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ASTUTE CLINICIAN REPORT

Antibody Deficiency Secondary to Chronic Lymphocytic Leukemia: Should Patients be Treated with Prophylactic Replacement Immunoglobulin?

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Abstract Hypogammaglobulinemia is a common finding in chronic lymphocytic leukemia (CLL). Its incidence increases with disease duration and stage such that it is present in up to 85 % of patients at some point in their disease course. It is therefore important to monitor patients for the development of an antibody deficiency. However, not all patients with antibody deficiency secondary to CLL are symptomatic with bacterial infections. In addition patients are susceptible to viral, fungal and opportunistic infections as a result of iatrogenic immunosuppression and through a variety of disease-related mechanisms, which affect cellular immunity and phagocytes. Published guidelines suggest that patients with a history of recurrent bacterial infections and a documented failure of antibody production should be treated with antibiotic prophylaxis in the first instance, with replacement immunoglobulin reserved for those who continue to suffer with significant bacterial infections. Here we present a review of the existing literature in order to provide a practical approach, based on best available evidence, to the investigation, monitoring and treatment of patients with antibody failure secondary to CLL; and we highlight areas in which further studies are needed.

Keywords CLL · hypogammaglobulinemia · replacement immunoglobulin

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Introduction

Infections are a major cause of morbidity and mortality in CLL, contributing to between 25 % and 50 % of deaths [1]. Their etiology is multifactorial, due to a combination of disease-related immune defects and iatrogenic immunosuppression affecting both humoral and cellular immunity [1, 2]. This is reflected in the spectrum of infections seen. Bacterial infections occur most frequently and predominantly affect the respiratory tract but also the skin, urinary and gastrointestinal tracts, and bloodstream [3]. Patients are at risk of reactivation of latent herpes viruses after treatment with purine analogues and alemtuzumab [2], and opportunistic infections after alkylating agents, alemtuzumab or combination chemotherapy [1, 2].

Hypogammaglobulinemia is present in up to 85 % of patients at some point during the disease [1]. Its prevalence and extent correlates with disease duration, advancing stage [3, 4] and infection frequency [3, 5]. The mechanisms by which hypogammaglobulinemia develops in CLL are poorly understood but thought to involve defective help and excessive suppression by T-cells [6], dysfunction of non-clonal $CD5^-$ B-cells [7], subversion of T-cell help by CLL cells in pseudofollicles [1] and direct suppression of $CD95^+$ bone marrow plasma cells via interaction with CD95L on CLL B-cells [8].

Strategies to prevent bacterial infections in patients with secondary antibody deficiencies include prophylactic antibiotics or replacement immunoglobulin. However, the cost-effectiveness of the latter has been criticized [9].

We have summarized the existing data in an attempt to provide a practical approach to the management of patients with antibody deficiency secondary to CLL. A new protocol, based on best available evidence, is proposed that can be used to collect prospective data in order to confirm or refute current guidelines.

Monitoring for and Investigation of Secondary Antibody Deficiency in CLL

Monitoring for a Symptomatic Antibody Deficiency

The British Committee for Standards in Hematology (BCSH) recommend that the initial assessment after CLL diagnosis should include an infection history and measurement of serum immunoglobulins [10], though this is not currently part of American guidelines [11]. Not all patients with hypogammaglobulinemia secondary to CLL have significant infections [5], although a proportion go on to become symptomatic. It is therefore of critical importance to seek a history of recurrent or severe bacterial infections so that *symptomatic* patients requiring further investigation can be identified. As the proportion of patients with hypogammaglobulinemia increases with disease duration, it is necessary to monitor patients with normal immunoglobulins at diagnosis, and to repeat the serum immunoglobulin levels every 6–12 months, and after significant bacterial infections or immunosuppressive therapy.

Immunization Responses

Antibody responses to protein and polysaccharide immunizations are used to define B-cell function in the investigation of suspected immunodeficiencies, in order to select patients likely to benefit from replacement immunoglobulin. Studies in *unselected* patients with CLL have demonstrated poor immunization responses, particularly to pneumococcal polysaccharide with response rates ranging from 0 to 22 % [12–14]; this increases to 35–47 %, depending on serotype, with the 7-valent conjugate vaccine [15]. 27–43 % respond to *Haemophilus influenzae* type b conjugate [13, 14] and 24–65 % to tetanus toxoid [12, 13]. Patients who make adequate responses are more likely to have early-stage CLL, normal serum immunoglobulins, and be chemotherapy naïve.

