

## Rituximab-induced Bronchiolitis Obliterans Treated with Intravenous Immunoglobulin

Christopher Halpin\*, Erica McGovern and Jeffrey Hoag

Center for Thoracic Oncology, Cancer Treatment Centers of America, Philadelphia, PA, USA

### Abstract

Bronchiolitis Obliterans (BO) is a clinical syndrome associated with dyspnea and airflow limitation due to fibroproliferative thickening of the bronchiolar walls which can progress to the complete obliteration. Varying etiologies have been known to incite this process, with no definitive course of treatment that has demonstrated consistent clinical benefit. Rituximab is a monoclonal antibody with antineoplastic properties, of which bronchiolitis obliterans has been described as a complication of therapy. This is a case describing Intravenous Immunoglobulin (IVIG) as therapy for bronchiolitis obliterans refractory to systemic steroids.

**Keywords:** Bronchiolitis obliterans; Rituximab; Intravenous immunoglobulins

**Received:** December 26, 2018; **Accepted:** January 16, 2019; **Published:** January 23, 2019

### Introduction

Bronchiolitis Obliterans (BO) is a clinical syndrome associated with dyspnea and airflow limitation that is not reversible to inhaled bronchodilator medication. This injury pattern has been described in response to a myriad of insults including inhalational toxins, infections, various systemic diseases, and after hematopoietic cell or lung transplantation. Histologically, it has been described as constrictive bronchiolitis or proliferative bronchiolitis, with fibroproliferative thickening of the bronchiolar walls causing narrowing of the bronchiolar lumen, which may progress to the complete obliteration of bronchioles. Unfortunately, the pathogenesis of BO is not well defined. Due to the insult, there is excessive proliferation of granulation tissue in the airway that causes narrowing or obliteration of the lumen, but sometimes there is submucosal fibrosis that can cause additional constriction of the airway. Symptoms are typically dyspnea and cough, but rarely with sputum production. There is no consistent treatment algorithm that has demonstrated significant clinical benefit, and the disease is typically progressive despite therapies leading to respiratory failure. Symptomatic therapy to improve cough and hypoxia are often employed. For transplant related BO, the use of macrolide antibiotics has improved outcomes and would be recommended for a trial of 3-6 months. Steroids have been tried, but due to lack of efficacy and high frequency of side effects, it is not ideal.

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes (package insert). The mechanism of antineoplastic action is through B-cell

signaling, complement activation and direct apoptosis. Cell lysis may be the result of complement-dependent cytotoxicity as well as antibody-dependent cellular cytotoxicity. Complement activation and cytokine secretion, in particular, seems to be the causative factors associated with rituximab infusion reactions. TNF- $\alpha$  has been postulated to be the major inflammatory mediator in ILD pathogenesis by inducing chemokines, other inflammatory cytokines, and angiogenic factors [1].

Herein, we describe a case of a patient treated with rituximab who developed bronchiolitis obliterans as a complication of therapy. He was successfully treated with Intravenous Immunoglobulin (IVIG) therapy with recovery of lung function and resolution of symptoms.

### Case

Our patient is 62-year-old man with stage III chronic lymphocytic leukemia/small lymphocytic lymphoma who was treated with rituximab and bendamustine therapy followed by maintenance rituximab. He had hypogammaglobulinemia with specific deficiencies in IgA, IgM, and IgG antibody isotypes, particularly IgG1, IgG2 and IgG3. The patient was not previously treated with adoptive immunotherapy as he did not suffer from recurrent sinopulmonary infections.

After nine months of maintenance rituximab, he developed

**\*Corresponding author:** Christopher Halpin

✉ Christopher.halpin@ctca-hope.com

Center for Thoracic Oncology, Cancer Treatment Centers of America, Philadelphia, USA

**Tel:** 215-537-7400

**Citation:** Halpin C, McGovern E, Hoag J (2018) Rituximab-induced Bronchiolitis Obliterans Treated with Intravenous Immunoglobulin. J Med Oncol. Vol.2 No.1:2

progressive exertional dyspnea prompting pulmonary evaluation. Imaging demonstrated a diffuse, bilateral mosaic pattern consistent with air trapping, and pulmonary function testing showed non-reversible severe obstruction, air trapping and a severe impairment in gas exchange. Cardiopulmonary exercise testing showed a limitation to exercise due to his obesity as demonstrated by a reduced maximum  $\text{VO}_2/\text{kg}$ . Pre-exercise spirometry demonstrated obstruction, and the flow limitation did not improve on post-exercise testing. Furthermore, his oxygen saturations dropped to 84% with exercise. Bronchoscopy was non-diagnostic. The patient was diagnosed with bronchiolitis obliterans secondary to medication (rituximab). Inhaled therapies did not alter his symptoms, so he was treated with moderate dose oral corticosteroids. The severity of airway obstruction and air trapping slowly improved; however, he was not able to wean below 18 mg daily of prednisone without worsening of symptoms. Trials of azithromycin (250 mg three times per week) and azathioprine (1 mg/kg titrated to 2 mg/kg) were unhelpful as steroid sparing agents. Mosaic attenuation persisted on repeat CT chest imaging.

He was then started on intravenous immunoglobulin, 300 mg/kg every 3 weeks. His IgG level increased to >400 mg/dL after the first treatment and remained >600 mg/dL after the third treatment. He received a total of 16 treatments over a period of 12 months. Along with improvement in flow limitation to normal, air trapping and hypoxia resolved as well as imaging resolution of the mosaic attenuation pattern. He was then successfully tapered off the prednisone, and the IVIG was stopped soon thereafter.

