LUPUS SCIENCE & MEDICINE™

Iatrogenic antibody deficiency from B-cell targeted therapies in autoimmune rheumatic diseases

Sonali Wijetilleka,[1] David Jayne,[2] Chetan Mukhtyar,[3] Mohammed Yousuf Karim[4]

To cite: Wijetilleka S, Jayne D, Mukhtyar C, *et al*. Iatrogenic antibody deficiency from B-cell targeted therapies in autoimmune rheumatic diseases. *Lupus Science & Medicine* 2019;**6**:e000337. doi:10.1136/lupus-2019-000337

Received 24 April 2019
Revised 14 July 2019
Accepted 17 July 2019

[1]Immunology, University Hospital of Wales, Cardiff, , UK
[2]Department of Medicine, University of Cambridge, Cambridge, UK
[3]Rheumatology, Norfolk and Norwich University Hospital, Norwich, UK
[4]Pathology, Sidra Medical and Research Center, Doha, Qatar

Correspondence to
Dr Mohammed Yousuf Karim; mkarim@sidra.org

ABSTRACT

B-cell targeted therapies (BCTT) are now widely used in autoimmune rheumatic diseases, including SLE, antineutrophil cytoplasmic antibody-associated vasculitis and rheumatoid arthritis. Early studies suggested that rituximab did not influence serum immunoglobulins. However, subsequently, with increased patient numbers, longer follow-up duration and many patients having received multiple BCTT courses, multiple subsequent studies have identified hypogammaglobulinaemia as a potential side effect. Patients developing hypogammaglobulinaemia appear to fit into two principal categories: the majority who develop transient, often mild reduction in immunoglobulins without increased infection and a much smaller but clinically significant group with a more sustained antibody deficiency, who display increased risk of infection. Monitoring immunoglobulin levels represents an opportunity for the early detection of hypogammaglobulinaemia, and the prevention of avoidable morbidity. In the two major studies, approximately 4%–5% of BCTT-treated patients required immunoglobulin replacement due to recurrent infections in the context of hypogammaglobulinaemia. Despite this, monitoring of immunoglobulins is suboptimal, and there remains a lack of awareness of hypogammaglobulinaemia as an important side effect.

Over the last 15 years, B-cell targeted therapies (BCTT) have been widely used for treatment of autoimmune rheumatic diseases (AIRD), particularly in severe/resistant cases of SLE, and in antineutrophil cytoplasmic antibody-associated vasculitis (AAV). These medications are also employed in rheumatoid arthritis (RA) and multiple sclerosis.[1]

Initial studies suggested that rituximab, the earliest and still most widely reported BCTT, did not influence serum immunoglobulins. This was based on early studies of limited doses and duration, and the premise that plasma cells did not express surface CD20, the molecular target of rituximab. It was also proposed that protective antimicrobial antibodies were not significantly affected, in contrast to reduction in pathogenic autoantibodies; based on findings that B-cell clones producing antinucleosome and antidouble-stranded DNA antibodies, had a relatively rapid turnover compared with B-cell clones with other specificities.[2]

Over time, large numbers of patients have been treated, with longer follow-up duration, and many patients have received multiple BCTT courses. In this context, multiple subsequent studies have now identified hypogammaglobulinaemia as a potential side effect. The patients developing hypogammaglobulinaemia appear to fall into two main categories: the majority who develop transient, often mild reduction in immunoglobulins without increased infection and a much smaller but clinically significant group with a more sustained antibody deficiency, who display increased risk of infection.[3] This may result from prolonged depletion of plasma cell precursors, with consequent effects on replenishment of mature plasma cells.

Monitoring immunoglobulin levels represents an opportunity for the early detection of hypogammaglobulinaemia, and can be performed using cheap, simple and widely available assays. The American Academy of Allergy, Asthma & Immunology, British Society for Rheumatology (BSR) and European League against Rheumatism (EULAR) advocate testing immunoglobulins at baseline, and BSR and EULAR at varying times after commencement of BCTT in AAV and RA. Although the 2018 BSR SLE guidelines advocate baseline and follow-up testing of immunoglobulins patients treated with rituximab (also with other drugs such as mycophenolate and cyclophosphamide), monitoring is not mentioned in the 2019 EULAR SLE recommendations.[4 5]

There still appears to be little awareness of this important side effect, with a lack of widespread adoption of immunoglobulin monitoring in patients treated with BCTT. This represents a lost opportunity in early prevention of avoidable morbidity. In a large Boston study, 3824/4479 (85%) of rituximab-treated

patients (including AIRD and haematological disorders) had never had immunoglobulins checked prior to BCTT commencement.[3] Of those who were checked at baseline, hypogammaglobulinaemia was present in 313 (47.8%) patients. The BSR Biologics Registry includes over 5000 patients who have received rituximab. Several BSR Biologics Registry publications emerged in late 2018, assessing the risk of infection in rituximab-treated patients. However, the Registry did not collect data on measurement of immunoglobulins, and this critical parameter was therefore not evaluated as a risk factor for serious infection.[6]

