


Polyvalent Immunoglobulin as a Potential Treatment Option for Patients with Recurrent COPD Exacerbations

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Dana Unninayar¹
Sara J Abdallah²
D William Cameron²⁻⁴
Juthaporn Cowan²⁻⁴

¹Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada; ²Clinical Epidemiology Program, The Ottawa Hospital Research Institute, Ottawa, Ontario, Canada; ³Division of Infectious Diseases, Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada; ⁴Centre of Infection, Immunity and Inflammation, Department of Biochemistry, Microbiology and Immunology, University of Ottawa, Ottawa, Ontario, Canada

Abstract: Chronic obstructive pulmonary disease (COPD) is characterized by chronic airway inflammation and episodes of worsening respiratory symptoms and pulmonary function, termed acute exacerbations of COPD (AECOPD). AECOPD episodes are associated with heightened airway inflammation and are often triggered by infection. A subset of COPD patients develops frequent exacerbations despite maximal existing standard medical therapy. It is therefore clear that a targeted and more effective prevention strategy is needed. Immunoglobulins are glycoprotein molecules that are secreted by B lymphocytes and plasma cells and play a critical role in the adaptive immune response against many pathogens. Altered serum immunoglobulin levels have been observed in patients with immunodeficiencies and inflammatory diseases. Serum immunoglobulin has also been identified as potential biomarkers of AECOPD frequency. Since plasma-derived polyvalent immunoglobulin treatment is effective in preventing recurrent infections in immunodeficient patients and in suppressing inflammation in many inflammatory diseases, it may be conceivable that immunoglobulin treatment may be effective in preventing recurrent AECOPD. In this article, we provide a review of the current knowledge on immunoglobulin treatment in patients with COPD and discuss plausible mechanisms as to how immunoglobulin treatment may work to reduce AECOPD frequency.

Keywords: chronic obstructive pulmonary disease, immunoglobulin treatment, exacerbation

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a burdensome illness associated with significant morbidity and mortality. Some individuals with COPD experience recurrent acute exacerbations (AECOPD), which are events characterized by a worsening of respiratory symptoms that are beyond normal day-to-day variation and lead to a change in medication and/or healthcare services.¹ AECOPD accelerate disease progression and are the major cause of emergency department visits and hospitalizations.^{2,3} Current strategies to prevent and reduce AECOPD frequency include pharmacotherapy, patient vaccination and general self-management education.⁴ However, the efficacy of this approach is moderate at best and it is clear that a targeted and more effective prevention strategy is needed.

Plasma-derived immunoglobulin treatment has been used widely and effectively in patients who are susceptible to recurrent respiratory tract infections due to immunodeficiency.^{5,6} Although COPD is not considered a medical condition featured by immunodeficiency, recurrent respiratory tract infections are common in

Correspondence: Juthaporn Cowan
The Ottawa Hospital, General Campus,
501 Smyth Road, Box 223, Ottawa,
Ontario, K1H 8L6, Canada
Tel +1 613-737-8899 X 79617
Fax +1 613-737-8352
Email jcowan@toh.ca

this population. We and other have reported a positive effect of immunoglobulin treatment in COPD with respect to AECOPD frequency reduction.^{7,8} In this paper, we review the current evidence of immunoglobulin treatment in COPD patients and propose plausible mechanisms as to how Ig treatment may work to reduce AECOPD frequency.

Immunoglobulin Treatment

Immunoglobulin or antibody is a glycoprotein molecule produced by B-lymphocytes and plasma cells. It plays a critical role in the immune response against microbes and foreign substances. Effector functions of immunoglobulins are: 1) they bind to and inactivate microbes or toxins; 2) they activate the complement system to form a membrane attack complex – a cytotoxic pore on the surface of microbes; 3) they facilitate phagocytosis by opsonization.⁹ Hence, people who have low or abnormal immunoglobulins are predisposed to recurrent infections. Polyvalent immunoglobulins can be isolated from the purified plasma of thousands of healthy donors and therefore offer protection against a diverse spectrum of pathogens.¹⁰ The currently available immunoglobulin products are predominantly comprised of immunoglobulin G (IgG) isotype.¹¹ Immunoglobulin treatment has been shown to reduce the number of serious and non-serious respiratory infections as well as the number of complications from recurrent infections (ie chronic lung diseases) in patients with primary and secondary immunodeficiencies.¹² In addition to its anti-infective properties, immunoglobulin possesses anti-inflammatory and immunomodulatory properties which make immunoglobulin treatment an effective tool in the management of many systemic inflammatory and autoimmune conditions.^{13–16} Immunoglobulin treatment can be administered intravenously or subcutaneously and is generally well-tolerated.

