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EDITORIAL COMMENTARY

New therapies, new concerns: rituximab-associated lung injury

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Abstract The indications for use of B-cell depleting therapy with the monoclonal antibody rituximab are progressively increasing in patients with renal disease. This includes patients with nephrotic syndrome and renal graft rejection. Late-onset pulmonary injury associated with rituximab therapy has been increasingly recognized. While frequently reversible, it can be fatal. The spectrum of pulmonary disease associated with rituximab therapy, its investigation, and treatment are briefly reviewed.

Keywords B-cell · Nephrotic syndrome · Transplantation · Bronchiolitis obliterans · Interstitial lung disease

Abbreviations

BOOP	Bronchiolitis obliterans organizing pneumonia
COP	Cryptogenic organizing pneumonia
PTLD	Post-transplant lymphoproliferative disorder
TNFα	Tumor necrosis factor-α

We are entering an era of targeted immunomodulatory therapies. However, the complexity of immune networks is such that important surveillance of unexpected adverse effects is required. In this issue, Bitzan and colleagues [1] highlight a relatively rare, but highly significant adverse effect of rituximab therapy.

Rituximab is a chimeric (human/mouse) monoclonal antibody directed against the CD20 B-lymphocyte surface antigen. CD20 is expressed only in the B-cell lineage from the pre-B-cell stage to late differentiation [2]. Most plasma cells are CD20-negative. CD20 may act to signal phosphorylation or as a calcium channel in human B-lymphocytes, although its role in mice is uncertain. CD20 is a good target for monoclonal antibody therapy as it is highly expressed, it is not shed or internalized upon antibody binding, and is minimally present in soluble form.

Work in rodent models of B-cell lymphomas suggested that anti-CD20 antibody therapy could be effective. As murine antibodies promote the production of human antimouse antibodies, chimeric or humanized monoclonal antibodies were developed for clinical use [3]. Rituximab consists of a human IgG1/κ constant region and murine variable, antigen binding regions. Rituximab invokes cell death through a variety of mechanisms including antibody-dependent cell-mediated toxicity, complement-dependent cytotoxicity, induction of apoptosis, and sensitivity to cytotoxic agents or corticosteroids. Natural killer cells and macrophages expressing Fc receptors are responsible for the antibody-dependent cell-mediated toxicity. Complement-dependent cytotoxicity occurs through the recruitment of C1 to rituximab's Fc domain, triggering the classical complement cascade.

Rituximab has been primarily used in the treatment of non-Hodgkin's lymphoma and other B-cell malignancies. However, expanded use includes antibody-mediated autoimmune disorders, such as rheumatoid arthritis and systemic lupus erythematosus [4], renal graft rejection [5], and post-transplant lymphoproliferative disease (PTLD) [6], nephrotic syndrome, and focal–segmental glomerulosclerosis [7]. Rituximab results in significant depletion of peripheral blood B-lymphocytes. Depletion in secondary and tertiary lymphoid structures appears to be less efficient and local humoral responses may not be affected [8].

The effect of rituximab on immunoglobulin levels is more modest, as plasma cells, the major producers of

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immunoglobulins, do not express CD20, and so are not directly affected by rituximab. However, reduction of autoantibodies may not be the major therapeutic mechanism for rituximab's clinical effectiveness in autoimmune disorders. Rather, the decrease in the ability to present antigen and produce cytokines and chemokines may have a more significant effect on the action of T-cells and dendritic cells.

Adverse effects from rituximab include acute infusion-related events and delayed events. The acute reactions include fever, cutaneous and mucocutaneous reactions, hypotension, and bronchospasm. Transient pulmonary infiltrates can occur. These reactions are typically associated with a surge in cytokine release, most notably tumor necrosis factor-α (TNFα), and complement activation. Rapid tumor lysis with attendant adverse effects can be seen in patients being treated for malignancies.

The various pulmonary adverse effects have been described as interstitial pneumonitis, alveolar–interstitial pneumonia, pulmonary fibrosis, and bronchiolitis obliterans organizing pneumonia (BOOP), also known as cryptogenic organizing pneumonia (COP). Bitzan and colleagues [7] have coined the phrase rituximab-associated lung injury (RALI). Most affected patients described to date have been older adults treated for malignancies. The case described by Bitzan and colleagues in this issue is an 11-year old female renal transplant recipient with COP.

