



Secondary antibody deficiency in neurology

Emma C. Tallantyre^{a,b}, Neil P. Robertson^{a,b}, and Stephen Jolles^{a,b}

Purpose of review

Induction of lymphocyte depletion is increasingly used as a therapeutic strategy for central and peripheral neuroinflammatory disease. However, there is also a growing recognition of the treatment-related complication of secondary antibody deficiency (SAD). Although the occurrence of hypogammaglobulinaemia is a recognized phenomenon during immunomodulation, robust data on the coexistence of impaired responses to immunization, and significant and/or atypical infections is scarce. Here we review the literature on SAD in anti-CD20 therapy.

Recent findings

Several factors that may increase the incidence of SAD have now been identified, including low levels of immunoglobulins prior to the commencement of B-cell ablation therapy, duration of maintenance therapy, and concurrent or prior use of other immunosuppressing agents such as cyclophosphamide and steroids. Measurement of disease-specific antibodies and vaccine response are likely to be helpful adjuncts to measurement of serum immunoglobulin levels during B-cell depleting therapy. Supportive treatment may include amending the treatment schedule to limit cumulative dose.

Summary

B-cell depleting agents offer considerable therapeutic benefit in neurology. We propose modifications in current practice that include risk stratification and early identification of SAD, with the aim of minimising morbidity and mortality related to this underappreciated condition.

Keywords

anti-CD19, anti-CD20, immunoglobulin replacement therapy, rituximab, secondary antibody deficiency

INTRODUCTION

The role of B-cells in neurological disease

B cells are known to play a significant role in the pathogenesis of a wide range of diseases affecting the central and peripheral nervous system. Some are directly attributable to the presence of pathogenic autoantibodies, for example, myasthenia gravis (antiacetylcholine receptor or antimuscle-specific tyrosine kinase antibodies), neuromyelitis optica (NMO; antiaquaporin-4 or antimyelin oligodendrocyte glycoprotein antibodies), and autoimmune encephalitis (anti-N-methyl-D-aspartate receptor or anti-voltage gated potassium channel antibodies). Although others are presumed to be antibody mediated because of their response to plasma exchange and/or lymphocyte depleting agents, even though a pathogenic antibody is not always demonstrated, for example, chronic immune demyelinating polyneuropathy (CIDP) or primary cerebral vasculitis. In multiple sclerosis (MS), B cells are thought to play a pathogenic role via other mechanisms. The presence of cerebrospinal fluid-specific oligoclonal IgG bands form part of the diagnostic

criteria of MS [1], and meningeal ectopic B-cell follicles have been observed, occurring in close proximity to areas of focal cortical demyelination, although their exact role remains unclear [2].

Following the increasing recognition of the key role that B cells play in neuroinflammatory disease, there is increasing focus on agents that are able to reduce circulating lymphocytes and act as disease-modifying drugs. These include alemtuzumab, azathioprine, bortezomib, cladribine, corticosteroids, cyclophosphamide, cyclosporine, dimethyl fumarate, fingolimod, mycophenolate mofetil, and teriflunomide, which are all used for disease modification in neurological disease and could all conceivably reduce levels of circulating immunoglobulin. However, in

^aUniversity Hospital of Wales and ^bCardiff University School of Medicine, Cardiff, Wales, UK

Correspondence to Dr Emma C. Tallantyre, Department of Psychological Medicine and Clinical Neurosciences, B4-C4 Corridor, University Hospital of Wales, Cardiff, CF14 4XW, Wales, UK. Tel: +44 02920 745403; e-mail: tallantyreec@cardiff.ac.uk

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KEY POINTS

- The use of anti-CD20 and anti-CD19 agents targeting B cells in neurology is growing and many disorders will require maintenance therapy.
- SAD is being increasingly recognized following B-cell ablation therapy for neurological disease.
- Baseline assessment of immunoglobulins, specific antibodies, infection burden, and co-morbidities is required before commencement of therapy.
- Risk factors for the development of SAD include lower immunoglobulin levels at baseline, maintenance and combined therapies, and significant immunosuppressive treatment prior to B-cell therapy.
- Monitoring of immunoglobulin levels, specific antibodies, memory B cells, and infection burden allows risk stratification and intervention.
- Selected patients may benefit from IGRT and a cross-specialty approach with the involvement of both Neurology and Immunology.

this review, we will focus on the relationship between biologic treatments that selectively deplete cells expressing CD19 or CD20 and may result in secondary antibody deficiency (SAD).

