Immunoglobulin replacement for secondary immunodeficiency after B-cell targeted therapies in autoimmune rheumatic disease: systematic literature review

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Abstract:

Background: Consensus guidelines are not available for the use of immunoglobulin replacement therapy (IGRT) in patients developing iatrogenic secondary antibody deficiency following B-cell targeted therapy (BCTT) in autoimmune rheumatic disease.

Objectives: To evaluate the role of IGRT to manage hypogammaglobulinemia following BCTT in autoimmune rheumatic disease (AIRD).

Methods: Using an agreed search string we performed a systematic literature search on Medline with Pubmed as vendor. We limited the search to English language papers with abstracts published over the last 10 years. Abstracts were screened for original data regarding hypogammaglobulinemia following BCTT and the use of IGRT for hypogammaglobulinemia following BCTT. We also searched current recommendations from national/international organisations including British Society for Rheumatology, UK Department of Health, American College of Rheumatology, and American Academy of Asthma, Allergy and Immunology.

Results: 222 abstracts were identified. Eight papers had original relevant data that met our search criteria. These studies were largely retrospective cohort studies with small patient numbers receiving IGRT. The literature highlights the induction of a sustained antibody deficiency, risk factors for hypogammaglobulinemia after BCTT including low baseline serum IgG levels, how to monitor patients for the development of hypogammaglobulinemia and the limited evidence available on intervention thresholds for commencing IGRT.

Conclusion: The benefit of BCTT needs to be balanced against the risk of inducing a sustained secondary antibody deficiency. Consensus guidelines would be useful to enable appropriate assessment prior to and following BCTT in preventing and diagnosing hypogammaglobulinemia. Definitions for symptomatic hypogammaglobulinemia, intervention thresholds and treatment targets for IGRT, and its cost-effectiveness are required.

Keywords: rituximab, anti-CD20, vasculitis, ANCA, hypogammaglobulinemia, infection

Abbreviations: AIRD = autoimmune rheumatic disease, **AAV =** ANCA-associated vasculitis, BCTT= B-cell targeted therapy, DoH = Department of Health, EULAR = European League Against Rheumatism, GPA = granulomatosis with polyangiitis, **IGRT=** immunoglobulin replacement therapy, RA =

Rheumatoid arthritis, SLR = systematic literature review, SPUR = serious, persistent, unusual or recurrent, UK= United Kingdom

Take home messages

1. Immunoglobulin replacement therapy for secondary hypogammaglobulinemia is increasing, due to B-cell targeted therapy use in autoimmune rheumatic diseases. There are no consensus guidelines available for immunoglobulin replacement in this population.
2. This review highlights the currently available literature, including risk factors for hypogammaglobulinemia after B-cell targeted therapy, how to monitor for development of hypogammaglobulinemia, and intervention thresholds for commencing immunoglobulin replacement.
3. The need for consensus guidelines is highlighted for the appropriate assessment to prevent and to diagnose hypogammaglobulinemia early, and to optimize the management of immunoglobulin replacement therapy in this group.

1. Introduction

Primary immunodeficiency (PID) is due to inherited or sporadic genetic mutation(s), and may have unknown environmental cofactors, but no other known cause [1,2]. Secondary immunodeficiency (SID) may occur consequent to disease or effects of drugs or therapies [3,4]. Immunoglobulin replacement therapy (IGRT) for drug-related secondary hypogammaglobulinemia is increasing, due to the use of B-cell targeted therapies (BCTT) for management of autoimmune rheumatic diseases (AIRD) and B-cell lymphoproliferative disease. Hypogammaglobulinemia is characterised by reduction in circulating immunoglobulins (Ig) and can predispose to severe and recurrent infections [6]. Underlying immune dysfunction and prolonged immunosuppressive drug use result in patients being at greater risk of infection, a major cause of morbidity and mortality in this population [3].

