**Original Article**

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TANAFFOS

# Bronchitis During Long-Term Treatment with Rituximab for ANCA-Associated Vasculitis: A Retrospective Cohort Study

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**Background:** To describe the frequency and risk factors for development of bronchitis in patients receiving prolonged rituximab.

**Materials and Methods:** We conducted a single-center retrospective cohort study of 113 consecutive adult patients with ANCA-associated vasculitis (AAV) who had continuous B cell depletion with rituximab for greater than 24 months. The primary outcome was an episode of cough measured with an ordinal scale as follows: 0=no cough; 1=daily cough, non-productive; 2=cough with sputum production once daily; 3 = cough with sputum production twice or more daily. Secondary outcome measures included serum immunoglobulin G (IgG) level, sputum culture, and antibiotic use. Logistic regression analysis was used to assess the odds ratio of developing cough.

**Results:** The median (IQR) follow-up was 3.4 years (IQR, 2.7–5.2). A non-productive cough was identified in 4.4% of patients (n=5). A daily cough with sputum production once daily was identified in 6.2% of patients (n=7), and a daily cough with sputum production twice or more daily was identified in 11.5% of patients (n=13). 44% of sputum cultures were positive for a pathogenic organism. The most common were *Haemophilus influenzae* and *Aspergillus fumigatus*. Antibiotics were used in 19.5% of patients (n=22). The median (IQR) nadir IgG level was 675 mg/dL (521–798). No patient received intravenous IgG supplementation. No associations were found to predict cough.

**Conclusion:** Bronchitis was seen in approximately one-fifth of patients with AAV on prolonged B cell depletion with rituximab.

**Keywords:** ANCA-associated vasculitis; Rituximab; Bronchitis; Adverse events

## INTRODUCTION

Long-term therapy with rituximab, an anti-CD20 monoclonal antibody, is an effective strategy for maintaining remission in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) (1, 2). Indeed, the length of treatment with B cell depletion from rituximab has extended beyond 2 years, with demonstrated superiority in disease control (3). However, the burgeoning use of long-term rituximab has also led to increased recognition of complications of B cell depletion, such as hypogammaglobulinemia, late-onset neutropenia, inflammatory vaginitis, among others (4-6).

Bronchitis is a clinical diagnosis of cough without pneumonia or an alternative explanation of symptoms (7). It is due to a self-limited inflammatory response to infections of the bronchial epithelium, with viral causes prevailing. It is relatively common, with an annual incidence in the United States of approximately 5% among

all ages (8). Bronchitis and bronchiectasis have been recognized as a complication of patients with primary antibody immunodeficiencies, such as common variable immunodeficiency. However, its description as a complication of pharmacologic B cell depletion therapy with rituximab remains limited.

We conducted a single-center retrospective analysis of bronchitis in a cohort of 113 patients with AAV in remission on long-term rituximab-induced continuous B cell depletion. Our objective is to describe the frequency, risk factors, and clinicoradiographic features of cough and bronchitis in patients receiving long-term rituximab.

## MATERIALS AND METHODS

### Study Design

This is a single-center retrospective study of 113 patients who have received more than 2 years of rituximab-induced continuous B-cell depletion for AAV at the Vasculitis and Glomerulonephritis Center at the Massachusetts General Hospital in Boston, Massachusetts. Of note, patients were prospectively identified as part of enrollment in the MAINTAINCAVAS trial (9). However, the present study pertains to patient data before trial enrollment; therefore, this study is retrospective in nature. All data were abstracted from the electronic medical record.

### Selection of patients

Patients were consecutively screened for entry. Inclusion criteria comprised: 1) a diagnosis of AAV as defined by a positive MPO- and/or PR3-ANCA test together with clinical features characteristic of ANCA-positive diseases as detailed in the 2012 Chapel Hill Consensus Conference Definitions; 2) estimated glomerular filtration rate ≥ 20 cc/min/1.73 $m^2$; 3) age inclusive between 18 - 82 years old; 4) treated with continuous rituximab at regularly scheduled intervals with a goal of undetectable B cells (< 10 cells/μL), as quantified by the number of $CD19^+CD20^+$ cells on peripheral blood flow cytometry, for at least 24 months; and 5) in sustained remission (defined by a modified Birmingham Vasculitis Activity Score – Wegener's Granulomatosis (BVAS-WG) = 0 and a prednisone dose of ≤ 7.5 mg for at least 12 months).