The use of B-cell depletion in the treatment of neurological disease

Monoclonal antibodies with a fragment antigen binding domain targeted to CD20 are used in several medical subspecialties to deplete B cells. Rituximab, a first generation, chimeric IgG1 mAb, was the first anti-CD20 mAb to be approved in 1997 for the treatment of B-cell lymphomas. Anti-CD20 mAbs induce B-cell depletion via a combination of mechanisms including antibody-mediated cytotoxicity, complement-mediated lysis, induction of apoptosis, and growth arrest [3]. Anti-CD19 therapies, which are now also available, may offer improved efficacy compared to anti-CD20 therapies but with potentially higher risks.

Rituximab has been licensed since 1998 for the treatment of B-cell leukaemia and lymphoma, refractory rheumatoid arthritis and severe antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. However, unlicensed use of rituximab in a number of neuroinflammatory diseases is also growing. There is support from phase II and uncontrolled cohort studies for the safety and effectiveness of rituximab in reducing disease activity in relapsing-remitting MS [4]. A phase II study of rituximab for primary progressive MS (PPMS) failed to reach its primary outcome of

time to confirmed disease progression. However, subgroup analysis demonstrating benefit in younger individuals with inflammatory MRI lesions has led to some off-label use of rituximab for PPMS [5]. Rituximab is now widely used for neuromyelitis optica spectrum disorder (NMOSD) in Europe and North America on the basis of a large body of observational evidence and some limited trial data on its efficacy in reducing relapse rates [6[■],7]. There is also growing evidence that rituximab is associated with favourable clinical outcomes (improved clinical scores and relapse rates) in people with refractory myasthenia gravis [8,9[■],10].

Repeated infusions of rituximab are usually employed to maintain remission in MS, NMOSD, and myasthenia gravis [9[■],10]. In contrast, short term use of rituximab has been employed in autoimmune limbic encephalitis (associated with anti-N-methyl-D-aspartate-receptor and anti-leucine-rich glioma-inactivated-1, anti-contactin-associated protein 2 antibodies), inflammatory neuropathies [CIDP, multifocal motor neuropathy, and anti-myelin-associated glycoprotein (MAG) neuropathy], stiff person syndrome, and primary central nervous system (CNS) vasculitis, often as second-line therapy in the context of refractory disease [11–20]. In some of these conditions, such as autoimmune limbic encephalitis, a single dose of rituximab can induce durable disease remission. In others such as CNS vasculitis, rituximab therapy is often followed by an alternative maintenance immunosuppressant regime to maintain remission.

Second and third generation anti-CD20 mAbs have now been designed, with the aim of improving B-cell depletion to enhance efficacy, and reducing immunogenicity to improve tolerability. Ocrelizumab, a humanized anti-CD20 mAb, administered by 6-monthly intravenous (i.v.) infusion, was recently approved to treat relapsing and progressive forms of MS. Ofatumumab, a fully humanized anti-CD20 mAb, administered by once-monthly subcutaneous injection, and ublituximab (TG-1101), a chimeric glycoengineered anti-CD20 mAb, administered by 6-monthly i.v. infusion, are both in phase 3 clinical trials for treatment of MS. Inebilizumab (MEDI-551), a humanized anti-CD19 mAb, is currently in a phase 3 trial in NMO spectrum disorders (NMOSD) [21].