BCTT are effective treatments, but concerns remain over the long-term effects on humoral immunity with potential development of hypogammaglobulinemia and increased risk of infection [7, 8, 9, 10].

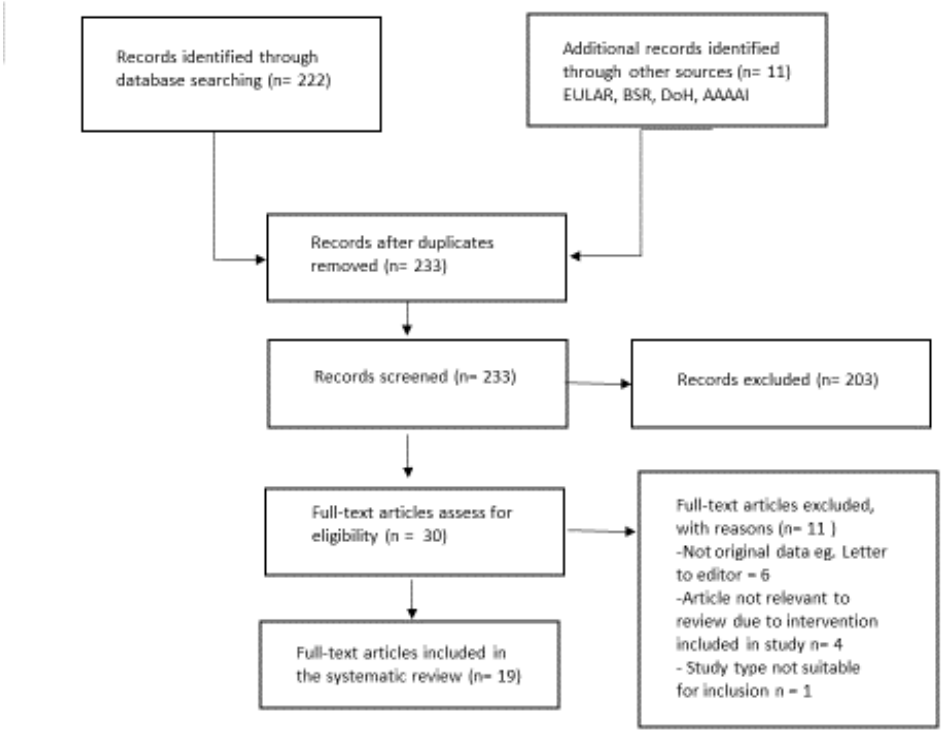
CD20+ B-cells are depleted by rituximab on average for 6–12 months, though there is substantial variability with longer periods of depletion observed in ANCA-associated vasculitis (AAV) [7]. Mature plasma cells do not express CD20 and are the source of 95% of circulating immunoglobulin G (IgG) [7]. Most patients do not have residual immune dysfunction as B-cell numbers typically recover, and early reports suggested no major effect on serum immunoglobulins [11, 12]. Hypogammaglobulinemia and associated infection risks are thought to be secondary to prolonged depletion of plasma cell precursors, which may contribute to reduced replenishment of mature plasma cells [7, 13]. There is limited data on the frequency of IGRT for rituximab-associated hypogammaglobulinemia, ranging from 6.6% in lymphoma to 14 -21% in systemic vasculitis [14]. Reports also are found in immune thrombocytopenia treated with BCTT [15].

Currently consensus guidelines are not available for the use of IGRT in patients developing iatrogenic secondary antibody deficiency following either BCTT or other immunosuppressive therapies in AIRD. This review evaluates the current literature in adults to aid diagnostic and therapeutic decision making for clinicians. We have not addressed the paediatric literature; however, the information may be of interest to paediatricians managing AIRD patients.