Exclusion criteria comprised: 1) the presence of secondary disease (disease suspected to be induced by levamisole-adulterated cocaine); 2) all transplanted patients; 3) additional immunosuppressive agents other than rituximab and/or total daily prednisone dose ≥ 7.5 mg; 4) serum immunoglobulin G (IgG) level < 300 mg/dL; 5) terminal cancer or other primary illness with life expectancy of less than 36 months; 6) active anti-GBM disease and other known autoimmune disease for which the need for additional immunosuppression is likely; and 7) pregnancy or breastfeeding.

### Rituximab treatment regimen and study follow-up period

Continuous B cell depletion was achieved by regularly scheduled rituximab intervals with a goal of undetectable B cells. Typically, rituximab was administered starting with two 1,000-mg intravenous (IV) doses separated by 2–4 weeks. Thereafter, rituximab was most commonly administered as a single 1,000-mg IV dose every 4–6 months.

The study follow-up period was defined as the date of the first rituximab infusion (as part of induction remission therapy), up to the point when continuous B cell depletion was stopped, defined by the last documented date of B cell depletion before documented peripheral B cell repopulation, defined as total $CD19^+CD20^+$ cell count ≥ 5 cells/μL.

### Outcomes

The primary outcome measure was an episode of bronchitis, defined by new persistent cough, with or without sputum production, occurring during the study follow-up period, and clinically attributed to airway inflammation without an alternative identifiable cause. To determine whether patients had an alternative identifiable etiology of cough (e.g., gastroesophageal reflux disease, post-nasal drip, asthma, use of angiotensin-converting enzyme inhibitor therapy), medical records surrounding the cough were reviewed. Determination of cough was

based on available history from the treating physician's documentation. Cough was measured with an ordinal scale as follows: 0= no cough; 1= daily cough, non-productive; 2= cough with sputum production once daily; 3=cough with sputum production twice or more daily. Bronchitis was defined as a binary event with any score ≥ 1 at any time point during the study period defined as a bronchitis event.

Secondary outcome measures included serum immunoglobulin G (IgG) level (nadir level during continuous B cell depletion), sputum culture results, chest imaging findings, and antibiotic use for bronchitis throughout the study follow-up period. Chest imaging obtained during follow-up was due to the development of a new or worsening respiratory clinical sign or symptom.

### Statistical analysis

Continuous variables are presented as median (interquartile range [IQR]) or mean (standard deviation), as appropriate. Categorical variables are presented as percentages. Univariate and multivariate logistic regression models were used to estimate the odds ratio (95% CI) for bronchitis associated with each potential predictor. The multivariable model was adjusted for smoking status (never, current/former), length of time on continuous B cell depletion (per 1 year), nadir serum IgG level (per 100 mg/dL) during the period of B cell depletion, pre-existing lung involvement from AAV (yes, no). All analyses were conducted using STATA 15 (StataCorp, College Station, TX).

## RESULTS

### Study population

We identified 113 adult patients between 2007 and 2018 with AAV in remission treated with rituximab-induced continuous B-cell depletion for more than 2 years. The mean±SD age at initiation of therapy was 57±12 years, and 47% of patients were female. Among the 113 patients, 62(55%) were PR3-ANCA and 51(45%) were MPO-ANCA. 54 (48%) patients had lung involvement of AAV, defined by clinical or imaging features of pulmonary hemorrhage/diffuse alveolar hemorrhage, tracheobronchial inflammation, pulmonary infiltrates, pulmonary nodules with or without cavitation, and interstitial lung disease. Smoking status included never (n=65; 57.1%), current (n=5; 4.5%), and prior (n=43; 38.4%). The median (IQR) nadir serum IgG level during the study period was 675 mg/dL (521–798). Seven patients (6.2%) had an IgG < 400 mg/dL. No patients received IVIG treatment. Study population characteristics are presented in Table 1.

