Pro/Con Review

Should Antibiotic Prophylaxis Be Routinely Used in Patients with Antibody-Mediated Primary Immunodeficiency?

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INTRODUCTION

There is no doubt that the use of gamma globulin in the early 1950s by Bruton and the eventual introduction of intravenous immunoglobulin in the early 1980s were major advances in the care of patients with antibody immune deficiency diseases. However, despite this major advance in the care of these patients, antibiotics were still needed to treat infections in these patients. It became almost commonplace to use prophylactic antibiotics in those patients with immunodeficiency who continued to have infections. In a report by Hernandez-Trujillo et al,[1] 40% and 49% of focused immunologists from the United States and Europe, respectively, who care for these patients used adjunct prophylactic antibiotics in addition to immunoglobulin replacement treatment in 11% to 50% of their patients with primary immunodeficiency diseases (PIDDs). Although the use of prophylactic antibiotics in immunodeficiency disorders is a common practice, there is very little data on their efficacy, and there are no controlled studies on the use of adjunct prophylactic antibiotics in patients with primary antibody deficiency (PAD) disorders.[2] This clinical commentary will review the advantages and disadvantages of the use of prophylactic antibiotics in both nonimmune deficiency disorders such as cystic fibrosis (CF) and those immune deficiency diseases in which clinical studies have been reported, and the potential benefits and risks of extrapolation of these studies to patients with PAD.

PRO ARGUMENT

Although it is true that there are no prospective studies looking at the use of prophylactic antibiotics in PAD disorders, it may be of some help to use other disease states to drive clinical decisions that may benefit patients. Indeed, we may also use our experiences with other disorders and immunodeficiency diseases in which there are published data regarding recommendations for the use of prophylactic antibiotics to help our patients reduce the frequency of infection. Examining data from CF and non-CF bronchiectasis, chronic obstructive pulmonary disease (COPD), and other PIDDs in which antibiotic prophylaxis has been shown to be effective, we may begin to understand how this clinical strategy could benefit our patients.

Chronic lower respiratory diseases—CF

CF is an important example in which infection has a major impact on lower airway inflammation, leading to bronchiectasis. Early on *Staphylococcus aureus* and *Haemophilus influenzae* are important pathogens in the lung infections of patients with CF. Chronic infection with *Pseudomonas aeruginosa* increases from 30% in infancy to 80% later in childhood.[3] Recently, macrolide antibiotics have been added to the antimicrobial treatment in patients with CF for pseudomonas infections. It is thought that the beneficial effect of macrolides is related to the anti-inflammatory properties including diminishing biofilm formation and interfering with bacterial virulence.[4] Controlled trials in patients with CF have shown improvement in function 3 months to 1 year after starting maintenance treatment with azithromycin.[5,6] A more recent meta-analysis of prolonged azithromycin in CF confirmed the improvement in lung function.[7] Tramper-Stranders et al[8] studied the emergence of macrolide resistance to *S aureus*, and assessed changes in pulmonary lung function in pediatric patients with CF on daily azithromycin therapy. Pulmonary function improved in the first year after initiation of azithromycin. Although pulmonary function declined in the second and third years after the initiation of macrolides, it was not related to staphylococcal resistance. Other studies have found improvement in lung function and the frequency of exacerbations especially in the first year of treatment.[5,6] Thus, these studies demonstrate that even though there is increasing staphylococcal resistance when using prophylactic macrolides in CF, there does seem to be a beneficial role of macrolides in CF, perhaps in part due to their anti-inflammatory properties. In contrast to beta-lactam and fluoroquinolones, macrolides and macrolide-like agents prevent the release of

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Abbreviations used
CF- Cystic fibrosis
CGD- Chronic granulomatous disease
COPD- Chronic obstruction pulmonary disease
CRS- Chronic rhinosinusitis
CVID- Common variable immunodeficiency
PAD- Primary antibody deficiency
PIDD- Primary immunodeficiency disease
TMP-SMX- Trimethoprim-sulfamethoxazole
XLA- X-linked agammaglobulinemia

proinflammatory protein toxins from both gram-positive and gram-negative bacteria.[9,10]

Non-CF bronchiectasis

As a follow-up on the data in CF on the use of macrolides, 2 large placebo-controlled studies have been published in non-CF bronchiectasis. In the EMBRACE (Effectiveness of Macrolides in patients with BRonchiectasis using Azithromycin to Control Exacerbations) study of azithromycin given 3 times weekly for 6 months, patients showed a reduction in exacerbation frequency, but no effect on lung function or quality of life.[11] The BAT (Bronchiectasis and long-term Azithromycin Treatment) trial, a multicenter, double-blind, placebo-controlled trial of 83 patients with at least 3 infectious exacerbations per year, showed a significant reduction in exacerbations and improvement in lung function in those patients treated with azithromycin daily.[12] When azithromycin was given to a cohort of patients with bronchiectasis, significant improvement was noted in sputum characteristics, cough, fatigue, wheeze, and breathlessness.[13]

Although the pathophysiology of the underlying disease is different in PAD, the development of end-organ damage in the form of bronchiectasis has such serious ramifications that using macrolide antibiotics in the hope that they may prevent this complication may make clinical sense in our patient population.