2. Methods

This systematic literature review (SLR) was performed in accordance with the Scottish Intercollegiate Guidelines Network (SIGN) methodology [16]. The search topics included in the SLR were identified through a Delphi process. We used the following search string on 1st September 2018- "(Immunologic Deficiency Syndromes"[Mesh] NOT "HIV Infections"[Mesh]) AND (("Antibodies, Monoclonal"[Mesh] OR "Abatacept"[Mesh] OR "TACI receptor-IgG Fc fragment fusion protein"[Supplementary Concept]) OR ("Immunoglobulin G/administration and dosage"[Mesh] AND "Immunoglobulin G/therapeutic use"[Mesh])) NOT ("case reports"[pt] OR "Review"[pt])". The results were limited by using the filters 'abstracts' 'English language' and 'published in last 10 years'. Of the 222 papers identified, data was harvested from 8 original articles. SIGN checklist screening of each article was performed prior to inclusion. Data from the current publications produced by national/international organisations were also reviewed, and the reference lists hand searched. These included: British Society for Rheumatology, UK Department of Health, European League Against Rheumatism, European Society for Immunodeficiencies, American College of Rheumatology, and American Academy of Allergy, Asthma, & Immunology, yielding a further 11 publications (Figure 1).

Figure 1: Selection of studies flowchart



3. Results

3.1 Distinction between purely numerical hypogammaglobulinemia and symptomatic hypogammaglobulinemia

The current literature provides no definition to differentiate purely numerical from symptomatic hypogammaglobulinemia. Studies included in this review defined hypogammaglobulinemia at varying levels of <4 to <7.5 g/L [Table 1]. The lower limit of the normal range may vary depending on age,

population, and the particular assay [8]. Specific cut-off IgG levels necessitating IGRT are unclear. Many patients are asymptomatic with low IgG levels and IgG levels may recover following BCTT. In one series of 243 patients with systemic autoimmune disease who received rituximab, 26% developed moderate (defined as 3-4.9 g/L) or severe (< 3 g/L) hypogammaglobulinemia. This was often transient and improved spontaneously in approximately 50% of cases [8]. This study reported IgG levels in patients who develop hypogammaglobulinemia within 6 months of the first rituximab dose may recover spontaneously without use of IGRT [8]. Hypogammaglobulinemia at the initiation of rituximab treatment is suspected to be multifactorial, such as due to active disease or other treatments, and may be transient. However later onset hypogammaglobulinemia after rituximab is considered more likely to be sustained, and related to prolonged B-cell depletion [8]. As by far the dominant BCTT agent in clinical use is rituximab, the available data are concentrated on this medication, with no data available for other depleting BCTT such as ocrelizumab in AIRD.

In an 11-year study incorporating 3595 rituximab-treated patients with rheumatoid arthritis (RA), 143/3595 (4%) developed IgG below the reference range for at least 4 months [17]. Interestingly, in patients who developed low IgG, serious infection rates were higher than patients who never developed low IgG and higher than the all-exposure population, both before and after development of low IgG levels. The author surmised these patients might have an intrinsically higher infection inherent risk.