**Table 1.** Study population*

| | Total (n = 113) |
|---|---|
| **Age - years, mean (SD)** | 57 (12) |
| **Female no. (%)** | 53 (47%) |
| **PR3 no. (%)** | 62 (54.9%) |
| **Lung involvement of AAV no. (%)** | 54 (47.8%) |
| **Duration of continuous B cell depletion – years (IQR)** | 3.4 (2.7 – 5.2) |
| **Smoking status** | |
| Never | 65 (57.1%) |
| Current | 5 (4.5%) |
| Prior | 43 (38.4%) |
| **Nadir IgG level (mg/dL)** | 675 (521 – 798) |
| **Hypogammaglobulinemia (IgG < 400)** | 7 (6.2%) |
| **Treatment with IVIG** | 0 |

*Except where indicated otherwise, values are the median (interquartile range). AAV=antineutrophil cytoplasmic autoantibody (ANCA) associated vasculitis; IgG=immunoglobulin gamma; IVIG=intravenous immunoglobulin G; PR3=proteinase 3

### Outcome measures

#### *Primary outcome*

The median (range, IQR) follow-up period (i.e., the median duration of continuous B cell depletion) was 3.4 (2–10.5, 2.7–5.2) years. Of the 113 patients during the follow-up period, an episode of bronchitis, defined as a cough score ≥ 1, was identified in 22.1% (n=25) of patients. A cough score of 1 (daily non-productive cough) was identified in 4.4% (n=5) of patients. A cough score of 2 (daily cough with sputum production 1x per day) was identified in 6.2% (n=7) of patients, and a cough score of 3 (daily cough with sputum production ≥ 2x per day) was identified in 11.5% (n=13) of patients. The remainder of patients (n = 88; 77.9%) were not noted to develop a cough (Figure 1).

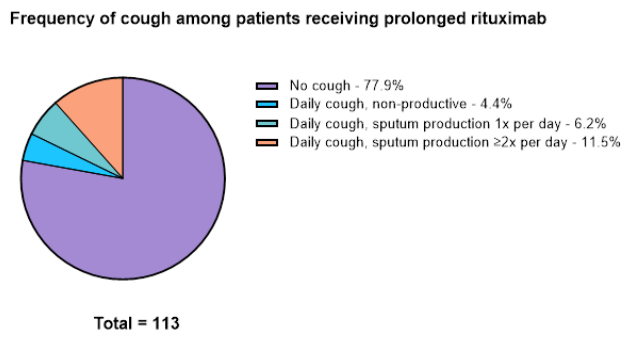



**Figure 1.** Frequency of cough among patients receiving prolonged rituximab. Display of the proportion of patients with ANCA-associated vasculitis receiving prolonged rituximab therapy who developed a coughing episode

### *Secondary outcomes*

During the study follow-up period, a CT chest was performed on 34 patients (30.1%). The most common findings were bronchiectasis (n=11) and bronchial wall thickening (n = 6) (Table 2). The bronchiectasis was not attributable to active vasculitis. Adequate data on pre-treatment CT chest imaging were not available for patients without lung involvement of AAV (n=59); however, 24% (n=14) obtained CT chest imaging during the study follow-up period due to the development of a new respiratory clinical sign or symptom. The CT findings were bronchiectasis (n=4), nodules (n=3), bronchial wall thickening (n=2), emphysema (n=2), interstitial lung disease (ILD) – nonspecific interstitial pneumonia (NSIP) (n=1), ILD – unspecified (n=1), pneumonia (n=1), non-specific scarring (n=1), and normal (n=1). On the other hand, of the 54 patients with lung involvement of AAV prior to treatment, 37% (n=20) obtained CT chest imaging during the study follow-up period due to the development of a new or worsening respiratory clinical sign or symptom. The CT findings were bronchiectasis (n=7), bronchial wall thickening (n=4), nodules (n=3), normal (n=3), cavitation (n=2), ILD – usual interstitial pneumonia (UIP) (n=2), atelectasis (n=1), pulmonary embolus (n=1), and pleural effusion (n=1). Of these 20 CT scans, 70% (n=14) are new findings that appeared during therapy.

