in all-cause mortality at 1 year ■ No serious AEs (mild chills or fever were the most frequent AEs)
Griffiths <i>et al.</i> , 1989 ⁴⁰	8 with CLL and 4 with NHL who had HGG or infections, or both	400 mg/kg IV Ig every 3 weeks for 1 year vs. placebo (saline), then crossed over to the other group for 1 year	<ul style="list-style-type: none"> ■ Fewer serious bacterial infections in IV Ig group ■ No difference in trivial infections between groups ■ No serious AEs
Sklenar <i>et al.</i> , 1993 ⁴¹	31 with CLL and 31 with multiple myeloma	100 mg/kg, 400 mg/kg, or 800 mg/kg IV Ig every 3 weeks	<ul style="list-style-type: none"> ■ Optimal dose for CLL was 400 mg/kg ■ Steady state reached after 11–12 weeks or 4 infusions ■ Suggest 400 mg/kg every 3 weeks until week 12, then 400 mg/kg every 5 weeks ■ Minor febrile reactions, shivering, and headache in 25% of patients
Chapel <i>et al.</i> , 1994 ⁴²	34 with CLL who had HGG or infections, or both	500 mg/kg or 250 mg/kg IV Ig every 4 weeks for 1 year	<ul style="list-style-type: none"> ■ No difference in infection frequency between groups ■ No difference in all-cause mortality between groups ■ No serious AEs (mild chills, fever, and back pain were the most common AEs)
Gamm <i>et al.</i> , 1994 ²¹	34 with CLL who had HGG or infections, or both	500 mg/kg or 250 mg/kg every 4 weeks for 1 year	<ul style="list-style-type: none"> ■ No difference between groups in number of infectious episodes ■ Mild chills and fever were the most common AEs ■ No serious AEs
Jurlander <i>et al.</i> , 1994 ⁴³	15 with CLL who had HGG and infections	Pre- and post-treatment with 10 g IV Ig every 3 weeks (mean duration: 1 year)	<ul style="list-style-type: none"> ■ Fewer hospital admissions with IV Ig ■ Fewer febrile episodes with IV Ig ■ No difference in antibiotic prescriptions between groups ■ No difference between groups in severe infections ■ Long stabilization period ■ Mild chills and dizziness were the most common AEs
Boughton <i>et al.</i> , 1995 ²⁰	42 with CLL who had HGG and infections	18 g IV Ig every 3 weeks for 1 year vs. human albumin placebo; if 3 breakthrough infections occurred, patients on placebo were given 18 g IV Ig; for those already on IV Ig, the dose was increased to 24 g	<ul style="list-style-type: none"> ■ Fewer serious infections overall with IV Ig: 21% vs. 56%, $p=0.02$ ■ Fewer infections overall with IV Ig: 29% vs. 61%, $p=0.04$ ■ Of patients who required dose increase, 50% were subsequently infection-free ■ Most infections (65%) occurred when IgG was below 3 g/L ■ Most common AE was pyrexia after infusion
Molica <i>et al.</i> , 1996 ⁴⁴	42 with CLL who had HGG and infections	300 mg/kg IV Ig every 4 weeks for 6 months vs. no treatment; switched to observed vs. IV Ig for 12 months, then received IV Ig or observation for 6 months	<ul style="list-style-type: none"> ■ Incidence of infections was lower in IV Ig prophylaxis phase than in observation phase ($p<0.01$) ■ Chills, fever, and back pain were the most common AEs leading to withdrawal (2 patients)

TABLE II Continued

Reference	Patient characteristics	Intervention	Results
Compagno <i>et al.</i> , 2014 ⁴⁵	(A) 61 with lymphoproliferative disorders and HGG (B) 33 previously treated with IV Ig	75 mg/kg weekly 16% or 20% SC Ig vs. previous IV Ig 300 mg/kg every 4 weeks Mean duration: 19 months SC Ig vs. 42 months IV Ig	<ul style="list-style-type: none"> ■ Compared with IV Ig, SC Ig achieved higher IgG trough levels and lower incidences of overall infection and need for antibiotics ■ Incidence of serious bacterial infections was similar with both treatments ■ Fewer AEs reported with SC Ig than with IV Ig, with no serious AEs ■ Fever reported in 34% receiving IV Ig and 7% receiving SC Ig ■ Other AEs with IV Ig included skin reactions (15%); any one or a combination of dizziness, nausea, and headache (9%); and dyspnea (9%) ■ Other AEs with SC Ig included infusion-site reactions (10%) ■ An overall improvement in quality-of-life parameters were demonstrated after the switch to SC Ig

^a Adapted from Dhalla *et al.*, 2014⁷.