Although no trial has specifically looked at the value of immunization responses in predicting infection risk or response to immunoglobulin treatment in CLL, a retrospective study found low levels of pre-existing anti-pneumococcal antibodies to be more significantly associated with a significant infection history ($p<0.00001$) than the serum IgG concentration ($p<0.001$) [5].

Although no specific data exists, the evidence above, together with that from plateau-phase multiple myeloma [16] and experience from primary antibody deficiencies, suggests that immunization responses to pneumococcal polysaccharide could be used to stratify infection risk and select patients for immunoglobulin therapy, provided that the infection history and degree of hypogammaglobulinemia are taken into account. Patients who fail to respond could be offered the conjugate vaccine as this might offer protection. Finally, caution is advised as although serotype-specific assays are commonly used to assess responses to pneumococcal immunization, interpretation is complex, cut-off levels vary and there is controversy surrounding what constitutes an adequate response [17]; each laboratory should therefore determine cut-offs using age-matched controls.

Other Investigations

The neutrophil count should be monitored, as neutropenia will contribute to infection risk and may affect the efficacy of replacement immunoglobulin therapy via impaired phagocytosis of opsonized bacteria [16]. In addition, pulmonary function tests and cross-sectional imaging of the lungs may be indicated, since prevention of development/progression of bronchiectasis should be a key objective.

Treatment of Secondary Antibody Deficiency in CLL

Prophylactic Antibiotics

The recommended first-line treatment for symptomatic antibody deficiency in CLL is antibiotic prophylaxis [10]. However clinical trials are lacking, and this does not distinguish between patients with and without bronchiectasis. In lieu of specific data, the choice of antibiotic will depend on the patient's infection history and cultures. In practice, infections are usually due to common respiratory pathogens, so azithromycin is often used. It has good mucosal penetration, a long half-life permitting three times per week dosing, and established efficacy in the setting of non-cystic fibrosis bronchiectasis [18]. If there are significant breakthrough bacterial infections or development/progression of bronchiectasis despite antibiotic prophylaxis, replacement immunoglobulin should be considered [10]. Patients who initially respond should be reassessed during winter as there may be seasonal variation in infection frequency [19].

Prophylactic Replacement Immunoglobulin

Randomized controlled trials conducted in the 1980s (see Table I) found IVIg to be effective in reducing the incidence of bacterial infections in patients with CLL and hypogammaglobulinemia and/or a history of infections [20–22]. Not surprisingly, no significant effect on all-cause mortality was detected after follow-up for 1 year [20].

In the 1990s, several other trials examined the effect of dose (see Table I) [22–25]; 500 and 250 mg/kg/month were equally efficacious [24]. An attempt to use antibodies against pneumococcal serotypes for monitoring found the optimal dose to be 400 mg/kg/3 weeks until steady-state is reached, followed by 400 mg/kg/5 weeks [26]. A trial of fixed dose IVIg (18 g/3 weeks) found that if the dose was increased to 24 g in patients with breakthrough infections, 50 % could be kept infection free [22]. Thus, as in primary antibody deficiency, the dose must be individualized to prevent breakthrough bacterial infections [19].

The impact of replacement immunoglobulin on mortality and quality of life, and therefore its cost-effectiveness in CLL was questioned [9]. However, the analysis was based on the first randomized controlled trial [20] before specific antibody testing was available and in the absence of selection criteria to identify patients most likely to benefit from IVIg. Since that time modern treatment strategies for CLL, including combination chemotherapy and monoclonal antibodies, have improved survival [27], and subcutaneous immunoglobulin and self-infusion programs have reduced costs [28] and improved quality of life [29].