Secondary antibody deficiency in association with B-cell depleting therapy

Hypogammaglobulinaemia is a well-recognized consequence of rituximab therapy for haematological and rheumatological disease, with a reported incidence as high as 40%. Serum IgM often appears to be most significantly affected, followed by IgG

[22–24,25[¶]]. However, some reports on the timing and duration of hypogammaglobulinaemia can be limited in value by the lack of systematic sampling and/or variations in treatment regimens [22,26]. One group has systematically studied change in serum immunoglobulin following induction (2 doses of 1 g rituximab administered i.v., separated by 2 weeks) and during maintenance therapy (1 g dose every 4 months for 2 years, followed by 1 g every 6 months over a median duration of 2.4 years) in 239 patients with ANCA-associated vasculitis [25[¶]]. Serum IgG levels fell by 6% per month during the induction period and then by 0.6% per year during maintenance therapy. Serum levels of IgM and IgA also declined rapidly during induction therapy (16 and 5% per month, respectively) and then continued to decline, albeit at a slower rate, during maintenance therapy (at a rate of 9 and 5% per year, respectively).

Hypogammaglobulinaemia is less well studied in neurological cohorts but data is valuable because of expected differences in the co-morbidity, concomitant treatments and B-cell depleting treatment regimens in other medical specialties. Bar-Or *et al.* [27] report safety outcomes of 26 patients with relapsing-remitting multiple sclerosis (RRMS) who received 2 g rituximab at baseline and at 6 months. Participants had 3-monthly measurement of serum immunoglobulin for 72 weeks. Of 25 patients who had normal baseline IgM values, 11 (44%) had a value below the lower limit of normal (LLN) at some time during the study. These 11 patients had an increased incidence of overall infections, none of which was severe or serious. Absolute serum IgG levels were not reported, so it was not possible to know whether absolute levels declined during treatment, but no patient had developed IgG or IgA levels below the LLN by week 72. Serum IgG titres for tetanus generally remained unchanged over 72 weeks, and no patient who was seropositive for mumps or rubella at baseline became seronegative during the study [27]. In a phase 2 placebo controlled trial of 6-monthly rituximab for RRMS, 108 participants had serum immunoglobulin levels measured at baseline, 24 and 48 weeks. Although median IgM, IgG, and IgA levels remained above the lower limit of the normal range in both groups throughout the trial, low IgG and IgM levels was found to occur in 7.9 and 22.4% of patients who received rituximab (versus 3.0 and 8.6%, respectively, in patients who received placebo) [4]. Similarly, in a randomized, placebo-controlled trial of 6-monthly rituximab in 439 patients with primary progressive MS, followed to 96 weeks, IgM levels were recorded below LLN in 31.7% of patients receiving rituximab and 5.9% of patients receiving

placebo. Serum IgG and IgA levels were below LLN in less than 5% of patients in either treatment arm [5]. None of these studies of rituximab in MS found an association between the occurrence of infections and the presence of SAD. During a large retrospective review of rituximab use for MS in 822 patients in Sweden, 25 out of 822 patients were reported to have low IgG levels at some point during treatment; however, serum immunoglobulins were not systematically measured in all patients [28[¶]].

Pellkofer *et al.* [29] reported long-term follow-up of a cohort of 10 patients who were treated with 2 g rituximab, 6–9 monthly up to five times, as a second-line therapy for NMO. Serum immunoglobulin levels, measured every 3 months, were found to fall below the LLN in 2 out of 10 patients after a median follow-up of 37 months. Kim *et al.* [30] report a cohort of 100 patients who received rituximab for NMOSD over a median period of 67 months (range 9–108 months). Low IgG developed in 29% of the 41 people who received at least 5 years of rituximab and 42% of the 24 people who received at least 7 years of rituximab (IgM 53 and 46%; IgA 10 and 25%, respectively).

Variation in the reported incidence of SAD during rituximab treatment is inevitably influenced by differences in the accepted LLN range for serum immunoglobulins [31], and the duration of follow-up. However, the risk of hypogammaglobulinaemia also appears to be higher in the individuals with lower serum immunoglobulin at treatment onset [22,23,26,32–35], previous or concurrent exposure to other immunosuppressive drugs [22,26,31,34–36], higher cumulative dose of rituximab [22,32,35,37–40], older age, or co-morbid chronic respiratory or cardiovascular disease [41].