^b Full name: Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia.

HGG = hypogammaglobulinemia; IV = intravenous; AE = adverse event; NHL = non-Hodgkin lymphoma; IgG = immunoglobulin G; SC = subcutaneous.

of severe bacterial infection (Table II). In addition, a study by Jurlander *et al.*⁴³ demonstrated a significant reduction in febrile episodes and hospital admissions related to infections in patients given iViG. Moreover, all studies have shown that iViG is relatively well tolerated in patients with CLL, with mild chills and fever being the most common toxicities (Table II). Such reactions can be managed with premedications such as acetaminophen and antihistamines as needed; steroids are also occasionally used in cases of severe reactions^{39,45}.

Dose and Administration

A number of trials have investigated the ideal dose of iViG in CLL (Table II). In studies examining iViG, the initial dose has ranged from 100 mg/kg to 800 mg/kg or a total dose of 10–24 g per infusion. The study by Sklenar *et al.*⁴¹ found the ideal dose to be 400 mg/kg every 3 weeks until a steady state is reached, followed by a maintenance dose of 400 mg/kg every 5 weeks. However, the study by Boughton *et al.*²⁰ that used a dose of 18 g every 3 weeks found that, by increasing the dose in patients with breakthrough infections, 50% were kept infection-free.

In PID, a meta-analysis of studies evaluating IgG trough levels showed a 27% reduction in the incidence of pneumonia with each 100 mg/dL increment in trough IgG, and individualized dosing has proved to be ideal in preventing infections^{46,47}. Similar results have been observed in dose evaluation studies in secondary immunodeficiency disorders, suggesting the need for regular medical evaluation of patients^{20,41}.

Studies to date have demonstrated that infections tend to occur when IgG levels are below approximately 6 g/L; however, not all patients with HGG develop infections²¹. That observation suggests that other factors—such as neutrophil count, functional ability, and natural killer cells—could play a part in the development of infections²¹. The study by Gamm *et al.*²¹ concluded that IGRT should be given at a lower dose (250 mg/kg monthly) in patients with either HGG (IgG < 6 g/L) or a history of serious infections and that the dose should be increased if breakthrough infections occur. Patients should therefore undergo regular monitoring for IgG level and titration of IGRT dosing to achieve an optimal IgG serum level that allows for freedom from recurrent infection⁷. As happens in PID, maintenance of higher IgG trough levels could be beneficial in patients with underlying comorbidities, particularly bronchiectasis⁷.

In addition to variability in dose, frequency of treatment has also varied, with IGRT being given every 3 weeks in five studies and every 4 weeks in four studies (Table II)^{20,21,39–45}. With respect to duration of therapy, most studies have been given iViG for a period of 1 year (Table II)^{20,21,39,40,42,43}. However, CLL is a chronic and progressive disease, with HGG becoming more prevalent with advanced disease. It stands to reason that IGRT might be required for more than the artificial 1 year cut-off used in experimental study designs.

More recently, subcutaneous formulations of IGRT have been developed that ease administration, reduce adverse effects, and improve quality of life (QOL). Table III presents a comparison of the advantages and disadvantages of iViG and sCiG. The sCiG formulation was examined in a study

TABLE III Advantages and disadvantages of intravenous and subcutaneous immunoglobulin

Variable	Intravenous	Subcutaneous
Administration	Once every 3–4 weeks by nurse in hospital	Flexible: weekly dose (or double dose every 2 weeks) administered by patient at home and when travelling
Efficacy	Reduces frequency and severity of serious bacterial infections equally	
Venous access required?	Yes	No
Nursing required?	Yes, to administer in medical facility	Yes, for initial training of patient
Systemic AEs ^a	More common	Infrequent
Local AEs	Infrequent	Expected and mild
Training required?	No special skills required by patient or family	Requires training of patient or family, good dexterity, good vision, capacity to learn new technique
Costs	Patient: Loss of work, travel, parking Hospital: Nursing hours, equipment	Saves patient: approximately \$1000–\$1500 annually Saves government: approximately \$2000–\$2600 annually

^a For example, anaphylactoid reaction.
AE = adverse event.

by Compagno *et al.*⁴⁵ of patients with lymphoproliferative disorders and HGG (Table II). Compared with IVIG, the SCIG formulation resulted in higher IgG trough levels, fewer infections, and less need for antibiotics. In addition, a reduction in the number of adverse events and an improvement in QOL parameters were seen with SCIG compared with IVIG. In the PID setting, SCIG has proved to be as effective as IVIG, with reduced variations in peak and trough IgG levels and a better safety profile²⁷. In addition, QOL is improved with SCIG because of improved convenience, making it suitable for self-injection by patients who are unable to travel or who have vascular access issues (Table III).