## Discussion

Patients with chronic lymphocytic leukemia are at risk for pulmonary complications, including recurrent respiratory infections due to impaired humoral and cell-mediated immunity. Patients with Chronic Lymphoblastic Lymphoma (CLL) are at risk of developing chemotherapy-related pneumonitis as well as developing a second malignancy such as primary lung cancer.

Our patient had BO diagnosed with functional assessment and imaging that developed several months into treatment with rituximab. Bronchiolitis obliterans complicating rituximab therapy has previously been described among several other pulmonary toxicities including interstitial pneumonitis, Bronchiolitis Obliterans with Organizing Pneumonia (BOOP), and alveolar hemorrhage [2-6]. Treatment of such pulmonary complications has had variable success, and no standard approach exists. Most

have used steroids with or without other medications aimed at minimizing treatment side effects. Unfortunately, outcomes of rituximab-related lung disease are poor.

Bronchiolitis obliterans has been described in association with Paraneoplastic Autoimmune Multi-organ Syndrome (PAMS) complicating CLL and other hematologic malignancies and develops in the absence of exposure to autoimmune therapies [7]. In fact, this syndrome has been treated with rituximab; however, the BO component did not respond suggesting a possible independent etiology [8]. Because our patient's course was progressing on steroid therapy and refractory to macrolid and azathioprine as adjuncts, we sought alternative therapy with intravenous immunoglobulins.

Primarily comprised of IgG, IVIG has been demonstrated to inactivate T-cells, down-regulate B-cell antibody production, block B-cell surface receptors responsible for inducing proliferation, prevent complement activation, reduce pro-inflammatory cytokines and down-regulate the activity of macrophages [9]. The mechanism of IVIG's therapeutic effects has in part been attributed to the polyclonal binding specificities encoded in the variable domains of the administered antibodies that may counteract the activity of auto-antibodies or inflammatory mediators. It has also been attributed to the anti-inflammatory component of the IgG Fc portion [10]. In a murine model, it was demonstrated that IVIG induces surface expression of an inhibitory Fc receptor in treating ITP. Modulation of the inhibitory signaling pathway attenuated the autoantibody-triggered, inflammatory disease [11].

Intravenous immunoglobulin has been used as an oral glucocorticoid-sparing agent in patients with steroid-dependent asthma, and resulted in significant reductions in both oral glucocorticoid requirements and hospitalizations in a group of patients with severe asthma [12]. There is limited data pertaining to IVIG replacement therapy for the treatment of bronchiolitis obliterans. IVIG therapy to target a serum IgG level greater than 500-600 mg/dL has been shown to improve spirometry in patients with bronchiolitis obliterans by reducing pulmonary infections [13,14].

## Conclusion

In patients with bronchiolitis obliterans refractory to conventional therapies, including systemic steroids, intravenous immunoglobulin should be considered as a steroid sparing agent, even without overt pulmonary infections.

## References

- 1 Ryu JH, Myers JL, Swensen SJ (2003) Bronchiolar disorders. *Am J Respir Crit Care Med* 168: 1277-1292.
- 2 Shen T, Braude S (2012) Obliterative bronchiolitis after rituximab administration: a new manifestation of rituximab-associated pulmonary toxicity. *Intern Med J* 42: 597-599.
- 3 Wagner SA, Mehta AC, Laber DA (2007) Rituximab-induced interstitial lung disease. *Am J Hematol* 82: 916-919.
- 4 Biehn SE, Kirk D, Rivera MP, Martinez AE, Khandani AH, et al. (2006) Bronchiolitis obliterans with organizing pneumonia after rituximab therapy for non-Hodgkin's lymphoma. *Hematol Oncol* 24: 234-237.
- 5 Alexandrescu DT, Dutcher JP, O'Boyle L, Albulak M, Oiseth S, et al. (2004) Fatal intra-alveolar hemorrhage after rituximab in a patient with non-Hodgkin's lymphoma. *Leuk Lymphoma* 45: 2321-2325.
- 6 Ergin AB, Fong N, Daw HA (2012) Rituximab-induced bronchiolitis obliterans organizing pneumonia. *Case Rep Med* 2012: 4.

- 7 Maldonado F, Pittelkow MR, Ryu JH (2009) Constrictive bronchiolitis associated with paraneoplastic autoimmune multi-organ syndrome. *Respirology* 14: 129-133.
- 8 Hirano T, Higuchi Y, Yuki H, Hirata S, Nosaka K, et al. (2015) Rituximab monotherapy and rituximab-containing chemotherapy were effective for paraneoplastic pemphigus accompanying follicular lymphoma, but not for subsequent bronchiolitis obliterans. *J Clin Exp Hematop* 55: 83-88.
- 9 Hartung HP (2008) Advances in the understanding of the mechanism of action of IVIG. *J Neurol Suppl* 3: 3-6.
- 10 Anthony RM, Wermeling F, Karlsson MC, Ravetch JV (2008) Identification of a receptor required for the anti-inflammatory activity of IVIG. *Proc Natl Acad Sci U S A* 105: 19571-19578.
- 11 Samuelsson A, Towers TL, Ravetch JV (2001) Anti-inflammatory activity of ivig mediated through the inhibitory Fc receptor. *Science* 291: 484-486.
- 12 Spahn JD, Leung DY, Chan MT, Szeffler SJ, Gelfand EW (1999) Mechanisms of glucocorticoid reduction in asthmatic subjects treated with intravenous immunoglobulin. *J Allergy Clin Immunol* 103: 421-426.
- 13 Roifman CM, Levison H, Gelfand EW (1987) High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinemia and chronic lung disease. *Lancet* 1: 1075-1077.
- 14 de Gracia J, Vendrell M, Alvarez A, Pallisa E, Rodrigo MJ (2004) Immunoglobulin therapy to control lung damage in patients with common variable immunodeficiency. *Int Immunopharmacol* 4: 745-753.