Table I Summary of evidence for the use of replacement immunoglobulin in CLL

Study	Design	Participants	Intervention	Comparator	Outcomes
Efficacy					
Cooperative Group 1988 [20]	Double blind, randomized	• 81 patients with CLL • Low Igs &/or infections	400 mg/kg IVIg every 3 weeks for 1 year	Placebo (saline)	• Fewer bacterial infections overall • Fewer moderate bacterial infections • Longer time to 1st serious bacterial infection • No difference in non-bacterial infections • No difference in all-cause mortality at 1 year • No serious adverse reactions
Griffiths et al. 1989[21]	Double blind, randomized, cross over	• 8 patients with CLL, 4 patients with NHL • Low Igs &/or infections	400 mg/kg IVIg every 3 weeks for 1 year	Placebo (saline)	• Fewer serious bacterial infections • Serious bacterial infection associated with IgG <6.4 g/l • No difference in trivial infections • No serious adverse reactions
Dose					
Chapel et al. 1994[24]	Double-blind, randomized	• 34 patients with CLL • Low Igs &/or Infections	500 mg/kg IVIg every 4 weeks for 1 year	250 mg/kg IVIg	• No difference in infection frequency • No difference in all-cause mortality • No serious adverse reactions
Jurlander et al. 1994[23]	Open Label	• 15 patients with CLL • Low Igs & infections	10 g IVIg every 3 weeks	Infection frequency before IVIg	• Fewer hospital admissions • Fewer febrile episodes • No difference in antibiotic prescriptions • No difference in severe infections • Long stabilization period
Boughton et al. 1995[22]	Double blind, randomized	• 42 patients with CLL • Low Igs & infections	18 g IVIg every 3 weeks for 1 year Dose increased to 24 g if 3 breakthrough infections	Placebo (albumin)	• Fewer bacterial infections overall • Fewer serious bacterial infections • 50 % who required dose increase subsequently infection free • Majority of infections occurred when IgG <3 g/L
Sklenar et al. 1993[26]	Randomized, parallel group Objective: to find optimal dose to produce protective titers of pneumococcal antibodies	• 31 patients with CLL, 31 patients with MM	3 groups: 100 mg/kg IVIg 400 mg/kg IVIg 800 mg/Kg IVIg every 3 weeks	3 groups compared	• Optimal dose for CLL was 400 mg/kg • Steady state reached after 11–12 weeks/4 infusions • Suggested 400 mg/kg every 3 weeks until week 12 then 400 mg/kg every 5 weeks

Igs immunoglobulins, *NHL* non-Hodgkin's Lymphoma, *MM* multiple myeloma

In conclusion, patients with antibody failure need to be identified by immunization and monitored. Those with a history of bacterial infections should receive prophylactic antibiotics for 3 months and if they fail to benefit, replacement immunoglobulin starting at 400 mg/kg/month [10]. Objective clinical measures and trough IgG levels should be used to guide dose adjustments. As in primary antibody failure, patients with bronchiectasis may benefit from higher doses [19]. Although hypogammaglobulinemia secondary to CLL has been regarded to be irreversible [2], there is evidence that newer treatment strategies, such as those involving high-dose Rituximab [30], can restore antibody production, so the ongoing need for immunoglobulin replacement should be reviewed in all patients. There is no data to support treating those with secondary antibody failure who have *not* had a bacterial infection, although these patients may go on to develop significant infections and should be closely monitored.

Suggested Protocol for Investigation, Monitoring and Treatment

Based on best evidence and experience in our center we have suggested a protocol (see Fig. 1) which provides a practical