Cost-Effectiveness of Ig Therapy

Despite multiple studies demonstrating efficacy, a common concern precluding the routine use of IGRT in patients with CLL pertains to cost-effectiveness. The concern stems, at least in part, from a paper published in 1991 by Weeks *et al.*⁴⁸ that analyzed the costs and benefits of IGRT in patients with CLL. In their economic model, which was based on data from the Cooperative Group trial³⁹, the statistically significant decrease in bacterial infections was offset by two variables: the detrimental impact of IGRT on QOL, and the absence of effect on 1-year survival.

The effect of IVIG on QOL was driven primarily by the inconvenience associated with intravenous infusion, which must be given in a hospital setting over several hours every 3 or 4 weeks. When the inconvenience of the treatment modality was not considered, IVIG resulted in a gain of 0.8 quality-adjusted days per patient per year of therapy at a cost of \$6 million per quality-adjusted life-year gained. Additionally, the absence of benefit on mortality at 1 year should be viewed with caution, given that CLL is a chronic, progressive disease and the effect of interventions on survival might not be detected at the censored 1-year mark. For example, Molica *et al.*⁴⁹ estimated the 5-year risk of developing severe infection in patients with low IgG (<6.5 g/L) to be 57.1%. The cost of infections can be substantial, with one U.S. study showing a cost of \$38,574 per hospitalized patient⁵⁰. Given the risk of infections in CLL patients with HGG, the improved survival

of such patients with emerging chemotherapies, and the development of more convenient SCIG formulations, the cost-effectiveness of IGRT should be reconsidered.

A number of studies have shown that, compared with IVIG, SCIG results in reduced resource utilization and improved cost-effectiveness. A study by Haddad *et al.*⁵¹ in PID showed that higher doses of SCIG (mean: 213 mg/kg vs. 120 mg/kg weekly) resulted in lower rates of nonserious infections (2.76 episodes vs. 5.18 episodes annually, $p < 0.0001$), hospitalization (0.20 vs. 3.48 days annually, $p < 0.0001$), antibiotic use (48.50 days vs. 72.75 days annually, $p < 0.001$), and missed work or school activities (2.10 vs. 8.00 days annually, $p < 0.001$). In addition, studies comparing the cost-effectiveness of SCIG and IVIG demonstrated savings of \$2000–\$2500 per patient per year with SCIG (Table III)^{52,53}. A study evaluating the cost savings of SCIG in a Canadian setting found the net economic gain from switching 1 patient with PID or secondary immunodeficiency disorder to home-based SCIG care to be \$2,603 in the first year and \$2,948 in each subsequent year⁵⁴. In addition, every 37 patients treated with SCIG instead of IVIG resulted in the gain of 1 nursing full-time equivalent. Although no similar pharmacoeconomic study has been formally conducted for SCIG in patients with CLL, the consistent savings with the SCIG formulation argue that that formulation could be a viable option for those who see IVIG as being cost-prohibitive.

CANADIAN PERSPECTIVE

Although the evidence is based primarily on studies that pre-date the modern chemotherapies used for CLL, the data indicate a consistent beneficial effect of IGRT in reducing serious bacterial infections in CLL. The utility of IGRT in reducing viral infections is unclear and is not currently supported by the evidence. Despite the evidence of benefit, the major ongoing debate in this area relates to the type of CLL patient who should be considered for IGRT. That debate requires a re-analysis of the inclusion criteria used in the studies.

The pivotal work by the Cooperative Study Group was explicit in stating that their data do not indicate that all

patients with CLL should receive Ig therapy³⁹. That conclusion was based on the fact that not all CLL patients receiving IVIG were prevented from having infections; however, that conclusion might not be any more realistic than assuming that chemotherapy cures all patients with leukemia. The Cooperative Study Group's enrolment criteria included CLL patients with an increased susceptibility to infection, defined either by an IgG level at 50% or less of the lower limit of normal (typically <4 g/L) or a history of 1 or more serious infections³⁹. In the era of evidence-based medicine, patients meeting those criteria are the ones to whom the study data could (or should) be applied. The beneficial effect noted in the crossover follow-up study by Griffiths *et al.*⁴⁰ used the same definitions, as did the studies by Chapel *et al.*⁴² and Molica *et al.*⁴⁴.