Current Evidence of Immunoglobulin Treatment in AECOPD Prevention

We conducted a literature search to review the current evidence of the effectiveness of Ig treatment in preventing recurrent AECOPD in COPD patients. Our search revealed that only three studies have been conducted to investigate this treatment option and as such have been summarized below and in Table 1.

In a double-blind placebo-controlled study published in an abstract format, Barth et al¹⁷ evaluated the effects of

16% immunoglobulin (dose 5mL; Beriglobin S) vs serum albumin administered monthly for 12-months on AECOPD rates in 56 patients (28 per group). Compared to placebo, immunoglobulin did not have a significant effect on AECOPD frequency or airway resistance. However, patients randomized to immunoglobulin required a lower daily dosage of prednisone at the end of the study period although the result is not statistically significant. It is important to note that the immunoglobulin dosage in this study was determined by a volume-based strategy instead of the standard weight-based dosing strategy used in the treatment of immunodeficiency. A typical immunoglobulin treatment dosage is 0.4–0.8 g/kg/month. Thus, for a 70kg immunodeficient patient, approximately 35g of immunoglobulin per month would be required. However, Barth et al only administered 0.8g per month regardless of body weight. While it was found that AECOPD frequency and severity did not significantly differ in patients before and after receiving immunoglobulin treatment, there were several limitations including a small sample size, incomplete reporting (full article was not published), and a low immunoglobulin dosage. Further, two more recent studies have found statistically significant decreases in AECOPD frequency and severity after treatment with immunoglobulin.

In a retrospective longitudinal cohort study, our group examined the effect of immunoglobulin replacement therapy on recurrent AECOPD.⁷ Immunoglobulin administered at standard doses (0.4–0.8 g/kg body weight per month) significantly decreased the total number of AECOPD from 4.7 ± 3.1 episodes to 0.6 ± 1.0 episodes ($p=0.0001$) in 14 cases. Strikingly, the number of AECOPD hospitalizations decreased significantly from 12 episodes to 1 episode per year following immunoglobulin treatment ($p=0.016$). This reduction in exacerbation and hospitalization frequency was consistent across all patients in the study regardless of COPD severity, presence of bronchiectasis, and baseline serum IgG levels. While these results are promising, the findings are limited by the retrospective nature, the absence of a control group, and a small sample size.

Finally, McCullagh et al reported a case series to describe the presence of concomitant antibody deficiency, diagnosed by pneumococcal vaccine response in 29 COPD patients with recurrent AECOPD.⁸ A subset of these patients (9/29) were treated with Ig. Using a self-comparative risk-interval analysis, they reported a significant reduction in the frequency of COPD