There also appears to be variation in the recovery of SAD in the context of anti-CD20 therapy, which is not fully explained by treatment schedule. Roberts *et al.* [26] followed 243 people who had received rituximab for systemic autoimmune disease, for a median of 42 months, and they found that severe hypogammaglobulinaemia (IgG <3 g/l) developed in 7 (3%) individuals, but resolved spontaneously in 5, 3 of whom continued to receive rituximab. Moderate hypogammaglobulinaemia was detected in 53 individuals (22%), but had resolved in 51% of them at the last follow-up. It is unclear whether there was an association between discontinuing rituximab and recovery of serum immunoglobulin levels. Rates of immunoglobulin replacement therapy (IGRT) in those experiencing SAD during rituximab therapy have been reported at ~15–20% [26,31,42].

SAD has been less well studied in newer anti-CD20 therapies. Several phase 3 studies of ocrelizumab in rheumatoid arthritis, published between 2012 and 2014, did not report data on serum

immunoglobulins [43–47]. More recent phase 3 trials in MS suggested that ocrelizumab has a deleterious effect on serum immunoglobulin levels. The proportion of patients with immunoglobulin below the LLN at baseline was 0–0.5% (IgG), 0.2–1.5% (IgA), and 0.1–0.2% (IgM). Following the treatment period (96–120 weeks), the proportion of participants with immunoglobulin below the LLN was 1–1.5% (IgG), 0.5–2.4% (IgA), and 15.5–16.5% (IgM) [48,49]. Similarly, serum IgG was found to be below the LLN at some stage in 4–10% of participants receiving ofatumumab for rheumatoid arthritis in phase 3 clinical trials [50]. So far, data on ublituximab is limited to small phase 1 and 2 studies, with no systematically collected serum immunoglobulin data [51,52].

The pathogenesis of secondary antibody deficiency in anti-CD20 therapy

A profound and durable depletion of circulating B cells occurs within days of rituximab infusion. Plasma cells do not express CD20 and should therefore be resistant to the immediate depletory effects of anti-CD20 therapy [53]. However, two main plasma cell populations are known to exist: short-lived plasma cells (SLPCs), which are thought to arise as a result of differentiation of activated B cells, and long-lived plasma cells (LLPCs), which arise as a result of secondary immune responses [54]. The SLPCs are seen to disappear within a few days of anti-CD20 therapy, when they cease to be replenished by memory B cells [54]. However, the LLPC population is thought to be a self-sustaining population with a lifespan approaching the host and has been shown to be resistant to anti-CD20 therapy in the short to medium term [55–57]. The longevity of LLPCs appears to depend upon residence in survival niches within the bone marrow or inflamed tissues; and the presence of crucial supporting factors maintains an antiapoptotic phenotype [54]. However, it remains unclear whether long-term humoral immunity results entirely from a self-sustaining LLPC population or whether replenishment of plasma cells by memory B cells is required [58]. Despite the apparent survival of LLPCs after B-cell depletion, several clinical studies have observed a dose-dependent reduction in serum immunoglobulins following anti-CD20 therapy [32,40,59,60]. This implies that long-term humoral immunity may be more reliant on replenishment of plasma cells from the B-cell progenitor pool than previously thought. Interestingly, although a protease inhibitor can be used to effectively abolish the LLPC population in mice, the LLPCs repopulate within 2 weeks unless B-cell progenitors are also depleted [61].

Conversely, it may be that the role of SLPCs in long-term humoral immunity has been underestimated. Anti-CD19 therapy induces B-cell lymphopenia and eliminates the CD19-positive SLPC population, but should spare the CD19-negative LLPCs [62]. In humans treated with anti-CD19 therapy, levels of some disease-specific antibodies (including pneumococcus, *Haemophilus*, and herpes simplex virus) have been seen to diminish within 90 days, suggesting that the SLPC fraction plays some role in maintaining levels [58]. It appears that a relative paucity of memory (CD27⁺) B cells, the precursors of the short-lived PC, within the reconstituted B-cell population occurs [63], which may shift B cells toward a more regulatory and less memory phenotype after rituximab. Although this effect is likely to offer therapeutic benefit for the underlying autoimmune disease [64,65], it is likely to diminish disease-specific immunity [66,67].