Table 1: Summary table of studies in systematic literature review

Study	Design	Number of patients	AIRD	RTX dosage and other	Other immunosuppression	Immunoglobulin levels	IGRT used No. of patients
Roberts et al. 2015 [8]	Retrospective study	243	GPA/MPA/ EGPA/SLE/ Other	Median 6g	Prior CYC 6g and glucocorticoids. Variable prior exposure to other DMARDs	IgG mild 5-6.9 g/L, moderate 3-4.9 g/L and severe <3 g/L	12
Roberts et al. 2015 [14]	Case series: subset from Roberts et al. 2014	12	GPA/MPA/ EGPA/SLE/ Other	Median 6g	Prior CYC 6g and glucocorticoids. Variable prior exposure to other DMARDs	IgG mild 5-6.9 g/L, moderate 3-4.9 g/L and severe <3 g/L	12 (10/12 SLE)
Cortazar et al. 2017 [18]	Retrospective evaluation	229	AAV	Induction therapy: combination therapy with RTX [2g], CYC, and high-dose steroids. Maintenance therapy: RTX with or without low-dose prednisone		Significant hypogammaglobulinemia, IgG<4g/L.	5 (maintenance group)
Gottenberg et al. 2010 [21]	Cohort study	1303	RA	416 patients treated with RTX alone and 821 patients treated with RTX plus a nonbiologic DMARD.	Prior anti-TNF and DMARDS. Pre-medication corticosteroids in 1004 patients.	Hypogammaglobulinemia IgG<6 g/L	-
Makatsori et al. 2014 [32]	Retrospective review Case series from audit of 114	19	4 RA 2 SLE 13 other (haematological)	Not specified	Yes but not specified	Hypogammaglobulinemia IgG≤4g/L.	18
Besada et al 2014 [20]	Cohort study	29	GPA	Median cumulative dose 9g after RTX initiation.	Prior CYC, concurrent prednisolone and other immunosuppression	Hypogammaglobulinemia <6 g/L	5
Marco et al. 2014 (7)	Retrospective review	177	Primary systemic vasculitis/ GPA/MPA/EGPA/ SLE/ Behcet's disease/ HSP	Median 5.9g	CYC, MMF, HCQ, AZA, MTX, 5% other	Mild (IgG 5–5.9 g/L), moderate (3–4.9 g/L) and severe (<3 g/L).	6
Venhoff et al. 2014 [22]	Retrospective analysis	37	GPA/MPA	RTX induction regimens : 2 infusions of 0.5 g each in 7 patients and 1 g each in 30 patients.	RTX induction therapy, followed by maintenance with DMARDs. Previous CYC in 92%.	Hypogammaglobulinemia IgG<5g/L	-

CYC = cyclophosphamide, RTX = rituximab, CTD =connective tissue disease RA= rheumatoid arthritis, GPA = Granulomatosis with Polyangiitis, MPA = microscopic polyangiitis, AAV= ANCA-associated vasculitis, EGPA = Eosinophilic Granulomatosis with Polyangiitis, SLE = systemic lupus erythematosus, HSP = Henoch-Schonlein purpura, TNF= tumor necrosis factor, DMARD = Disease-modifying anti-rheumatic drugs, AZA =azathioprine, MMF= mycophenolate mofetil, MTX = methotrexate, LEF = leflunomide, HCQ = hydroxychloroquine, SIE = serious infection events.

3.2 Identification of risk factors for the development of numerical or symptomatic hypogammaglobulinemia

The identification of patients at risk of hypogammaglobulinemia can help reduce associated infection-related morbidity. A low IgG prior to rituximab treatment is a predictor of sustained hypogammaglobulinemia, highlighted in several ~~3~~ studies [8, 14, 18]. The other possible risk factors are cumulative cyclophosphamide dose prior to rituximab therapy and use of other immunosuppressive agents [7, 19,20].

Cortazar *et al* reported that baseline IgG level at the start of maintenance therapy for AAV was the only factor associated with subsequently developing 'significant' hypogammaglobulinemia, defined as IgG <4 g/L, during maintenance rituximab therapy (HR 0.25 per 0.5 g/L increase in IgG level [95% CI 0.11, 0.56]; p= 0.001) [18]. Only patients with baseline maintenance IgG in the lowest quartile (4.08–5.59 g/L) were noted to develop hypogammaglobulinemia. However, 82% of patients in the lowest baseline IgG quartile maintained IgG >4 g/L during continuous maintenance rituximab therapy. Neither time since initial AAV diagnosis, nor duration of B-cell depletion before onset of maintenance BCTT was associated with future hypogammaglobulinemia. The stability of IgG levels was independent of repeated rituximab doses. This was suggested to be due to a long-lived plasma cell population resistant to immunosuppressive agents and able to maintain the IgG pool. Increasing age [adjusted incident rate ratio {IRR}= 1.46 (95% CI 1.19, 1.78) p<0.001] and baseline maintenance IgG < 4 g/L [adjusted IRR= 2.13 (95% CI 1.04, 4.36) p= 0.04] were associated with developing a serious infection during maintenance therapy [18].