Furthermore, 25 patients (22.1%) had sputum cultures obtained, 11 of which grew pathogenic organisms (Table 3). Two patients grew *Haemophilus influenzae* and *Aspergillus fumigatus*, each. However, most of the sputum cultures showed no growth / normal flora (56%). 22 patients (19.5%) received antibiotic therapy for suspected bacterial bronchitis.

**Table 2.** Primary findings on CT chest imaging

| | n = 34 |
|---|---|
| Bronchiectasis | 11 (32%) |
| Bronchial wall thickening | 6 (18%) |
| Nodule(s) | 6 (18%) |
| Emphysema | 2 (6%) |
| Atelectasis | 1 (3%) |
| ILD – NSIP | 1 (3%) |
| ILD – UIP | 2 (6%) |
| ILD - unspecified | 1 (3%) |
| Pneumonia | 1 (3%) |
| Pulmonary embolus | 1 (3%) |
| Pleural effusion | 1 (3%) |
| Cavitation | 2 (6%) |
| Scarring | 1 (3%) |
| Normal | 4 (12%) |

ILD=interstitial lung disease; NSIP = nonspecific interstitial pneumonia; UIP = usual interstitial pneumonia.

Numbers do not add up to equal 100% due to overlapping imaging findings

**Table 3.** Sputum culture results by microorganism

| | **n = 25** |
|---|---|
| *Haemophilus influenzae* | 2 |
| *Aspergillus fumigatus* | 2 |
| *Enterobacter cloacae* | 1 |
| Gram-negative rods | 1 |
| Methicillin-sensitive *Staphylococcus aureus* | 1 |
| Methicillin-resistant *Staphylococcus aureus* | 1 |
| *Moraxella catarrhalis* | 1 |
| *Serratia marcescens* | 1 |
| *Streptococcus pneumoniae* | 1 |
| No growth / normal flora | 14 |

The proportion of patients who developed bronchitis was numerically higher in patients who received > 3 years of continuous B cell depletion compared to those who received ≤ 3 years but did not reach statistical significance (24.7% versus 17.5%, p=0.38 by chi-squared analysis; Figure 2). In a multivariable model, smoking status, lung involvement of AAV, nadir serum IgG level, and time on

continuous B cell depletion were not associated with the development of bronchitis (Table 4).

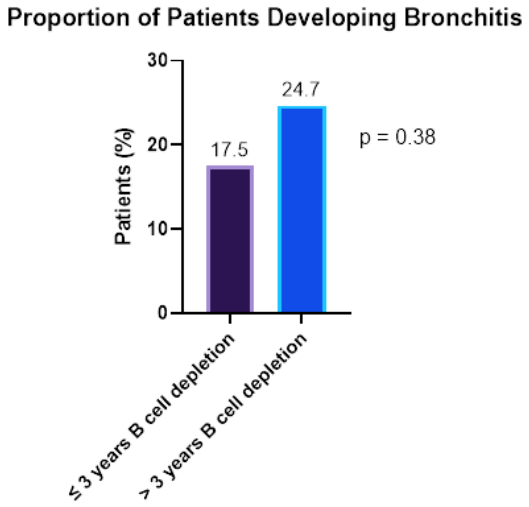



**Figure 2.** Proportion of patients developing bronchitis during treatment with rituximab. Approximately 18% of patients who were exposed to > 3 years of B cell depletion developed an episode of bronchitis, compared to approximately 25% of patients exposed to ≤ 3 years of B cell depletion. The difference was not statistically significant (p=0.38 by chi-squared analysis)