Chronic obstructive pulmonary disease

Prophylactic azithromycin therapy has also been studied in patients with COPD. Several randomized controlled studies showed that daily azithromycin (250 mg) for 1 year reduced the frequency of exacerbations and improved the quality of life. In a large controlled study of COPD, 250 mg of azithromycin daily reduced the frequency of exacerbations and improved the quality of life.[14] The response was less clear in younger patients, smokers, and those with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 4. In a meta-analysis of 6 randomized controlled trials, there was a 37% relative risk reduction in COPD exacerbations in those patients on macrolide prophylaxis. There was also a 21% reduction in hospitalization rate, and there was a trend for decreasing mortality.[15] In a recent randomized, double-blind, placebo-controlled trial of adult patients with persistent uncontrolled asthma, azithromycin prophylaxis reduced asthma exacerbations, improved asthma control, resulted in a lower number of antibiotic courses, and demonstrated an improvement in asthma-related quality of life.[16] It is possible that the population of antibody-deficient patients with frequent lower respiratory tract infections or a history of asthma may benefit in a similar way to the patients described above.

Immune deficiency diseases in which data support antibiotic prophylaxis

Many immunologists chose to use prophylactic antibiotics in PAD on the basis of experience with other immunodeficiencies in which the standard of care mandates their use and clinical outcomes are clearly better when they are routinely used. Yong et al[17] surveyed members of the American Academy of Allergy, Asthma and Immunology in their care of patients with PIDDs covering a number of treatment areas including immunoglobulin replacement therapy and the use of prophylactic antibiotics. Their survey data were analyzed by general immunologists (<10% of their time in clinical practice of patients with PIDDs) and focused immunologists (>10% of their time in the care of patients with PIDDs). A total of 88.1% of focused and 47.7% of general immunologists reported using prophylactic antibiotics to prevent infection in at least some of their patients with PIDDs. More than 75% of all respondents found prophylaxis clinically useful in at least some patients with PIDDs, and focused immunologists found prophylaxis moderately or extremely useful.

Most of the "good data" are confined to patients with chronic granulomatous disease (CGD) in which there have been trials, or severe combined immunodeficiency in which the risk of fatal infection with opportunistic organisms nears 100%. Prophylactic antibiotics, primarily trimethoprim-sulfamethoxazole (TMP-SMX), have been reported to be beneficial in patients with CGD.[18-20] Mouy et al[21] reported that prophylaxis decreased the average incidence of infection from 2.06 to 0.43 infections per year. Because of the concern of fungal infection in these patients, Margolis et al[20] reviewed the National Institutes of Health experience between 1970 and 1988 on the incidence of nonfungal and fungal infections in patients with CGD with and without TMP-SMX. Nonfungal infections decreased from 7.1 to 2.4 per 100 patient-months in patients with autosomal CGD, and from 15.8 to 6.9 infections per 100 patient-months in patients with X-linked CGD. There was no significant change in fungal infections in those patients receiving TMP-SMX. In a more recent study by Gallin et al,[22] itraconazole prophylaxis was effective and well tolerated at a dose of 200 mg daily (≥50 kg) in reducing the frequency of fungal infections. A study dating back to 1977 demonstrated the effectiveness of daily TMP-SMX prophylaxis in preventing pneumocystis pneumonia in children with leukemia.[23] Although no studies are available, it is now standard of practice to use prophylaxis for *Pneumocystis* infections in patients with severe combined immunodeficiency diseases before transplant (Summary Statement 29 in Bonilla et al[24]). Use of TMP-SMX has also been proposed for patients with hyper-IgM syndrome due to mutations in CD40 Ligand and CD40, and for those with Wiskott-Aldrich syndrome given the inherent risk for *Pneumocystis jirocevii* pneumonia.

Although the above shows the efficacy of antimicrobials in diseases not solely amenable to IgG replacement, the diseases being discussed here do respond well to immunoglobulin replacement therapy, with reduction of infection frequency and severity. The efficacy of immunoglobulin replacement in preventing infection is without question. Although long-term administration of immunoglobulins reduces the incidence of infections, some patients with PAD may still experience respiratory tract infections that lead to lung damage despite optimal trough levels for serum IgG. However, many of these patients had chronic bronchitis or even bronchiectasis before starting