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B cell therapies in ANCA associated vasculitis: why measure B cells and immunoglobulins?

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## **Introduction**

B cell targeted therapies are becoming more widely used to treat inflammatory kidney disease. However, even within specific diseases, there is significant heterogeneity in disease phenotype and response to therapy. Antineutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) is an example of a disease in which use of B cell targeted therapies are increasingly common. Rituximab, a murine chimeric monoclonal antibody depleting B cells expressing CD20, is an alternative induction immunosuppression agent to cyclophosphamide and offers an alternative to azathioprine as maintenance immunosuppression (1). We will focus on experience of rituximab use in AAV to illustrate the role of monitoring differential white cell counts and immunoglobulins.

## **Why measure B cell counts?**

Modern treatments for AAV are effective at inducing disease remission in most patients. A greater challenge lies in maintaining ongoing remission and limiting progressive chronic kidney disease, whilst avoiding treatment-related morbidity and mortality, particularly from infections. B cell depleting therapy can have variable pharmacodynamic effects, with significant variability in timing of B cell reconstitution. B cell reconstitution following rituximab is delayed in AAV compared to use in other rheumatic diseases (2).

The optimum duration and dosing frequency of rituximab in AAV remains unknown. Fixed dose rituximab appears to be a safe and effective maintenance regimen in AAV. B cell return within 12 months of the last rituximab infusion is a risk factor for further disease relapse (3), however individualised approaches to rituximab dosing based on biomarkers have so far failed to show improved outcomes. Rituximab administration tailored to CD19 B cell reappearance or rising ANCA titre was associated with non-statistically significant trends towards increased relapses but reduced rituximab usage in AAV, compared to a fixed dose regimen (17.3% versus 9.9%;  $P=0.22$ )(4).

Differential white cell counts may not reflect all sources of autoreactive B cells. High sensitivity flow cytometry reveals minimal residual autoimmunity below the detection of standard assays (5), with evidence for ANCA-memory B cells detectable following rituximab therapy (6). Furthermore, B cell depletion in the peripheral blood does not correlate with depletion of tissue resident cells (7). Belimumab is an antibody targeting B cell-activating factor (BAFF; also known as BLYS), a critical B cell survival factor associated with autoimmunity. In a randomised controlled trial belimumab did not improve remission rates in AAV compared to placebo, however it was noted that relapses only occurred in belimumab treated patients who had received cyclophosphamide induction with those induced with rituximab remaining in remission (8). The COMBIVAS study is testing the hypothesis that belimumab in combination with rituximab, may negate the rise in serum BAFF levels seen following B cell depletion, promote migration of tissue resident memory B cells into the circulation exposing them to rituximab mediated depletion and modulate the phenotype of reconstituting B cells (1).

Differential white cell counts may detect late onset neutropenia, a recognised complication of rituximab therapy, occurring in around 10% of those treated with repeated doses of rituximab in AAV (9). Neutropenia appears to be associated with more prolonged B cell depletion, occurring at a median time of 102 days (range 40–362 days) following rituximab dosing (10). Treatment with granulocyte colony-stimulating factor should be considered when neutropenia is symptomatic. Discontinuation of rituximab is not required.

### **Why measure immunoglobulins?**

Antibodies are an important component of the adaptive immune response. Although B cell targeted therapies seem to preferentially target pathogenic antibodies they can cause generalised hypogammaglobinaemia. Hypogammaglobinaemia predisposes to recurrent and severe infections.

Among 243 patients who received rituximab for autoimmune rheumatic disease (AIRD), IgG hypogammaglobinaemia was present in 26% at the time of rituximab initiation and 56% during follow up; 26% of cases in this cohort were classified as moderate or severe (IgG <5 g/L), with half of these showing spontaneous improvement (11). Mature plasma cells, the source of most circulating IgG, do not express CD20 and are not depleted by rituximab. Early immunoglobulin decline after rituximab is often transient, with underlying disease and prior or concomitant immunosuppression therapy believed to contribute. Late onset immunoglobulin decline can be sustained, with a median time to immunoglobulin nadir of 35 months (range 1-70 months) (12). This is considered to reflect prolonged depletion of plasma cell precursors leading to reduced replenishment of mature plasma cells.