**Table 4.** Covariates of rituximab-associated bronchitis*

| | Odds Ratio (95% CIs) | |
|---|---|---|
| **Variable** | **Univariate** | **Multivariate** |
| **Smoking** | | |
| Never | - | - |
| Former/Current | 1.44(0.58–3.57) | 1.44(0.58–3.60) |
| **Lung involvement of AAV** | 1.53(0.62–3.73) | 1.34(0.53–3.36) |
| **Nadir serum IgG level (per 100 mg/dL)** | 0.86(0.69–1.08) | 0.87(0.69–1.11) |
| **Time on continuous B cell depletion (per 1 year)** | 0.99(0.80–1.23) | 0.92(0.72–1.18) |

* Odds ratios and 95% confidence intervals were calculated using logistic regression. The multivariable model was adjusted for smoking status (never, current/former), length of time on continuous B cell depletion (per 1 year), nadir serum IgG level (per 100 mg/dL) during the period of B cell depletion, pre-existing lung involvement from AAV (yes, no). AAV=antineutrophil cytoplasmic autoantibody (ANCA) associated vasculitis; IgG=immunoglobulin gamma (G)

## DISCUSSION

In this retrospective cohort study of 113 patients with AAV in remission undergoing continuous B cell depletion with rituximab for >2 years, we provide several observations on bronchitis as a possible complication of rituximab therapy. First, we describe that approximately 22% of patients develop bronchitis. Second, we noticed a numerically higher proportion of patients who have received > 3 years of B cell depletion to develop bronchitis compared to those who have received ≤ 3 years. Third, in a multivariable model, we did not measure an association with serum IgG level, smoking status, time on continuous B cell depletion, or lung involvement of AAV. Fourth, we observed CT findings in this cohort to be enriched with bronchiectasis and bronchial wall thickening, and microbiologic findings on sputum culture to show no predominant organism.

In our cohort, approximately 1 in 5 patients (20%) developed bronchitis over a median of 3.4 years of continuous B cell depletion. A prior study found the use of biologics, including rituximab, in the treatment of chronic inflammatory rheumatic disease associated with pre-existing bronchiectasis, raised the odds of developing a lower respiratory tract infection 9-fold (10). Moreover, our findings are partly consistent with prior data on long-term use of rituximab in ANCA vasculitis. In 2012, Cartin-Ceba *et al*. published on their 10-year experience at the Mayo Clinic using rituximab in refractory granulomatosis with polyangiitis (11). The most common infectious adverse events were related to the respiratory tract, with 9 upper respiratory tract events and 6 bronchitis events observed over 230 patient-years. While bronchitis is typically mild in severity, randomized controlled trials have reported serious adverse events (i.e., resulting in hospitalization or death) due to bronchitis in patients receiving rituximab. For example, in 2014 in MAINRITSAN 1, three SAEs due to bronchitis occurred in the 57 patients in the rituximab arm, compared to zero in the 58 patients in the azathioprine arm (1). In 2018, in MAINRITSAN 2, bronchitis was observed 6 times in 81 patients in the tailored-rituximab arm, and 4 times in 81 patients in the fixed-schedule arm (12). In 2020 in MAINRITSAN 3, only 1 SAE was noted in the rituximab arm (n = 50), and 0 were noted in the placebo arm (n=47) (2). These data suggest that bronchitis requiring hospitalization or death is uncommon, which would be expected with bronchitis in contrast to pneumonia.

The mechanistic link between rituximab and development of bronchitis remains undefined. Speculation can be drawn from other disorders of B cells, such as X-linked agammaglobulinemia or common variable immunodeficiency, which are associated with hypogammaglobulinemia and a predisposition for recurrent sinopulmonary infections. Immunoglobulins play a role in antigen clearance and neutralization, activation of the classical complement pathway, antibody-dependent cytotoxicity, and opsonization with phagocytosis (13). Notably, we did not observe the level of serum IgG to be associated with bronchitis. It is possible that mucosal humoral immunity is functionally impaired despite normal circulating levels of IgG, consequently leading to both infectious and sterile inflammation of the airways. A similar phenomenon of mucosal inflammation at other anatomic sites in patients receiving rituximab has been observed, such as vaginitis and colitis, which provides support for an underlying dysregulation of mucosal immunity despite normal serum IgG levels (6, 14). Anecdotally, we have observed resolution of recurrent or chronic bronchitis upon discontinuation of rituximab and restoration of normal peripheral B cell levels. Another possibility is that it is not the quantity of the IgG or IgA, but rather the lack of ability to target new infections. Additional investigation is needed to define the potential mechanism of airway inflammation because of B cell depletion.