Table I Summary of Study Characteristics and Study Outcomes

Study	Study Design	Number of Patients	Ig Dosage	Observation Period	Outcomes
Barth 2001 (abstract only) ¹¹	Randomized control trial	28 – IG 28 - Albumin	5 mL of 16% Intravenous Immunoglobulin (IVIg) monthly	1 year	No significant difference in <ul style="list-style-type: none"> • Number and duration of exacerbations • Change of airway resistance • Time to first exacerbation • Duration of hospitalization due to exacerbation • Number of proven infections But a trend in less prednisolone use in the Ig group ($p=0.1$)
Cowan 2015 ⁷	Retrospective longitudinal cohort	14	Did not specify but standard dosing as a replacement therapy for immunodeficiency - ~30 g/ month.	1 year	The incidence of AECOPD was consistently and significantly reduced in frequency from mean 4.7 (± 3.1) per patient-year before, to 0.6 (± 1.0) after immunoglobulin (Ig) treatment ($p=0.0001$). There were twelve episodes of severe AECOPD (in seven cases) in the year prior; and one in the year of Ig treatment ($p=0.016$).
McCullagh 2017 ⁸	Retrospective case series	Total = 29 (9 Ig treatment, 13 prophylactic antibiotics, 7 no treatment)	300–600 mg/kg/4-week period every 3–4 weeks for IVIg or every 1–2 weeks for SCIg. Antibiotic regimens: trimethoprim/ sulfamethoxazole 1 double strength tablet twice daily alternating with doxycycline 100 mg twice daily every two weeks, or azithromycin 250–500 mg three times/ week	At least one and up to 10 years before and after diagnosis and treatment initiation	In those receiving Ig, there was a reduction in annual courses of steroid from 12 (4.5–12) to 0.5 (0–1.5) ($p=0.031$) and annual courses of rescue antibiotic from 9 (5.5–12) to 0 (0–1.5) ($p=0.016$). Annual acute exacerbations in this group decreased from 4 (3–5.5) to 0.5 (0–1.5) ($p=0.016$). Numbers were too small to see a difference in annual rates of hospital admission for AECOPD pre-treatment 1.5 (1–3) and post-treatment 0 (0–1.5) ($p=0.25$).

exacerbations, hospitalizations due to AECOPD, corticosteroid use, and rescue antibiotics administration in those who received Ig. Their report of an apparent steroid-sparing effect due to Ig treatment is consistent with earlier findings from Barth et al.¹⁷

Based on the studies described above, there is a limited evidence on the use of immunoglobulin treatment in COPD. However, the existing data invites further research on this topic. While determining the therapeutic effect of immunoglobulin treatment in a well-designed prospective

study is essential, it is also important to explore the potential mechanisms of immunoglobulin treatment in COPD in order to better target COPD patients who will benefit from the treatment.

Proposed Mechanisms of Immunoglobulin Treatment in AECOPD Prevention

Below is a summary of several mechanisms by which immunoglobulin treatment could act to reduce exacerbation frequency and severity.

Replacement Therapy for Hypogammaglobulinemia

Low serum immunoglobulin G (IgG) level, or hypogammaglobulinemia, has been shown to be associated with frequency of AECOPD in a large cohort of 653 patients with COPD.¹⁸ An additional study of 262 stable COPD patients followed prospectively for five years in Norway also showed that hypogammaglobulinemia was associated with higher risk for AECOPD.¹⁹ The cause of hypogammaglobulinemia in these cases is not well known. However, it should be recognized that corticosteroids have been the mainstay treatment for AECOPD, and hence frequent or prolonged use of corticosteroids is inevitable in individuals at high-risk of exacerbations.²⁰ It is well-known that administration of corticosteroids such as prednisone can suppress the immune system and is associated with reduced serum IgG levels.^{21,22} This poses a causality dilemma of whether frequent use of corticosteroids in COPD patients induces hypogammaglobulinemia or whether hypogammaglobulinemia predisposes patients to recurrent AECOPD and hence prolonged corticosteroid use. Regardless of causal direction, correction of hypogammaglobulinemia with immunoglobulin treatment may interrupt the AECOPD-hypogammaglobulinemia process. It should be noted however that we observed a reduction in AECOPD rates in COPD patients at high-risk of exacerbations despite having normal baseline serum IgG level.⁷ Therefore, immunoglobulin treatment is unlikely to be working solely by replacement of the diminished level of serum IgG.

Treatment of Humoral Immunodeficiency

Humoral immunodeficiency or antibody deficiency is a result of any abnormality in the humoral immune system that contributes to an ineffective immune response and recurrent infections. Hypogammaglobulinemia is only a subset of humoral immunodeficiency and hence patients may have normal or elevated IgG levels but may still have humoral immunodeficiency due to other mechanisms. Humoral immunodeficiency may be broadly categorized as primary humoral immunodeficiency, which is inherited, and secondary humoral immunodeficiency, which is acquired. Examples of primary humoral immunodeficiency include common variable immunodeficiency disease and X-linked agammaglobulinemia. Secondary humoral immunodeficiency conditions are most commonly caused by hematological malignancies (eg, chronic lymphocytic leukemia) and immune-modulating medications (eg, rituximab, which depletes B cells).²³