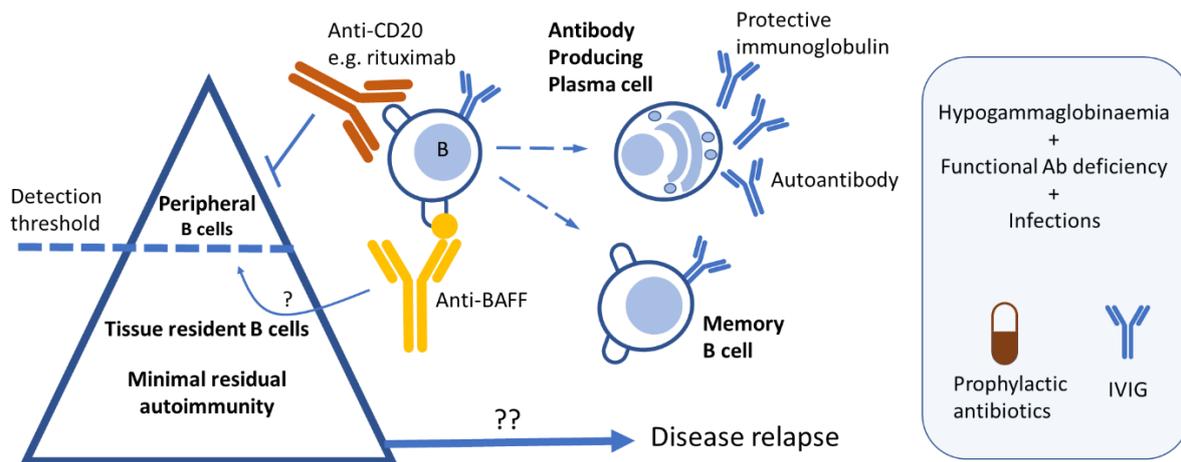
Low immunoglobulin levels prior to initiation of rituximab predict subsequent sustained hypogammaglobinaemia and are associated with increased risk of infection post rituximab, but should not be viewed as a contraindication to therapy. Concomitant or prior immunosuppression, especially cyclophosphamide may have a synergistic effect. Recent consensus recommendations suggest checking immunoglobulin levels prior to commencement of B cell targeted therapy and repeating every 6-12 months up to a minimum of one year after stopping treatment, with longer monitoring in selected patients (13).

Patients with sustained hypogammaglobinaemia with severe, persistent, unusual or recurrent infections, who fail to make antibody responses to unconjugated polysaccharide vaccines may benefit from immunoglobulin replacement therapy following a trial of antibiotic prophylaxis (13). Retrospective case reports suggest requirement for immunoglobulin replacement in 4.2% to 21% of patients treated with rituximab for AIRD (11, 12). Discontinuation of rituximab on the grounds of worsening symptomatic hypogammaglobinaemia must be weighed against the benefits of controlling underlying disease and availability of alternative immunosuppressant therapy.

## Conclusions

Measurement of the phenotype of reconstituting B cells in a research setting may allow us to better understand the role of B cells in pathogenesis, identify risk factors for treatment failure and limit treatment-related adverse events. This may guide optimal duration and frequency of B cell depleting treatment and open the door for more patient-tailored approaches providing disease suppression to patients at high risk of disease relapse whilst limiting potential treatment toxicity in those at low risk. Greater understanding of the relevance of findings and how they impact on clinical outcomes is required before this becomes part of standard of care. Vigilance for symptomatic late onset neutropenia and prompt treatment of associated infections is important but there is no evidence to suggest monitoring for asymptomatic neutropenia. Monitoring of immunoglobulin levels is useful to limit treatment associated infectious complications and guide immunoglobulin replacement therapy.

Figure 1: Treatment with rituximab induces variable duration of peripheral B cell depletion and optimal frequency and duration of dosing is unclear. Minimal residual autoimmunity below the threshold of detection or present within tissue niches may be treatment-resistant and drive recurrent disease. Combination therapies may better target autoimmune B cells. Belimumab, an anti BAFF monoclonal antibody, is hypothesised to promote migration of tissue resident B cells into the periphery. Long term depletion of plasma cell precursors may cause hypogammaglobinaemia resulting in infectious complications due to loss of protective immunity. Prophylactic antibiotics and Intravenous immunoglobulin (IVIG) replacement are recommended in line with guidelines for secondary immunodeficiency



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