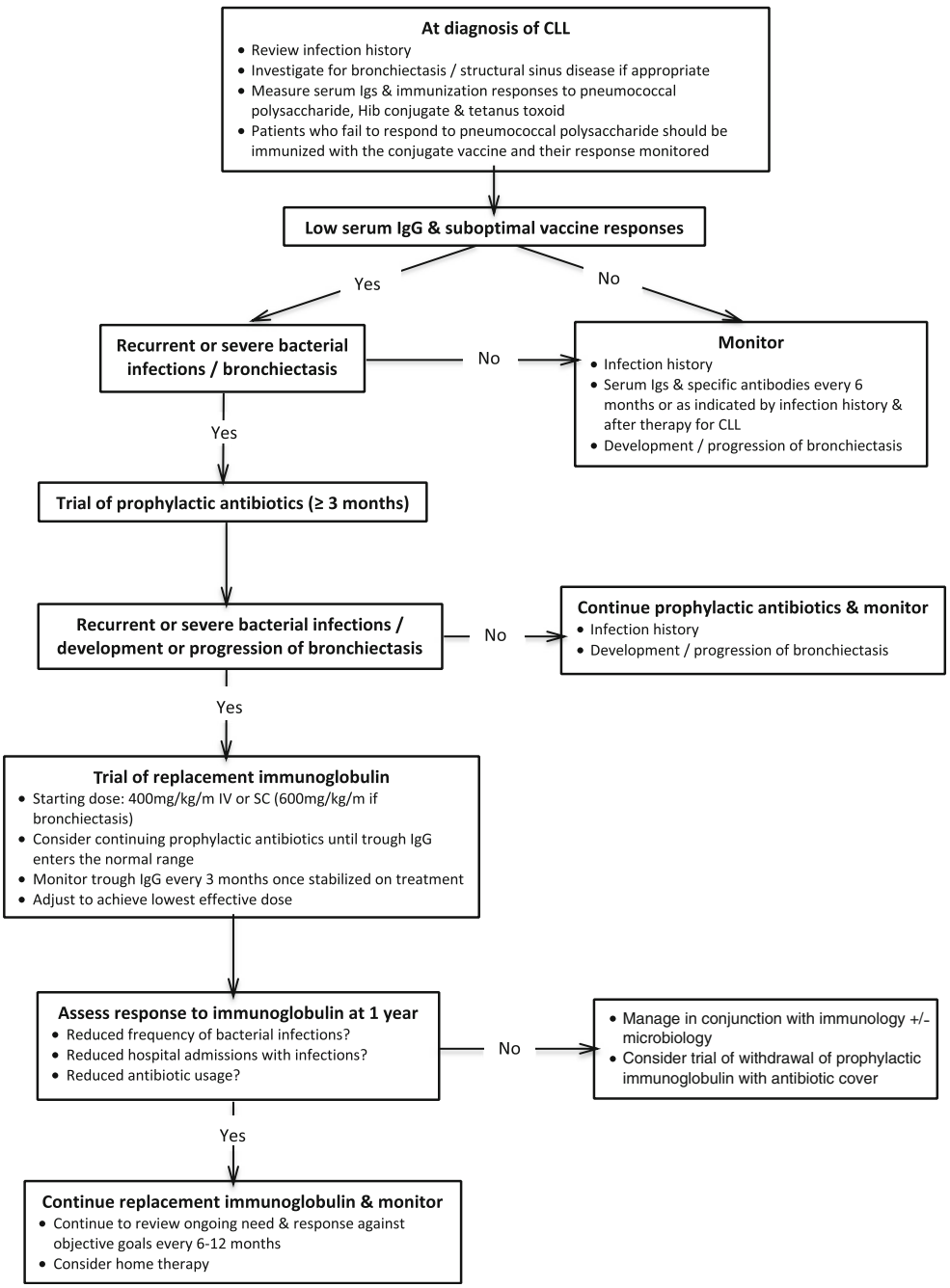

Fig. 1 Suggested protocol for the investigation, monitoring and management of antibody failure in CLL. Abbreviations: *Igs* immunoglobulins, *Hib* H. influenzae B, *mg/kg/m* milligrams per kilogram per month, *IV* intravenous, *SC* subcutaneous

approach to the management of antibody failure secondary to CLL and serves as a framework for collecting prospective data necessary to validate current practice.

Future Directions/Conclusions

The evidence suggests that replacement immunoglobulin is effective in carefully selected patients with antibody deficiency secondary to CLL. New trials are needed to determine the efficacy and safety of long-term prophylactic antibiotics as well as the predictive value of immunization responses. For those requiring immunoglobulin therapy, data is needed regarding its efficacy, cost-effectiveness and impact on quality of life since the advent of careful patient selection, newer chemotherapeutic strategies, and subcutaneous immunoglobulin, which can be self-administered at home.

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