Our experience with bronchitis in our rituximab-treated patients has generated an approach to its management (Figure 3). For patients who develop a cough productive of sputum, we attempt to obtain an expectorated sputum culture to guide antimicrobial therapy. For patients who develop recurrent bronchitis and who need ongoing maintenance therapy, we hold further scheduled rituximab infusions and pursue B cell-directed therapy for tailoring rituximab infusions, thereby allowing B cell repopulation between doses (12).

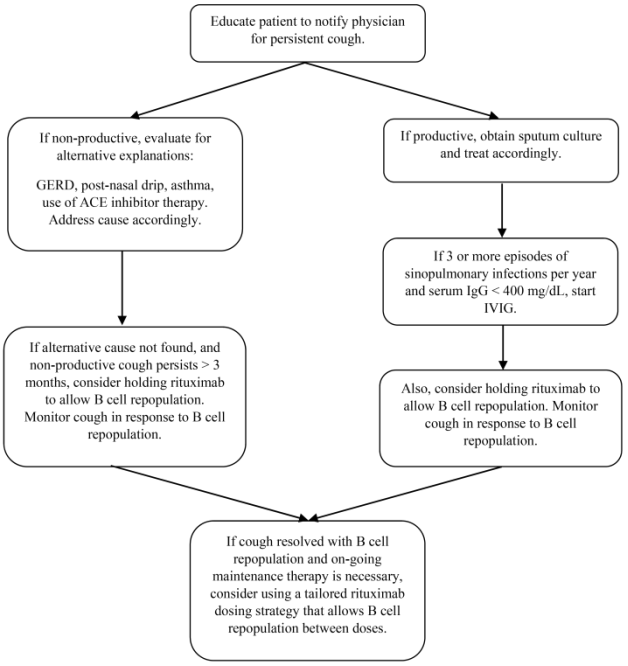



**Figure 3.** General protocol for management of bronchitis during treatment with rituximab. The general strategy we use at the Vasculitis and Glomerulonephritis Center at the Massachusetts General Hospital for the management of bronchitis while on rituximab. For patients who develop a cough productive of sputum, we attempt to obtain an expectorated sputum culture to guide antimicrobial therapy. For patients who develop recurrent bronchitis, we hold further scheduled rituximab infusions and pursue a dosing strategy that allows B cell repopulation between doses if ongoing treatment is necessary. This entails scheduling the rituximab at incrementally longer intervals where at least moderate peripheral B cell repopulation is achieved prior to the next infusion

ACE=angiotensin-converting enzyme; GERD=gastroesophageal reflux disease; IVIG=intravenous immunoglobulin.

This study has several strengths and weaknesses. The strengths include a large size, long duration of follow-up, and a detailed description of a potentially underrecognized complication of an important therapy. The main weakness is the presence of a selection bias, meaning a patient with a complication related to rituximab would likely have had their continuous rituximab stopped prior to 2 years, and therefore would not be included in our study. Therefore, our results may underestimate the frequency of bronchitis. Other weaknesses include that the data are derived from a single center, it is retrospective in nature, and the study lacks a comparator group. Bronchitis is common, being the ninth most common diagnosis in the outpatient setting amongst all comers in the United States (15). In addition, other risk factors for cough, such as smoking or chronic

obstructive pulmonary disease, are common. Therefore, despite using a multivariable model, there is still a risk of confounding, and it is difficult to be certain if bronchitis was directly related to B cell depletion or coincidence. The findings presented in this study are descriptive and hypothesis-generating only. Prospective scientific studies with comparator groups are needed to better define this phenomenon.

## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Competing interests

RZ reports receiving consulting and speaker fees from Amgen. There is no other relevant financial support or other benefit that any of the authors have that would create a potential conflict of interest regarding this work.

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