In granulomatosis with polyangiitis (GPA), the largest reduction in immunoglobulin levels occurred after remission induction with rituximab [20]. Subsequent maintenance therapy increased the risk of discontinuation due to hypogammaglobulinemia (HR 8.4, 95% CI 1.14 – 63, p= 0.037) [20]. Cumulative rituximab dose did not influence immunoglobulin levels, in contrast to cumulative cyclophosphamide [20]. Cumulative cyclophosphamide dose of 10g increased the risk of discontinuing rituximab due to hypogammaglobulinemia (HR 1.14 95% CI 1.01- 1.3 p= 0.034), suggesting a synergistic effect of cyclophosphamide and rituximab on B-cells in GPA patients [20]. Cyclophosphamide-associated hypogammaglobulinemia pre-rituximab may increase the risk of hypogammaglobulinemia during long-term maintenance. Of the variability in the IgG level during rituximab maintenance, 40% was reported to have been due to patient age, total cyclophosphamide cumulative dose (R^2 = 0.107, p = 0.047) or baseline IgG (R^2 = 0.179, p = 0.013) [20]. Roberts *et al* noted a weak association between prior cyclophosphamide exposure and nadir IgG concentration (Spearman r = -0.1364, p = 0.035), but no association with cumulative rituximab dose [8].

In another study of 177 patients with multisystem autoimmune disease treated with rituximab, baseline IgG levels were lower in patients who had received prior cyclophosphamide treatment (69% of patients) at the time of the first rituximab dose [(8.85 g/L vs. 10.4 g/L) (p = 0.025)], but not at 60 months [(7.9 g/L vs. 9.7 g/L) (p=0.138) (N=51)]. No association between prior cyclophosphamide exposure and development of hypogammaglobulinemia during rituximab therapy was seen. Higher cumulative corticosteroid exposure during follow-up was associated with hypogammaglobulinemia. A reduction in severe infection rates over the study period was noted with minimisation of corticosteroids and avoidance of concomitant immunosuppression. There was no association between diagnosis and development of hypogammaglobulinemia (Chi-square = 3.24; df = 2; p = 0.198). The authors concluded that transient mild to moderate hypogammaglobulinemia or occasional severe

hypogammaglobulinemia observed with repeat rituximab dosing were not dominant factors in infection risk, provided careful monitoring with judicious use of prophylactic therapies occurred [7].

Results from Gottenberg *et al* showed that low IgG <6g/L before initiation of rituximab treatment (OR 4.9 [95% CI 1.6–15.2], p = 0.005) was independently associated with higher risk of severe infection in the year following rituximab administration in RA patients. Six of 29 patients (20.7%) with low baseline IgG subsequently developed a severe infection, compared with 31/605 patients (5.1%) with normal baseline IgG [21].

3.3 Monitoring for the development of hypogammaglobulinemia

There are no specific biomarkers which are proven to guide rituximab treatment, though flow cytometry measurements of CD19+ B-cells are often performed [22]. Early recognition of hypogammaglobulinemia in BCTT-treated patients is important to prevent infection-associated morbidity. Cortazar *et al* concluded that immunoglobulin levels fall more rapidly during induction than in maintenance therapy. IgG levels declined at a mean rate of 6% per month (95% CI 4, 8%) during induction therapy [(52% per year when standardized to a common time unit (95% CI 39, 61%)]. During maintenance, IgG levels fell by a mean of 0.6% per year (95% CI -0.2, 1.4%) [18].

In patients with multisystem autoimmune disease, Marco *et al* observed that following rituximab treatment, 61/177 patients (34%) had hypogammaglobulinemia for at least 3 consecutive months during follow-up (10% mild [IgG 5-5.9 g/L], 20% moderate [IgG 3-4.9] and 4% severe [IgG<3]). Excluding those with hypogammaglobulinemia at baseline, the median time to numerical hypogammaglobulinemia was 18 months (range 1–65 months) and it took 35 months to develop maximum severity hypogammaglobulinemia (range 1–70 months) [7].