On the other hand, the prevailing paradigm, iterated by Rai and Sawitsky⁵⁵ in 1991 and used in the studies by Jurlander *et al.*²⁰ and Boughton *et al.*⁴³, suggests that IVIG should be used only for CLL patients with reduced serum IgG levels and a history of 1 major infection. However, the caveat to that condition is that the sentinel major infection could be fatal, because the HGG might lead to any one or more of severe respiratory tract infection, extrapulmonary dissemination (for example, bacteremia, meningitis), and sepsis⁵⁶. Prophylaxis against such infections might be preferable to a preemptive strategy of selecting a cohort of patients who have survived a severe infection for eventual IGRT.

Although IGRT does not improve survival in patients with CLL, various chemoimmunotherapeutic regimens have shown a survival advantage and can be associated with significant immunosuppression. Some of those agents predispose patients to distinct opportunistic infections (for example, cytomegalovirus with alemtuzumab), necessitating routine antimicrobial prophylaxis. However, none restore humoral immunity, which is the underlying problem in patients with CLL. Given the improvement in survival with newer CLL regimens and the profound B-cell depletion after B cell-directed therapy (for example, monoclonal antibodies, chimeric antigen receptor T cells), re-evaluation of immunoprophylaxis with IGRT should be considered.

With respect to the cost-effectiveness of IGRT, Weeks *et al.*⁴⁸ justifiably argued that the inconvenience and costs associated with IVIG are a major barrier to its use. On the other hand, because of the availability of SCIG, IGRT need no longer be given intravenously; in fact, SCIG is now the mainstay of administration in patients with a genetic basis for HGG⁵⁷. In such patients, SCIG is considered equally as efficacious as IVIG with respect to a reduction in the frequency and severity of respiratory tract infections⁵⁷. Additionally, SCIG achieves steady serum levels, avoiding the peaks and troughs associated with IVIG administration; whether that lesser variation is associated with fewer periods at risk for infection remains plausible, but unproven^{34,45}.

Suggested Algorithm for the Use of IGRT in CLL

The protocol presented in Figure 1 outlines a proposed algorithm for the use of IGRT in patients with CLL. It is based on current evidence and the clinical experience of the authors.

CONCLUSIONS

Infections are a major cause of morbidity and mortality in patients with CLL and are largely associated with the HGG related to CLL and its treatment. The use of IGRT reduces the frequency of bacterial infections and associated hospitalizations in patients with HGG or a history of infection, or both. Patients with CLL should therefore be monitored to determine the potential benefit of IGRT in reducing their risk of infection.

Data for the use of IGRT in CLL are limited and largely based on studies conducted before the advent of standard chemoimmunotherapy. Given that the newer treatment regimens do not correct the HGG associated with CLL, the use of IGRT has to be re-evaluated in the current setting. In addition, the availability of subcutaneous formulations of IGRT appears to reduce the cost and inconvenience of hospital-based intravenous administration, suggesting that the cost-effectiveness of IGRT should be reassessed. Finally, as the development of novel CLL treatments continues, the impact of therapy on humoral immunity and infection risk will have to be closely monitored and periodically reassessed.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare the following interests: All authors received an honorarium from CSL Behring for their participation in this paper. EH has received honoraria for advisory board participation and has received funding for an investigator-initiated trial from CSL Behring Canada. DCV is supported by a Chercheur-boursier clinicien award from the Fonds de recherche du Québec en Santé (FRQS) and has received honoraria from CSL Behring Canada, Pfizer Canada, and Sunovion for advisory board participation and from CSL Behring Canada, Sunovion, and Merck Canada for speaking events. DCV has also received funding from Astellas Canada and CSL Behring Canada for an investigator-initiated trial. CLT and CS have received honoraria from CSL Behring Canada for advisory board participation. JKL has received grants and research support from CSL Behring, Sanofi, AstraZeneca, Novartis, GlaxoSmithKline, and ALK-Abello Pharmaceuticals. JKL has also received honoraria for speaking events and consulting fees from Pfizer, Merck, Teva, Meda, AstraZeneca, Novartis, Sanofi, CSL Behring, Takeda, ALK-Abello Pharmaceuticals, Hollister-Stier Laboratories, and Alcon. BCR has provided unpaid consulting advice to Baxter, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Canadian Blood Services, Canadian Hemophilia Society, Covidien, CSL Behring, Dyax, Genzyme, Leo Pharmaceuticals, Novartis, Novo Nordisk, Octapharma, Pharmacyclics, Pfizer, Sanofi, Shire, Talecris, and Wyeth. BCR has also received funding for investigator-initiated studies from Baxter, CSL Behring, Novartis, Novo Nordisk, Pfizer, and Wyeth. LHS, DAS, and SL have no other conflicts of interest to declare.

