Secondary antibody deficiency and immunoglobulin replacement

Abstract: Antibody deficiencies can be either primary or secondary, leading to significant morbidity and mortality without appropriate management. Secondary antibody deficiency can be due to various diseases or iatrogenic causes, especially with the use of immunosuppressive agents such as B-cell depleting therapies. Unlike its primary counterpart, little is known regarding the management of secondary antibody deficiency and it remains an underappreciated entity. This is a growing concern with the growing numbers of patients on various immunosuppressant therapies and increasing survivors of autoimmune diseases and haematological malignancies. In this report, we review the diagnosis and management of secondary antibody deficiency, especially after rituximab-induced hypogammaglobulinemia.

Keywords: secondary; antibody deficiency; hypogammaglobulinemia; humoral deficiency; immunodeficiency

1 Introduction

Antibody deficiencies, or hypogammaglobulinemia (HG), are characterized by decrease in the absolute number or function of circulating antibodies (immunoglobulins (Ig)), which predispose patients to severe and recurrent infections. Primary antibody deficiencies, such as X-linked agammaglobulinemia and common variable immunodeficiency (CVID), are due to intrinsic genetic mutations commonly resulting in defects of B-cell development or function.[1] Patients with untreated primary antibody deficiencies experience significant morbidity and mortality from recurrent infections. However, the availability of Ig replacement has led to significantly better outcomes with reduced infection rates as well as improved morbidity, mortality and quality of life.[2-5]

Secondary antibody deficiencies can be caused by protein-losing states (such as protein losing enteropathy and nephrotic syndrome), lymphoproliferative disorders (particularly chronic lymphocytic leukemia and multiple myeloma), infections and iatrogenic causes such as use of immunosuppressive therapies. Common causes of iatrogenic HG include the use of various immunosuppressive therapies, anti-epileptic agents, gold-based drugs and radiotherapy that are commonly overlooked. For example, both short and long term steroid use frequently leads to HG because of enhanced catabolism with reduced synthesis of Ig.[6-9] Although frequently asymptomatic, IgA deficiency was identified in almost 20% of patients on common anti-epileptics such as phenytoin,[10] while profound hypogammaglobulinemia has also been reported with the use ofocarbamazepine, lamotrigine, levetiracetam, phenytoin and valproate.[11-15] Examples of various common drugs implicated in iatrogenic HG are summarized in Table 1. This list continues to expand with the rapid development of novel immunosuppressive and biologic therapies. In particular, the increasing popularity of anti-CD20 therapies, such as rituximab, has led to increasing reports of secondary antibody deficiency and fueled more research into its significance and treatment.

Despite this increasing awareness, there is still limited evidence available in the current literature regarding the clinical significance and management of this growing problem. Especially in the case of iatrogenic HG, studies have been challenging as it is often difficult to ascertain the influence from underlying disease rather than the suspected treatment – the overall clinical phenotype is likely to be a mixture of both. In this report, we review the current evidence regarding the management in secondary
antibody deficiency, especially after rituximab-induced HG.

2 Iatrogenic hypogammaglobinemia after rituximab

Since its discovery in 1991, the human-mouse chimeric monoclonal anti-CD20 antibody rituximab has been employed for its potent B-cell depleting ability in a myriad of hematological malignancies and autoimmune diseases. [16-18] CD20 is a B cell-specific differentiation antigen that is expressed on pre-B and mature B cells, which is lost upon differentiation into plasma cells. Rituximab specifically binds with the CD20 antigen expressed on B-cells and leads to rapid depletion of a majority of these CD20-expressing B cells in the peripheral blood via the complement-mediated and antibody-dependent cell-mediated cytotoxicity. Stem cells, pro-B-cells and plasma cells that do not express CD20 are spared, which allows for B cell recovery after anti-CD20 therapy. Depending on marrow regeneration, peripheral B cell levels usually remain low or undetectable for up to 6 months before returning to pre-treatment levels.[19] HG likely results from the prolonged B-cell depletion, resulting in the exhaustion of short-lived plasma cells over time.[20] There is also evidence to suggest that rituximab also has an effect on T-cell regulation, which may also further contribute to its immunosuppressive effects.[21-23]