Patients with humoral immunodeficiency are at increased susceptibility to recurrent bacterial sinopulmonary tract infections, which often lead to chronic lung diseases such as bronchiectasis and COPD.^{24,25} Early recognition of humoral immunodeficiency and early treatment with immunoglobulin infusions reduces infections, prevents complications, and improves quality of life.⁵ More than 60% of AECOPD episodes are triggered by a viral and/or bacterial infections.^{12,26} Therefore, recurrent AECOPD may be due to recurrent infections. Since recurrent respiratory tract infections are common manifestations of humoral immunodeficiency, we suggest that impairments in the humoral immune response could lead to recurrent AECOPD in people with COPD, and that humoral immunodeficiency is more prevalent in COPD patients with a “high-risk of exacerbations phenotype” than those with a “low-risk of exacerbations phenotype” (Figure 1). Based on the Canadian Thoracic Society recommendation on stratified risk of future exacerbations, individuals with ≤ 1 moderate AECOPD (requiring antibiotics and/or oral corticosteroids) in the last year are considered at low-risk of future exacerbations, while those with ≥ 2 moderate or ≥ 1 severe exacerbation (requiring hospitalization or emergency room visit) are at high-risk of future exacerbations.²⁷

The relationship between AECOPD and humoral immune function, specifically humoral immunodeficiency, was not assessed in the reviewed studies and hence warrants further investigation. Humoral immunodeficiency can be diagnosed by dynamic testing of a specific immune response to a polysaccharide vaccine antigen, which induces an antibody response without T-cell help, the so-

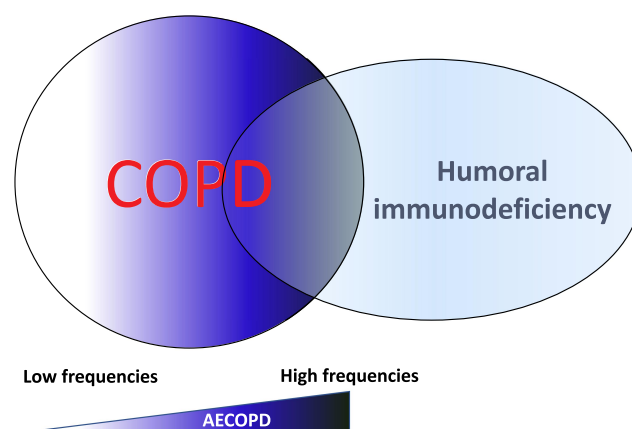


Figure 1 Author's proposed hypothesis. Humoral immunodeficiency is more prevalent in COPD patients with “high-risk of exacerbations phenotype” than those with a “low-risk of exacerbations phenotype”.

called T-independent antibody response. The most common polysaccharide antigen used in clinical practice is the unconjugated pneumococcal vaccine. The validity of this diagnostic test is compromised if a patient has previously responded to these vaccine antigens. Since many patients with COPD receive this vaccine as recommended, or have responded to natural infection, the pneumococcal vaccine response is not an ideal method of evaluating humoral immune function in this population. Therefore, an alternative diagnostic tool of humoral immune function is needed to investigate the effect of humoral immunity on AECOPD frequency and response to immunoglobulin treatment.

Improvement of Mucosal Immunity

Similar to the systemic immune system, the mucosal immune system is comprised of innate and adaptive components. Immunoglobulins play a major role in mucosal adaptive immunity. Among immunoglobulin classes or isotypes, IgA is considered a hallmark of mucosal antibody because surface epithelia are the principal sites of IgA synthesis and secretion. Nevertheless, IgG concentrations exceed those of IgA in the bronchoalveolar fluids, where it is the predominant antibody isotype.^{28,29} IgG is transported through the intact epithelial layer from the basal epithelial or sub-epithelial layer by the neonatal fragmentable crystallizable (Fc) receptor (FcRn).³⁰ Parenteral administration of passive neutralizing IgG has been shown to prevent lung infection by *Streptococcus pneumoniae* in mice.³¹ It is therefore possible that parenteral administration of IgG increases IgG concentrations in the luminal airway, which enhances mucosal immunity. An improved mucosal immunity by this mechanism may reduce the risk of respiratory infections, and hence reduce the risk of AECOPD in COPD patients.