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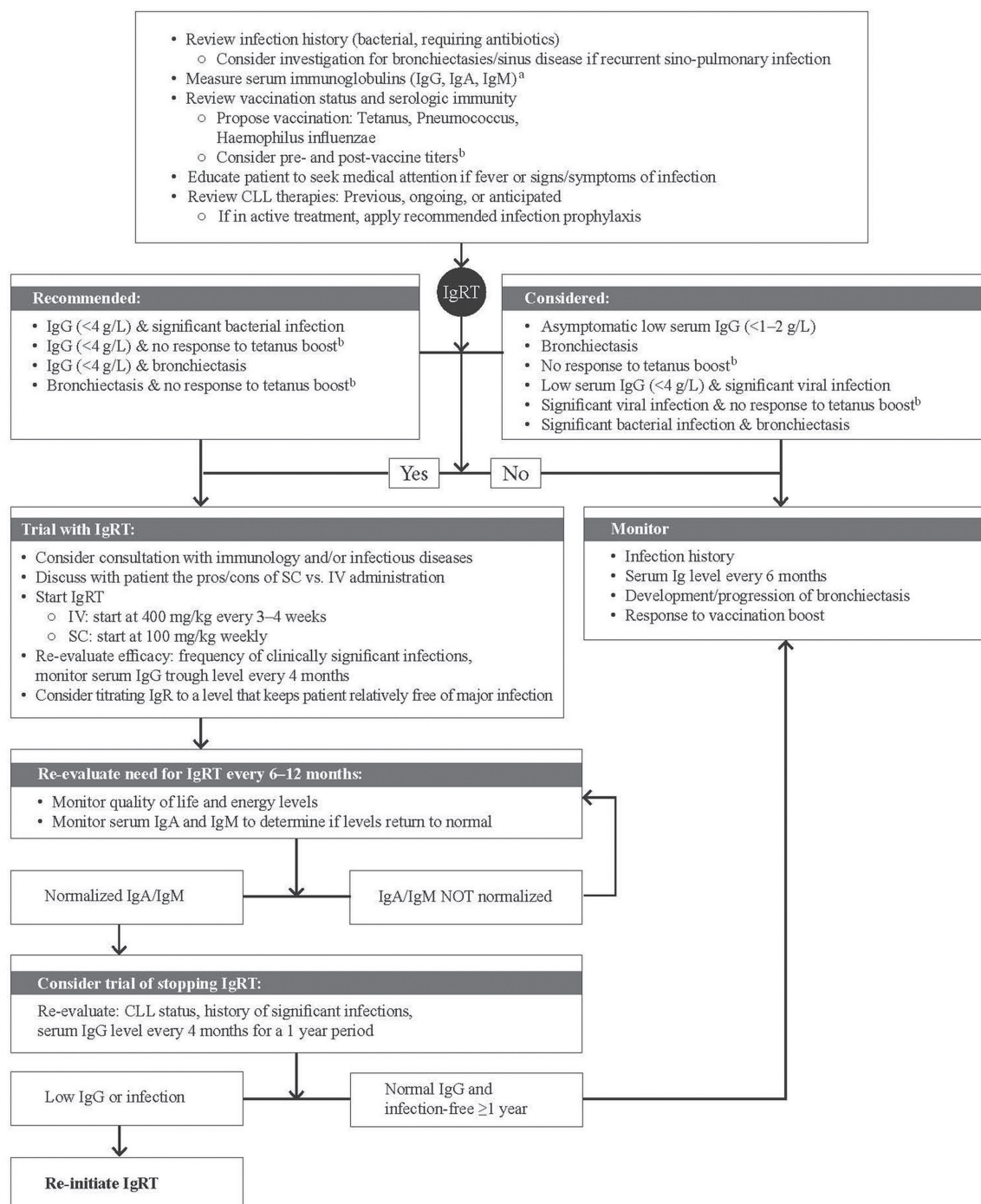


FIGURE 1 Treatment algorithm for the use of immunoglobulin replacement therapy in chronic lymphocytic leukemia (CLL). ^a Where a patient has “normal” levels of immunoglobulin G (IgG), but a phenotype consistent with humoral immunodeficiency, the patient should be evaluated for monoclonal gammopathy. ^b Response to vaccination before and after boost. For example, for tetanus, obtain serum for a pre-vaccine titer, then administer the vaccine (same day), and 4 weeks later, measure the response to boost. IgA/M = immunoglobulin A/M; IGRT = immunoglobulin replacement therapy; SC = subcutaneous; IV = intravenous; IgR = immunoglobulin replacement.

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