Although most patients with hypogammaglobulinaemia do not have problems with infections, hypogammaglobulinaemia has been shown to be a risk factor for infections in several BCTT studies. In AAV, logistic regression analysis after adjustment for age, race and estimated glomerular filtration rate showed increased risk of hospitalisation from infection (OR 21.1; 95% CI 1.1 to 404.1; p=0.04) for patients with IgG <3.75 g/L.[7] In RA, patients with hypogammaglobulinaemia (<6 g/L) were more likely to experience severe infections (26.1% vs 6.3%, p=0.033).[8]

Infections characteristic of hypogammaglobulinaemia are usually sino-pulmonary, caused by encapsulated organisms such as pneumococci. The diagnostic delay common in primary antibody deficiency is now known also to occur in secondary antibody deficiency, and may extend to several years. This often avoidable delay can result in unnecessary admissions and complications such as bronchiectasis.[9 10] In some cases, patients with hypogammaglobulinaemia can present for the first time with sepsis, for example, related to pneumococci or meningococci, without an antecedent history of recurrent infection. In addition, enteroviral encephalitis has been described in rituximab-induced hypogammaglobulinaemia.[11]

Hypogammaglobulinaemia at initiation of anti-CD20 treatment may be transient, and multifactorial, including effects of other medications (eg, corticosteroids, cyclophosphamide, mycophenolate mofetil), or active disease (eg, nephrotic syndrome). However, hypogammaglobulinaemia occurring later after BCTT may be sustained, and related to prolonged B-cell depletion. Predictive factors for such hypogammaglobulinaemia include low baseline immunoglobulins (especially IgG) at BCTT commencement, and possibly previous or concomitant immunosuppressive therapies (such as cyclophosphamide).[12] The frequency of hypogammaglobulinaemia appears higher in certain AIRD, for example, AAV, SLE compared with RA, although the exact reasons are not yet known.

Immunological disorders were previously categorised into those due to allergy, autoimmunity or immunodeficiency. However, there is now recognition that more than one type of immunopathology may co-exist in the same patient, with the common underlying pathology being immunodysregulation. Hence, common variable immunodeficiency (the most frequent cause of primary antibody deficiency) may display several different autoimmune phenomena, including cytopenia, inflammatory arthritis and SLE.[13] *Baseline* measurement of immunoglobulins is thus *also* important to help exclude a more complex immunological phenotype.[3]

With this increased risk of infection, it is critical that the recommended monitoring schedules are incorporated into routine clinical protocols for currently available BCTT. It is important that clinicians are aware of hypogammaglobulinaemia as a potential side effect, and counsel their patients appropriately prior to commencement of treatment. Clinicians treating AIRD should be cognizant of local clinical immunology services and referral pathways. In patients with hypogammaglobulinaemia with recurrent or serious infections, consideration can be made for referral to clinical immunology to evaluate for immunoglobulin replacement therapy (IGRT). It is important to bear in mind that IGRT is an expensive treatment, a major commitment by both patients and clinical staff of medium-term or long-term (potentially lifelong) duration, with attendant risks including thrombosis and infusion-related infections from known and unknown agents. Thankfully, with improved donor screening, and three-step antiviral processes, there have been no recent cases of hepatitis C, HIV or prion disease acquired through IGRT.[14] IGRT should be reviewed at regular intervals, primarily to ensure that the therapy is effective and side effects minimised, and there is the chance that endogenous antibody production may return in the long-term.

Our group has recently published recommendations for management of secondary hypogammaglobulinaemia due to BCTT in AIRD.[1] Clinical evaluation should take into account the degree of hypogammaglobulinaemia, infection history, assessment of antibody responses to polysaccharide antigens and whether a trial of antibiotic prophylaxis is appropriate. Measurement of antibody responses 4–8 weeks after administration of the non-conjugated pneumococcal polysaccharide vaccine is typically used in the assessment of hypogammaglobulinaemia to identify functional/specific antibody deficiency.[1 15–17] The UK[16] guidelines recommend initiating IGRT in patients with secondary hypogammaglobulinaemia of any cause (IgG <5 g/L), functional antibody deficiency and failure of antibiotic prophylaxis over 3 months in preventing infections.[16] These guidelines are currently in the process of revision. Although there is no supportive evidence available, we would suggest that in some settings, for example, a history of severe/life-threatening infections with very low IgG levels (<1–2 g/L) together with absent/very impaired (postvaccination) specific antibody responses, it may be appropriate to consider IGRT without a trial of antibiotic prophylaxis. In 2018, the European Medicines Agency Guideline for Human Normal Immunoglobulin for Intravenous Administration advised IGRT in secondary immunodeficiency with severe or recurrent infections, ineffective antimicrobial treatment and either serum IgG level of <4 g/L or proven specific antibody failure.[15] An IgG value of 4 g/L is also noted as a level for consideration of IGRT in other reviews of secondary

antibody deficiency.[17 18] In hypogammaglobulinaemia related to chronic lymphocytic leukaemia, the majority of infections occurred when IgG was below 3 g/L.[19] Canadian guidelines from 2018 refer to IgG below the lower limit of the reference range on two occasions.[20]