Although serum Ig levels mostly remained stable after rituximab therapy and serious infections were not identified in initial meta-analyses,[24, 25] there has been a growing body of literature regarding rituximab-induced HG and increased infection rates in recent years. Although often transient, rituximab-induced HG has been well reported and can persist for years following the cessation of treatment and necessitate long term Ig replacement.[26] The reported frequencies vary and results are likely to be confounded by the influences from underlying primary disease and concomitant immunosuppressive therapies, but a study in lymphoma reported rituximab-induced HG in 39% of patients with normal baseline serum Ig levels. Given its profound B-cell depleting properties, the number of doses of rituximab also correlate to the development of symptomatic HG and 6.6% required Ig replacement.[27] The reported frequencies of reported rituximab-induced HG are generally lower in studies of autoimmune patients (generally less immunocompromised compared to patients with hematological malignancies). For example, major trials in the use of rituximab in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) have demonstrated favorable safety profiles. Analyses of pooled safety data from multiple RA trials did not show any significant increase in serious infections despite fall in immunoglobulin levels.[28] Similarly, there was no increase in the infection rate for patients receiving rituximab of the two landmark randomized SLE trials (EXPLORER and LUNAR).[29, 30] Nonetheless, in a dedicated study of rituximab-induced HG in autoimmune diseases, 26% of patients developed HG (IgG <5g/l) and 4.2% required Ig replacement.[31] Generally, low baseline serum IgG (<6g/l) has been associated with increased risk of serious infections.[32-36] Further dedicated studies on the incidence and significant of rituximab-induced HG in various rheumatological diseases will be required.

Moreover, humoral responses to immunizations have also decreased and it is now generally recommended that vaccinations should be administered prior to the commencement of rituximab therapy.[36, 37] The risks of reactivation of various latent viruses such as cytomegalovirus, hepatitis B and John Cunningham virus after rituximab are well documented.[36] It has also been suggested that this persistent B-cell dysfunction might also be a result of the unmasking of latent humoral immunodeficiencies or intrinsically susceptible individuals with certain genetic polymorphisms.[38-41]

Table 1: Common examples of drug-induced hypogammaglobinemia

<table>
<thead>
<tr>
<th>Anti-epileptics</th>
<th>Immunosuppressants</th>
<th>Monoclonal antibodies</th>
<th>Others</th>
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<tbody>
<tr>
<td>Carbamazepine</td>
<td>Azathioprine</td>
<td>Belimumab</td>
<td>Antimalarial agents</td>
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<td>Lamotrigine</td>
<td>Cyclophosphamide</td>
<td>Ofatumumab</td>
<td>Captopril</td>
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<td>Levetiracetam</td>
<td>Cyclosporine</td>
<td>Rituximab</td>
<td>Fenclofenac</td>
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<td>Oxcarbazepine</td>
<td>Gold salts</td>
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<td>Phenytoin</td>
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<td>Valproate</td>
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Clinically, rituximab-induced HG likely resembles other primary antibody deficiencies – especially CD20 deficiency, a described rare monogenic CVID-like form of immunodeficiency.\[5, 42\]

Likewise, long term data for newer B-cell depleting therapies remain scarce but some preliminary experiences warrant heightened physician vigilance. Up to 9% of patients participating in phase III trials with ofatumumab, a fully humanized monoclonal anti-CD20, developed low serum IgG levels although without increased rate of infections.\[43\] Alarmingly, the development ofofezalizumab, another humanized monoclonal anti-CD20, in use for RA was prematurely terminated due to increased rate of serious infections, particularly in Asia.\[44\]

3 Role of immunoglobulin replacement

Prophylactic Ig replacement has been shown to significantly decrease infection, antibiotic use and hospitalization rates in patients with HG secondary to lymphoproliferative disorders with recurrent infections, with or without anti-CD20 therapy.\[45, 46\] It has also been demonstrated that Ig replacement reduces infection frequency regardless the underlying cause of antibody deficiency. Interestingly, patients with secondary antibody deficiency seem to respond at least as well, and possibly better, to Ig replacement.\[47\] However, evidence regarding iatrogenic HG remains scarce and there have not been any dedicated studies studying the benefits of Ig replacement in rituximab-induced HG.