Disease-specific factors are also likely to contribute to the pathogenesis of B-cell depletion and hypogammaglobulinaemia during anti-CD20 therapy. For instance, haematological diseases such as lymphoma may cause dysfunction of B-cell proliferation and maturation that predisposes toward hypogammaglobulinaemia, whereas some autoimmune diseases are associated with high levels of circulating immunoglobulins, which may protect against the development of SAD [68]. Previous or concurrent treatments are also likely to play an important role. The use of steroids and cyclophosphamide has been observed to be particularly relevant to the risk of SAD [26,33,36,68]. It follows that data from Haematology and Rheumatology studies must be extrapolated with caution to a neurological population.

Secondary antibody deficiency and risk of infection

The presence of SAD arising in the context of anti-CD20 treatment is expected to have several consequences. Low serum immunoglobulin levels are likely to predispose to higher rates of infection, especially bacterial and sinopulmonary infections. There is evidence from some studies suggesting an excess of bronchitis, sinusitis, otitis media, or pneumonia in those receiving rituximab [25,37,69–71]. However, there are also case reports of opportunistic viral or fungal infections in those with anti-CD20-related SAD [72–75]. Although there are likely to be confounding factors that influence infective risk in those receiving anti-CD20 therapy, several studies have linked lower levels of serum immunoglobulins to a higher incidence of infection [22,35,42,76–78]. IgM levels appear to be most commonly depleted in anti-CD20-related SAD [5,23,24,27,79], but the clinical

implications of IgM deficiency are thought to be less significant than IgG deficiency [23,78,80[■],81].

Diagnosis and monitoring of secondary antibody deficiency

Diagnostic considerations of SAD should begin prior to the initiation of B-cell ablation therapy and would involve a baseline risk assessment covering four main areas – the amount and duration of immunosuppressive therapy to date, the current levels of serum immunoglobulins and disease-specific antibodies, the baseline infection burden alongside any additional risk factors known to increase likelihood of SAD. Baseline evaluation should be followed by risk reduction strategies, if appropriate, prior to commencement of B-cell depleting therapy. It is apparent from the available data on SAD in Neurology that the majority pertains to immunoglobulin levels IgG, IgA, and IgM – a measure of antibody quantity – however, it should be noted that important additional information is added by measurement of specific antibodies (tetanus, *Haemophilus*, and pneumococcus) and potentially vaccine responses (a measure of antibody quality).

Although for some indications rituximab and other agents targeting B cells may become more first line, many patients will have potentially been treated with prior immunosuppressive medications for some years and it is important to document this, both to aid risk stratification and interpretation of the immunological assessment. It is clear that even single-agent corticosteroid therapy may cause SAD, reducing in particular IgG more than IgA and IgM [82].

Immunoglobulin levels and specific antibodies (tetanus, *Haemophilus*, and pneumococcus) are helpful in determining both the quantity and quality of humoral immunity [83[■]]. SAD may already be present or immunoglobulin levels may be at the lower end of the reference range which would itself be associated with a further increased risk of subsequent SAD. A careful clinical assessment of infection burden is important in terms of the frequency of infections in the previous 12 months, their site, severity, duration, and whether antibiotics (oral and intravenous) were required and how many courses. Hospitalization for infection and the use of intravenous antibiotics would suggest greater severity. There is an opportunity to identify additional risk factors such as smoking, chronic obstructive pulmonary disease, asthma, diabetes, chronic sinusitis and bronchiectasis, so on, which, if appropriate, may require imaging studies to define the site and extent of suspected bronchiectasis. Risk reduction may involve optimization of therapy for existing co-morbidities where possible. Vaccination may

also be indicated where specific antibodies have been identified to be below protective levels, checking postvaccination response after 4 weeks [84]. There is also the opportunity to assess whether the patient would benefit from varicella zoster vaccination and also to determine whether an emergency home supply of antibiotics would be indicated. Response to vaccinations is likely to be diminished once anti-CD20 therapies are established [67].

Monitoring following the initiation of anti-B cell therapy

Monitoring for the development of SAD should be undertaken every 6–12 months and would similarly include an evaluation of the infection burden, serum immunoglobulins, and disease-specific antibody levels. Some neurologists find it helpful to monitor the return of B cells and class-switched memory B cells in terms of individualization of the retreatment interval.