The literature suggests only a minority of patients developing BCTT-induced hypogammaglobulinaemia will require IGRT. In the two largest series of IGRT in BCTT-treated patients, the rates of immunoglobulin use are remarkably similar. In the Cambridge (UK) study, 12/288 (4.2%) patients with AIRD treated with BCTT went on to receive IGRT, while in the Boston study 201/4479 (4.5%) received IGRT, although this study also included patients without AIRD.[3 21] There is early evidence for the efficacy of IGRT in reducing infection in BCTT-related hypogammaglobulinaemia, as well as substantial evidence from other secondary antibody deficiencies.[9 17 22] In the Boston study,[3] higher cumulative IGRT dose was associated with a reduced risk of serious infectious complications (HR 0.98; 95% CI 0.96 to 0.99; p=0.002).

The importance of vaccination in relation to biologic therapy in SLE and other AIRD is highlighted in multiple guidelines, both from rheumatology and microbiology perspectives.[5 23] The importance of early vaccination is emphasised for appropriate organisms (such as influenza, *Streptococcus pneumoniae*, *Haemophilus influenzae*) in patients with AIRD, as there is reduction in antibody responses to vaccinations for 1–6 months following anti-CD20 treatment. If vaccination cannot be administered early, then it may be prudent to wait until beyond this period. As mentioned in the 2018 BSR SLE guidelines, postvaccination antibody levels can be measured to assess response.[4]

Based on recent guidelines and recommendations, we have summarised a possible approach to management of hypogammaglobulinaemia in patients treated with BCTT (Box 1).

Over time, further experience will emerge for different BCTT, and different BCTT regimens, and predictive factors for hypogammaglobulinaemia may be identified. There is insufficient data from other B-cell depletors ocrelizumab and epratuzumab in autoimmune disease, and no data demonstrating clinically significant hypogammaglobulinaemia in SLE with non-depleting BCTT such as atacicept or belimumab.[12] However, it would be prudent to avoid definite conclusions at this stage given the inadvertent reassurance regarding potential effects of rituximab on humoral immunity based on early data.

Consequently, it is important to re-evaluate all BCTT with larger numbers of patients treated, long-term follow-up and also the effects of repeat dosing and multiple drug interventions. Although use of conventional immunosuppressive agents is reducing, corticosteroids, cyclophosphamide, mycophenolate can all influence B-cell function and prior use may influence the development of hypogammaglobulinaemia following biologic use.[8 12] Combinations of biologics affecting B-cells are used in clinical trials, for example, rituximab and belimumab in the BEATLupus, BLISS-BELIEVE and CALIBRATE studies. It is too early to evaluate the data assessing the long-term effects on protective humoral immunity from such combinations.

Monitoring of immunoglobulins is important to consider with biosimilars and with newer BCTT, both in current clinical trials and for future agents. This monitoring should be considered both as an essential component of trial data, and as part of routine clinical care. This should include all B-cell active agents, to include B-cell monoclonal antibodies, other BCTT such as *btk*-inhibitors as well as plasma cell agents (eg, anti-CD38, proteasome inhibitors).

Box 1. Practical guidance for management of hypogammaglobulinaemia in B-cell targeted therapies (BCTT)-treated patients

- Assess infection history.
- Check specific antimicrobial antibodies±vaccine responses.
- If no infections, continue to monitor immunoglobulins pre-infusion and/or at regular intervals.
- Consider referral to clinical immunology if IgG <4 g/L and/or significant infection history.
- Consider if there is potential alternative immunosuppression to BCTT.
- Consider prophylactic antibiotic therapy.
- Immunoglobulin replacement therapy in selected cases.

Contributors All authors contributed to this project in article concept and planning, manuscript writing, expert critical review of manuscript and manuscript editing. All authors read and approved the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests DJ has received research grants from Roche/Genentech. From August 2017 to February 2018, SW was a Clinical Research Fellow supported by an unrestricted grant from Roche Products (UK) to undertake a Systematic Literature Review on hypogammaglobulinaemia after B-cell targeted therapies. MYK, CM and DJ were co-applicants on that grant (grant number GDRC-FEB-001-2017).