No specific guidance for secondary antibody deficiency is available and recommendations vary; most authors generally agree to Ig replacement in symptomatic HG with recurrent infections, while others recommend specific IgG cut-offs, additional criteria such as impaired vaccine responses or only in patients with inadequate response to prophylactic antibiotics.\[47-50\] It has even been suggested that Ig replacement should be given to all infants and very young children who are treated with rituximab \[48\]. The outcome after Ig replacement or related adverse effects have not been well reported and target IgG levels have mostly been based on experience with primary antibody deficiencies. There is also much controversy regarding the optimal route of Ig replacement since the advent of subcutaneous Ig. Studies have demonstrated that subcutaneous Ig replacement can achieve lower variability of IgG serum levels with substantial improved cost-effectiveness and quality of life compared to intravenous replacement.\[51\]

4 Conclusion and recommendations

Unlike its primary counterpart, little is known and no formal guidance is available regarding the management of secondary antibody deficiency. This underappreciated entity is a growing concern with the growing number of patients on various immunosuppressant therapies as well as survivors of autoimmune diseases and hematological malignancies.

Physicians should be more aware of the possibility of this entity and serum Ig levels should be routinely monitored, especially in symptomatic and high risk patients (Box 1). In view of available evidence, we would propose screening of Ig levels before the commencement of immunosuppression (even in the case of “milder” immunosuppression, e.g., anticipated chronic steroid use equivalent to ≥5mg of prednisolone \[7\]). Regular interval monitoring of Ig levels, such as every 3-6 months, during “stronger” immunosuppression (e.g., cytotoxic chemotherapy, anti-CD20 therapy) or prolonged duration of immunosuppression should also be encouraged. For anti-CD20 therapies, a longer period of observation to at least 6-12 months after the last dose of treatment is warranted. Additionally, symptomatic patients with recurrent or severe infections should also have their Ig levels rechecked and monitored more frequently. The index of suspicion would be even greater in the face of particular pathogens, such as encapsulated bacteria (e.g., \textit{Streptococcus pneumoniae}, \textit{Haemophilus influenzae}), parasites (e.g., \textit{Giardia})

<table>
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<th>Box 1: Recommendations on screening for secondary hypogammaglobulinemia</th>
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<td><strong>When to screen for hypogammaglobulinemia:</strong></td>
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<td>- History of infection with unusual severity or frequency, or lack of response to therapy</td>
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<td>- History of characteristic pathogens (e.g., encapsulated bacteria or severe/persistent viral infections)</td>
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<tr>
<td>- Before commencement of any immunosuppressive therapies</td>
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<td>- Every 3-6 months while on “stronger” immunosuppression (such as cytotoxic chemotherapy, anti-CD20), and until at least 6-12 months after last dose of anti-CD20 therapy</td>
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lamblia, Cryptosporidium) or severe/persistent viral infections (e.g., chronic norovirus or enteroviruses). Other causes of antibody deficiencies, such as primary antibody deficiencies, manifestation of underlying primary disease, protein-losing states, infections and other possible causative drugs (Table 1) should also be excluded. Further workup such as diagnostic vaccination, lymphocyte and IgG subsets and formal immunologist referral should also be considered.

The decision for Ig replacement in secondary antibody deficiency is controversial and remains individualized. Based on limited evidence and the experience extrapolated from primary antibody deficiencies, we would recommend a low threshold for Ig replacement in any symptomatic patient regardless of the severity of HG. The underlying primary disease, reversibility of antibody deficiency, severity of infection, concurrent immunosuppression, patient co-morbidities and vaccine responsiveness (if available) need to be carefully considered on a case-by-case basis. When offered, Ig replacement should be started promptly (starting at 0.4g/kg/month, then titrated according to clinical response and individual patient factors). The choice between intravenous and subcutaneous replacement, targets IgG trough levels (usually at least >5g/l or level associated with complete infection reduction) and need for other adjunct therapies (such as antibiotic prophylaxis) should be individualized, preferably with immunologist involvement. Further studies with dedicated and prospective cohorts are required to validate the benefit of Ig replacement, identify at-risk patients and optimize the management of secondary antibody deficiency in the future.

References