If impairment of humoral immunity is identified with reduced total immunoglobulin levels, poor response to vaccination, and a significant infection burden, prophylactic antibiotics and potentially IGRT may be needed. There are now a range of options for IGRT including, intravenous, conventional subcutaneous, subcutaneous rapid push, and facilitated subcutaneous, which allow individualization, a greater proportion of patients able to undertake their infusions themselves at home, and improved adherence and quality of life [85,86]. Decisions relating to IGRT are best addressed in a multidisciplinary manner alongside Clinical Immunology deciding on the location (hospital or home infusions) and the route (intravenous or subcutaneous) dose, cycle duration, number of sites for subcutaneous Ig, product choice and whether training and home care will need to be put in place alongside haemovigilance monitoring [83[■],85]. Once the decision has been made to commence IGRT, efficacy will be monitored both in terms of reduction of the infection burden from the baseline assessment as well as ensuring the IgG levels are appropriately within the reference range. In SAD, we tend to aim for IgG levels above 7 g/l at trough in uncomplicated cases but will increase this to above 9 g/l if there is structural lung damage such as bronchiectasis. These levels are for guidance only as there is a wide range of inter-individual variation and doses and treatment regimens will need to be adjusted for each individual.

A further consideration in the context of SAD is whether to modify the anti-CD19/antiCD20 treatment schedule. The finding that B-cell depletion

lasts an average of 6 months [87], has commonly led to a 6-monthly dosing regimen of rituximab and ocrelizumab in neurology. However, the considerable inter-individual variation in repopulation time has led several authors to recommend that retreatment with rituximab should be guided by B-cell repopulation, using CD19⁺ (a pan B-cell marker) or CD27⁺ (a marker of memory B cells) as a way of reducing the cumulative dose of rituximab without compromising disease control [30,59,65]. Alteration of dose schedule according to B-cell repopulation has been shown to be associated with resolution of SAD in some cases [37].

CONCLUSION

The range of current licensed and unlicensed uses of B-cell ablation therapies for neuroinflammatory indications is expanding and includes MS, neuromyelitis optica, myasthenia gravis, CIDP, MMN, autoimmune limbic encephalitis, anti-MAG neuropathy, stiff person syndrome, and primary CNS vasculitis. This alongside the development of more effective B-cell targeting is likely to lead to an increase in the prevalence and burden of SAD. The proportion of patients who develop SAD and a significant infection burden varies with the disease (e.g. CLL and MM may cause immunodeficiency in the absence of therapy) and degree of prior therapy. Several factors appear to predispose to a higher likelihood of SAD including low immunoglobulin levels prior to commencement of B-cell ablation therapy, maintenance therapy, combination therapies, and prior therapy with cyclophosphamide and steroids. Infections are also more likely if there are additional co-morbidities such as chronic lung disease, diabetes, and older age. Infections may be insidious and patients may present with established bronchiectasis but is also often missed despite recurrent infections as an infection history may not form part of routine neurological review.

There is a need for increased awareness as well as screening for SAD beginning prior to the initiation of B-cell ablation therapy to risk stratify and aid identification to avoid infection-related morbidity and mortality. This also facilitates individualized intervention, which may involve vaccination, antibiotics (emergency or prophylactic), or IGRT. It may also be necessary to adjust treatment regimens. The care and treatment of patients with both neurological disease and SAD is best facilitated in a multidisciplinary approach with Neurology and Clinical Immunology.

Although there are clear overlaps in the clinical management with primary antibody deficiency, the evidence base for therapeutic decisions in SAD remains limited. In addition, the rapidly evolving

therapeutic environment means that ongoing prospective studies, potentially facilitated by biologics databases as in other disease areas, will be key to informing future therapeutic strategies, the identification of biomarkers, and widening the understanding of this often poorly recognized treatment-related side-effect.

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Conflicts of interest

Rituximab is not labelled for all the uses under discussion in this article, and therefore use in certain conditions described is still investigational.

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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