As previously reviewed by Bitzan [7], non-productive cough and hypoxemia are frequently noted. Fever is often seen, less commonly, fatigue, and rarely, hemoptysis [9]. The time to symptoms from first dose is variable and ranges from 1–3 months. Symptoms are more frequently acute, but can be more insidious in onset.

Chest radiographs and computed tomography (CT) scans typically show bilateral diffuse infiltrates. Rarely, nodules are seen. These changes appear to be reversible in survivors. Positron emission tomography can demonstrate abnormalities, even in asymptomatic individuals [10]. Bronchioalveolar lavage fluid can be unremarkable or lymphocyte-rich. In the few patients tested for signs of systemic inflammation, sedimentation rates or C-reactive protein and selected cytokines were elevated.

As many of the affected patients are receiving immune suppression and complicated medical regimes at the time of diagnosis, the differential diagnosis includes infection, particularly infection with opportunistic organisms, and adverse effects of other treatments known for pulmonary toxicity, such as cyclophosphamide. These should be ruled out using CT scans and bronchoscopy. Positron emission tomography may also be helpful. A lung biopsy may be required to differentiate the observed disease from PTLD.

As disease can worsen if additional doses of rituximab are administered, it is recommended that this be discontinued should respiratory disease develop. Treatment typically involves the use of high-dose systemic corticosteroids [11], but it is important to note that RALI may occur in patients already receiving corticosteroids. In their review, Bitzan and colleagues [7] noted that treatment with high-dose corticosteroids (≥60 mg/day or ≥1 mg/kg/day) was not associated with a better outcome than that of patients receiving doses <1 mg/kg/day. The use of cytokine-directed treatments, such as those directed against TNFα, are more speculative at this time, given the limited understanding of the pathogenesis of the disease. Many patients receive broad-spectrum antibiotics pending culture results. Oxygen should be administered as needed; however, it is important to note that the need for mechanical ventilation is a bad prognostic factor.

In this issue, Bitzan and colleagues report on a pediatric renal transplant recipient who developed COP. This case has many of the vexing elements concerning RALI. There was a history compatible with PTLD, the need for enhanced immune suppression with the development of acute cellular rejection, and the development of COP in a nodular form that appeared to resolve with a change from sirolimus to mycophenolate mofetil. There was subsequent development of asymptomatic new nodules that were positive on positron emission tomography and were not treated. Several years later she developed Hodgkin's lymphoma with multiple nodules. This case underscores the complex interplay between B-cells and Epstein-Barr virus (EBV), the difficulties in making the diagnosis of RALI, and the approach to its treatment.

Bitzan and co-workers previously reported a 14-year-old boy with relapsing nephrotic syndrome treated with rituximab who developed interstitial pneumonitis that responded to corticosteroids and antibiotics. In addition to the cases reviewed in that report by Bitzan and co-workers [7], one by Wagner and colleagues [11] and one by Lui and co-workers [12], there are several other recent descriptions of importance to nephrologists. Fehr and colleagues reported that 1 out of 4 patients receiving rituximab for chronic antibody-mediated renal allograft rejection developed interstitial pneumonitis [13]. This adult patient developed respiratory failure 6 weeks post-treatment, requiring oxygen for 4 months and improved on corticosteroids over a 6-month period. Chaumais and colleagues reported a case of a 9-year-old girl treated with rituximab for unresponsive nephrotic syndrome who developed fatal pulmonary fibrosis [14]. In a response letter to this report, Kamei and colleagues reported that of 28 patients with nephrotic syndrome (21 steroid-dependent and 7 steroid-resistant) treated with rituximab, 10, or a staggering 36%, experienced some sort of respiratory event [15].

Because of the complex interaction amongst the various cellular layers of the immune system, highly directed therapies may have untoward adverse effects. RALI is still relatively rare, but underreporting is certainly partly to blame. The effects can be disastrous and the response to

corticosteroids variable. Although it is more commonly seen in adult patients, clearly children can be severely affected. The onset of disease is typically weeks to months after the start of treatment; therefore, prolonged vigilance for the appearance of disease is required.

B-cell-depleting therapy must be used with caution. It would seem prudent to obtain a chest radiograph and oxygen saturation prior to commencing such treatment. Potential other diagnoses such as infection or toxicity secondary to other treatments should be ruled out. Prompt stoppage of rituximab and commencement of systemic corticosteroids also are warranted. It is vital that such adverse events continue to be reported.

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