For AAV, current EULAR guidelines recommend testing serum immunoglobulin levels prior to each course of rituximab and in patients who develop recurrent infection [23]. Involvement of a clinical immunologist is recommended in patients who develop persistent hypogammaglobulinemia [23]. BSR guidelines for rituximab in RA recommend immunoglobulin levels should be checked prior to commencing therapy, 4–6 months after infusions and before re-treatment [24]. The AAAAI note the importance of checking baseline immune function in AIRD patients started on rituximab [25]. Checking baseline immunoglobulins may also assist in distinguishing drug-induced hypogammaglobulinemia from uncovering of undiagnosed PID such as common variable immunodeficiency [25].

3.4 Intervention thresholds for commencing IGRT

The United Kingdom (UK) DoH guidelines recommend initiating IGRT in patients with secondary hypogammaglobulinemia of any cause (IgG < 5 g/L) provided there is demonstrable functional antibody deficiency[1] and antibiotic prophylaxis for a period of 3 months is unsuccessful in preventing infections [26]. Currently there is no evidence base for the use of prophylactic antibiotics in drug-induced secondary hypogammaglobulinemia. In this group of patients there are no controlled trials of antibiotic prophylaxis versus IGRT. There is an unresolved debate regarding the benefits of IGRT, when considered against its costs and risks, as opposed to long-term antibiotic prophylaxis, which is cheaper but with attendant risks of microbial resistance.

[1] Functional antibody deficiency refers to failure of antibody response to polysaccharide antigens such as pneumococcus (measured as response to the unconjugated polysaccharide vaccine, rather than the conjugate vaccine)

In a case series of 12 patients (10 with vasculitis), the threshold for commencing IGRT was either moderate hypogammaglobulinemia (IgG<5g/L) or severe (<3 g/L), plus recurrent or persistent infections despite antimicrobial prophylaxis and functional antibody deficiency [14]. IGRT was initiated as per DoH guidelines and titrated dependent on infection rate and IgG levels [14]. A minimum trough IgG concentration of 8-10 g/L was used, similar to treatment guidelines for common variable immunodeficiency. An overall reduction in the frequency and severity of infections following commencement of IGRT was described [14].

Cortazar *et al* noted during maintenance therapy with BCTT, median IgG level was 4.08 g/L at initiation of IGRT for the 5 patients requiring IGRT for recurrent infections [18]. Marco *et al.* reported IGRT was used in patients with infections despite antibiotic prophylaxis and moderate or severe hypogammaglobulinemia (IgG < 5 g/l) [7].

Currently there is no agreement on a particular threshold level of IgG for intervention with IGRT in AIRD.

3.5 Initiation and administration of IGRT

Although there are no specific guidelines for the management of drug-induced hypogammaglobulinemia in AIRD, the principles of management are essentially the same as that for secondary antibody deficiency associated with B-cell lymphoproliferative disease.

The decision to start IGRT should involve the patient, clinical immunologist and the patient's autoimmune disease physician. DoH clinical guidelines for all causes of secondary antibody deficiency recommend immunoglobulin initially dosed at 0.4/kg/month [26]. The dose should be titrated to achieve an IgG trough level within the reference range, to achieve a significant reduction in the burden of bacterial infections. Evidence from IGRT in PID suggests that this approach is likely to optimise patient care [27]. Target trough IgG levels should be adjusted on an individual basis, and may be higher in patients with complications such as bronchiectasis [27]. Both intravenous and subcutaneous routes of administration should be considered [26].