Reestablishment of Healthy Lung Microbiome and Reduction of Airway Inflammation

Healthy lungs contain resident commensal microbes that colonize the lining of the respiratory tract, reminiscent to what has been reported for the gastrointestinal tract. The most common bacterial genera in the lower airway among healthy individuals are *Prevotella*, *Veillonella*, and *Streptococcus*.³² On the other hand, pathogenic bacteria such as *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*^{33,34} are predominant in the diseased lungs of patients with COPD.

Microbial components and their metabolites have the potential to maintain immune homeostasis in the host. For example, commensal neomycin-sensitive bacteria regulate protective immune responses in the lungs against influenza A virus infections. They do so by generating virus-specific CD4 and CD8 T cells through inflammasome activation and dendritic cell migration from the site of infection to lymph nodes. Disruption of composition or the number of microbiota termed “dysbiosis” may contribute to the development, progression, or exacerbation of various inflammatory disorders of the lungs, including asthma, COPD and cystic fibrosis.³⁵ Pathogenic bacteria can increase airway inflammation by stimulating production of inflammatory cytokines^{34,36} and by degrading IgA.³⁷ We hypothesize that immunoglobulin treatment may reset ‘dysbiosis’ by reducing pathogenic microbes which can result in decreased airway inflammation. Given that AECOPD is characterized by heightened airway inflammation, it is indeed plausible that improved respiratory microbiome composition may reduce AECOPD frequency.

Reduction of Autoantibodies in the Airways

Over the past decade, there has been an increasing body of evidence linking autoimmunity and COPD.³⁸ Although it has not been clearly established, serum and sputum autoantibodies (antibodies against self-antigens) may correlate with a certain COPD phenotype such as those with recurrent AECOPD.³⁹ Immunoglobulin treatment has been used successfully to treat many immune-mediated diseases caused by autoreactive B lymphocytes. Immunoglobulin is found to exert its effect through modulation of expression and function of FcR, interference with complement activation and the cytokine network.⁴⁰ Antibodies in immunoglobulin products recognize and neutralize idioypes of disease-associated and natural autoantibodies as well as B-cell antigen receptors. Reduction in the autoantibody titer in vivo has been observed in several conditions following immunoglobulin treatment.^{41,42} Thus, it could be suggested that immunoglobulin may reduce AECOPD by interfering with the production or effect of autoantibodies in the airways. However, immunoglobulin dosage required for the treatment of autoimmune conditions is generally higher than the dosage used in the treatment for immunodeficient patients. We and others observed a reduction in AECOPD using the standard dosage recommended for immunodeficiency.^{7,8} In other words, the higher immunoglobulin dosage required for the treatment of autoimmune conditions was not needed to reduce

AECOPD frequency in COPD patients. Thus, it seems less likely that immunoglobulin treatment in patients with COPD would work by this mechanism of reducing auto-antibodies in the airway.

Conclusion

In summary, the evidence of immunoglobulin efficacy in prevention of frequent recurrent AECOPD is limited. Several mechanisms have been proposed to explain how immunoglobulin might reduce recurrent AECOPD frequency and severity. It is possible that immunoglobulin works by improving IgG levels in patients with hypogammaglobulinemia or by improving humoral immune function in immunodeficient patients or by enhancing mucosal immunity in general. However, the current method of evaluating humoral immune response is not reliable in all COPD patients and hence an alternative diagnostic test is needed. It should also be noted that immunoglobulin might reduce recurrent AECOPD frequency by other mechanisms, such as via anti-inflammatory or immunomodulatory effects. Hence, identifying and treating only immunodeficient cases with COPD and recurrent AECOPD may overlook others who could benefit from immunoglobulin treatment. Rigorous and high-quality prospective trials are therefore warranted in order to identify individuals with COPD at high risk of recurrent AECOPD and to evaluate the efficacy of immunoglobulin in the prevention of AECOPD. Further, individualized evaluation of quantitative and functional antibodies in COPD patients may provide better insight into the mechanisms underlying recurrent AECOPD and also identify patients with COPD phenotypes who may benefit from immunoglobulin treatment.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

The ethics approval was waived due to the nature of the study. This study did not involve human or animal subjects.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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