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. Wijetilleka S, Jayne DR, Mukhtyar C, *et al*. Recommendations for immunoglobulin replacement therapy after treatment of autoimmune rheumatic diseases with B-cell targeted therapies. *Rheumatology* 2018.
2. Cambridge G, Leandro MJ, Teodorescu M, *et al*. B cell depletion therapy in systemic lupus erythematosus: effect on autoantibody and antimicrobial antibody profiles. *Arthritis Rheum* 2006;54:3612–22.
3. Barmettler S, Ong M-S, Farmer JR, *et al*. Association of immunoglobulin levels, infectious risk, and mortality with rituximab and hypogammaglobulinemia. *JAMA Netw Open* 2018;1:e184169.
4. Gordon C, Amissah-Arthur MB, Gayed M, *et al*. British Society for rheumatology Standards, audit and guidelines Working Group. The

British Society for rheumatology guideline for the management of systemic lupus erythematosus in adults. *Rheumatology* 2018;57:e1–45.
5. Fanouriakis A, Kostopoulou M, Alunno A, *et al*. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis* 2019:pii: annrheumdis-2019-215089.
6. Silva-Fernández L, De Cock D, Lunt M, *et al*. Serious infection risk after 1 year between patients with rheumatoid arthritis treated with rituximab or with a second TNFi after initial TNFi failure: results from the British Society for rheumatology biologics register for rheumatoid arthritis. *Rheumatology* 2018;57:1533–40.
7. 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;10:470–4.
8. 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;48:149–54.
9. Duraisingham SS, Buckland MS, Grigoriadou S, *et al*. Secondary antibody deficiency. *Expert Rev Clin Immunol* 2014;10:583–91.
10. Duraisingham SS, Buckland M, Dempster J, *et al*. Primary vs. secondary antibody deficiency: clinical features and infection outcomes of immunoglobulin replacement. *PLoS One* 2014;9:e100324.
11. Palacios T, Bartelt L, Scheld W, *et al*. Fatal Coxsackie meningoencephalitis in a patient with B-cell lymphopenia and hypogammaglobulinemia following rituximab therapy. *Ann Allergy Asthma Immunol* 2015;115:148–50.
12. Wijetilleka S, Mukhtyar C, Jayne D, *et al*. Immunoglobulin replacement for secondary immunodeficiency after B-cell targeted therapies in autoimmune rheumatic disease: systematic literature review. *Autoimmun Rev* 2019;18:535–41.
13. Azizi G, Kiaee F, Hedayat E, *et al*. Rheumatologic complications in a cohort of 227 patients with common variable immunodeficiency. *Scand J Immunol* 2018;87:e12663.
14. Guo Y, Tian X, Wang X, *et al*. Adverse effects of immunoglobulin therapy. *Front Immunol* 2018;9:1299.
15. European Medicines Agency. Guideline on core SMPC for human normal immunoglobulin for intravenous administration (IVIg): EMA, 2018. Available: https://www.ema.europa.eu/documents/scientific-guideline/guideline-core-smpc-human-normal-immunoglobulin-intravenous-administration-ivig-rev-5_en.pdf [Accessed June 2019].
16. Department of Health. *Clinical guidelines for Immunoglobul use (second edition*, 2011. (Accessed July 2019).
17. Patel SY, Carbone J, Jolles S. The expanding field of secondary antibody deficiency: causes, diagnosis, and management. *Front Immunol* 2019;10:33.
18. Srivastava S, Wood P. Secondary antibody deficiency - causes and approach to diagnosis. *Clin Med* 2016;16:571–6.
19. Boughton BJ, Jackson N, Lim S, *et al*. Randomized trial of intravenous immunoglobulin prophylaxis for patients with chronic lymphocytic leukaemia and secondary hypogammaglobulinaemia. *Clin Lab Haematol* 1995;17:75–80.
20. Alberta Ministry of Health, Shared Health Manitoba. Saskatchewan Ministry of health criteria for the clinical use of immune globulin, 2018. Available: https://www.ihe.ca/download/criteria_for_the_clinical_use_of_immune_globulin_first_edition.pdf [Accessed 6 June 2019].
21. Roberts DM, Jones RB, Smith RM, *et al*. Immunoglobulin G replacement for the treatment of infective complications of rituximab-associated hypogammaglobulinemia in autoimmune disease: a case series. *J Autoimmun* 2015;57:24–9.
22. Perez EE, Orange JS, Bonilla F, *et al*. Update on the use of immunoglobulin in human disease: A review of evidence. *J Allergy Clin Immunol* 2017;139:S1–S46.
23. Mikulska M, Lanini S, Gudiol C, *et al*. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Agents targeting lymphoid cells surface antigens [I]: CD19, CD20 and CD52). *Clin Microbiol Infect* 2018;24(Suppl 2):S71–S82.