Sustained hypogammaglobulinemia is reported to occur in a minority of patients after rituximab treatment, who may require long-term IGRT. In the largest study where data is available, 12/243 (4.2%) patients with a range of AIRD required IGRT [14, 25]. In an AAV study, 7/55 (21%) patients treated with cyclophosphamide followed by rituximab required IGRT [19]. The decision to discontinue rituximab can be considered in patients with an IgG < 5 g/l, with a downward trajectory and recurrent infections [7]. This decision should be balanced against ongoing disease activity, the benefit derived from rituximab treatment and the availability of alternative therapeutic options [7].

3.6 Hypogammaglobulinemia with other immunosuppressive drugs

There is no evidence *to date* of hypogammalobulinaemia as a clinical problem in patients treated with non-depleting B-cell medications such as belimumab or atacicept, but numbers of patients treated are much less than with rituximab [28, 29]. No significant difference was noted between belimumab and placebo in development of hypogammaglobulinemia [28]. While reductions in immunoglobulin levels were noted with atacicept, no cases of severe hypogammagloblinaemia (< 3g/L) were noted, and no increase in serious infections [29].

Patients with AIRD have often had previous exposure to other medicines associated with hypogammaglobulinemia, including corticosteroids, cyclophosphamide (as discussed above), gold,

mycophenolate mofetil, alemtuzumab, sulfasalazine and ciclosporin [14]. These drugs may also confound the potential relationship between IgG levels and infection due to effects beyond the B-cell lineage [14].

3.7 The potential role for memory B-cell monitoring

B-cell repopulation following rituximab treatment in patients with AIRD has not been studied systematically over a long-term period. There is evidence to suggest a direct correlation between numbers of switched memory (CD27+ IgM- IgD-) B-cells and risk of disease relapse following rituximab treatment in AAV, but this data awaits confirmation [22]. Disease relapse reported in AAV is common following rituximab cessation, and it is often heralded by B-cell reconstitution [18]. Persistent loss of memory B-cells may be a clue to development and persistence of hypogammaglobulinemia [22].

3.8 Vaccination strategies and performance

EULAR recommendations state that vaccination status should be assessed during the initial work-up of patients with AIRD. The decision to vaccinate patients should be decided on a case by case basis, following evaluation of the risks and benefits in the context of a patient's immunocompetence [30].

EULAR recommend avoiding live attenuated vaccines in immunosuppressed patients with AIRD when possible. Ideally all indicated non-live vaccinations should be administered at least 4 weeks prior to the initiation of BCTT therapy [31]. However this should not delay BCTT in urgent cases. In particular vaccination against influenza, pneumococcus, tetanus toxoid every 10 years and hepatitis B for at-risk populations should be considered [31]. Patients receiving conventional immunosuppressive therapy or undergoing BCTT may have impaired response to vaccination with pneumococcal polysaccharide or novel antigens [18]; testing vaccination responses may be indicated [32]. B-cell recovery may provide a marker to guide revaccination schedules [33]. Influenza and pneumococcal vaccinations are recommended as there is a high level of respiratory tract infections in rituximab treated patients.

Test vaccinations currently are recommended by DoH to evaluate for functional antibody deficiency in secondary hypogammaglobulinemia (utilising polysaccharide vaccines such as unconjugated pneumococcus). However, as there is substantial data showing rituximab impairs protective humoral responses, this may be superfluous in some cases, particularly if there is severe hypogammaglobulinemia. EULAR reported from a systematic review that humoral responses to pneumococcal vaccine were impaired for 28 weeks after treatment with rituximab, and to influenza vaccine for 1-3 months after rituximab [30].

3.9 Health economics

There is limited data regarding health economics of IGRT for secondary hypogammaglobulinemia. Further evaluation in the UK is required. There is more experience and established data for the health economics for IGRT in PID and in some haematological malignancies. There is data on health costs in AAV where hospitalisation more than doubles the annual health costs per patient, to over $80,000 (2013 US prices) [34].

4. Discussion

In this review, we have assessed the role of IGRT in the management of BCTT-induced secondary hypogammaglobulinemia in AIRD. At present there are few studies focused on BCTT and these are

mostly retrospective cohort studies. The main limitations are the small numbers of such patients receiving IGRT in these studies, and the lack of randomised controlled trials.

The evidence supports pre-existing low IgG levels being a risk factor for developing hypogammaglobulinemia during BCTT, however this should not be a contra-indication to commencing or continuing BCTT. It has not been definitively established that patients with previous cyclophosphamide or other immunosuppressive drug exposure are at a higher risk of developing hypogammaglobulinemia. Independent of the effect of non-rituximab disease treatment, different diseases appear to vary in their susceptibility to low IgG levels after rituximab. The most common diagnosis was AAV in patients receiving IGRT subsequent to BCTT. The explanation for this variability is not yet known. It is recommended that all patients should have serum immunoglobulin measurements prior to commencing BCTT, to establish a baseline and exclude underlying immunodeficiency. These levels should be monitored for long-term changes during follow-up [32].

We consider numerical hypogammaglobulinemia as a low IgG level below the local laboratory reference range. Patients with numerical hypogammaglobulinemia may not be symptomatic and therefore may not require IGRT. Agreement regarding definitions of mild, moderate and severe hypogammaglobulinemia is lacking. Evidence is limited for clear intervention thresholds for IGRT, such as asymptomatic patients with numerical hypogammaglobulinemia.

Currently there is no standardised definition for recurrent infection. However, infections characteristic of hypogammaglobulinemia are typically sino-pulmonary, caused by encapsulated organisms such as pneumococcus [35]. The decision to start IGRT should consider a history of serious, persistent, unusual or recurrent (SPUR) infections. IGRT should be considered in patients with a significant burden of infections accompanied by hypogammaglobulinemia [36]. The role of measurement of baseline specific antibodies and responses to test vaccinations has not been universally agreed upon.

Treatment targets for IGRT would be valuable, as the current evidence is unclear and is largely based on evidence from PID. Guidelines on when to refer a patient to Clinical Immunology during BCTT are needed, especially for complex cases. For example, if a patient is symptomatic without hypogammaglobulinemia or where a patient is asymptomatic but has numerical hypogammaglobulinemia, would referral be indicated by the autoimmune disease physician?

Health economic data for secondary hypogammaglobulinemia in AIRD and patient assessment tools would aid the evaluation of current IGRT practice and improve quality of life outcomes. While BCTT for AIRD can be efficacious, the risk of hypogammaglobulinemia and infections (particularly when pursuing prolonged maintenance therapy) needs balancing against the risk of disease relapse if BCTT is discontinued. In this context IGRT has an important role in the management of (symptomatic) hypogammaglobulinemia [14].

We recognise the limitations of this SLR, due to the sparse data available on the use of IGRT for BCTT associated hypogammaglobulinemia in AIRD. Long-term outcome data and randomised controlled studies from this group of patients are not present in the current literature.

5. Research Agenda

The effect of IGRT in reducing infection frequency and prevention of hospital admissions has been demonstrated in small studies in SID. IGRT initiation appeared to be associated with a reduction in the number of infections in moderate or severe hypogammaglobulinemia in a case series of AAV [14] and in mixed study populations of Haematology and Rheumatology patients [30]. Further research in larger prospective studies is required in AIRD.

BCTT use is likely to increase in AIRD, with a wider range of B-cell agents (including biosimilars). The findings from this review have highlighted areas in need of further research. At present data from PID and haematological malignancies provides guidance, whilst awaiting further studies in AIRD. Research regarding immunoglobulin recovery following BCTT, the safety of continuing BCTT in patients with low or falling IgG, use of memory B-cell panels for monitoring hypogammaglobulinemia development, and long-term prognosis of AIRD patients with hypogammaglobulinemia are needed [8]. Studies of IGRT efficacy and cost-effectiveness in this group of patients are warranted.

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