Original article:

Azithromycin and Co-Trimoxazole in Antimicrobial Prophylaxis: Special Emphasis on Primary Immunodeficiencies in Children

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Abstract:

Patients with primary immunodeficiency diseases (PID) are prone to infectious, and they often determine the course of the disease. Antimicrobial prophylaxis for patients with PID includes co-trimoxazole, amoxicillin and macrolides.

Co-trimoxazole is a widely used antimicrobial agent for pneumocystosis prophylaxis in immunocompromised patients, including patients with primary cellular immunodeficiency. Antiinflammatory effect of azithromycin made it a drug of choice in the management of chronic lung diseases in the patients with primary immunodeficiencies, especially in those with antibody deficiencies. Further randomised controlled studies are needed to define the optimal agent for all types of primary immunodeficiencies, its dose, duration of treatment, benefits and safety of long-term use.A recommendation for the prophylactic use of long-term therapy should consider the balance between benefits and risk of adverse events.

Keywords: primary immunodeficiency diseases, infection, co-trimoxazole, azithromycin.

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Introduction

Infectious manifestations are one of the main features of primary immunodeficiency disorders (PID).[1] Infections often determine the outcome of PID. So, their prevention may resultsin the increased overall survival, improved quality of life, and reduced long-term healthcare costs.

Patients with PID are advised for use measures to minimize the risk of infections: maintain hand and dental hygiene, keep good nutrition, and avoid unnecessary exposure.[2]

Prevention of infections in patients with PID also includes chemoprophylaxis (with antipneumocystis, antibacterial and antifungal agents), immunotherapy (immunoglobulin replacement, granulocyte colony-stimulating factor (G-CSF), interferon gamma (IFN-γ)), and vaccination.[3, 4]

Early diagnostic of PID is very important for prevention and management of infectious complications.[5] A choice of prevention strategy depends on the type of primary immunodeficiency and the sensitivity of microorganisms.[2]

Long-term prophylaxis to prevent episodes of certain opportunistic infections, in particular *Pneumocystis* pneumonia, have become a standard of care in the patients with human immunodeficiency virus infection.[6]

Antibiotic prophylaxis is also suggested for patients with T cell deficiencies, combined immunodeficiencies (Wiskott-Aldrich syndrome, hyper-IgE syndrome, ataxia-teleangiectasia), phagocytic disorders (chronic granulomatous disease), and disorders with predominant defects in antibody production.[1, 2] However, a number of studies highlighted the lack of standard protocols and guidelines on antibiotic prophylaxis in primary immunodeficiencies.[2, 7]

Antimicrobial agents for long-term prophylaxis in patients with PIDs include trimethoprim-sulphamethoxazole (TMP-SMX), amoxicillin or macrolides (azithromycin)].[1, 2, 8] Prophylactic treatment with these medications has been proposed

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for the cases where the number of recurrent infections exceeds three per year or severe infection occur despite adequate immunoglobulin replacement therapy.[8]

Co-trimoxazole

Co-trimoxazole is a well-known combined antimicrobial drug widely for the last 50 years (since 1968) that consists of sulfamethoxazole and trimethoprim. In vitro studies demonstrated that these two agents act synergistically against a broad range of bacteria, inhibiting the synthesis of microbial folic acid.[9] Sulfamethoxazole binds to dihydropteroate synthetase, while trimethoprim binds to bacterial dihydrofolate reductase, blocking bacterial synthesis of tetrahydrofolic acid.

Combinations of trimethoprim with sulfonamides are characterized by a wide spectrum of anti-bactericidal activity, including pathogens that resistant to many antibiotics and to common sulfonamides (Table-1). The antimicrobial spectrum of trimethoprim is close to sulfanilamides, but its activity is 20-100 times higher. Therefore the activity of co-trimoxazole is largely calculated by trimethoprim. Sulfamethoxazole is an important treatment option for toxoplasmosis, pneumocystis pneumonia and nocardiosis.

Table 1. Co-trimoxazole activity spectrum

Gram (+) cocci	• *Streptococci*, • *Staphylococci*, including PRSA, some MRSA species
Gram (-) cocci	• *Moraxella catarrhalis*, • *Neisseria meningitidis*
Gram (-) coccobacilli, bacilli	• Enterobacteriaceae: *Escherichia coli, Salmonella spp., Klebsiella spp, Shigella spp, Brucella;* *Haemophilus influenzae, Haemophilus ducreyi*; *Burkholderia cepacia, Stenotrophomonas maltophilia*.
Other microorganisms	*Nocardia spp.* *Pneumocystis jirovecii* *Toxoplasma*

Microorganisms insensitive to this drug are *Ent erococcusspp.,Pseudomonasspp*.,gonococci and anaerobes.

Today co-trimoxazole remains one of the most frequently prescribedantibiotics for urinary tract infections in many countries.[10] Itis used to treat pulmonary and disseminated nocardiosis and for the prophylaxis of spontaneous bacterial peritonitis. It is also widely used for prophylaxis and treatment *Pneumocystis* pneumonias in immunocompromised patients.[6, 11]

Primary immunodeficiency

The French National Reference Center for PIDs recommends co-trimoxazolefor anti-infectious prophylaxis for all patients with chronic granulomatous disease (CGD), at a daily dose of 25 mg/kg/day of sulfamethoxazole and 5 mg/kg/day of trimethoprim; the maximum dose of 800 mg/day of sulfamethoxazole (strength of recommendations A, evidence level II).[3] Co-trimoxazole is the treatment of choice (strength of recommendations A, evidence levelIII) in the patients with severe congenital neutropenias if there are no severe infections or mucosal manifestations. Co-trimoxazole is recommended as an alternative medicine for antibiotic prophylaxis after splenectomy in the cases of penicillin allergy (strength of recommendations B, evidence levelIII).[3] Co-trimoxazole prophylaxis against pneumocystosis should be prescribed immediately after identification of cellular immunodeficiency (strength of recommendations A, evidence level II). It is recommended for all patients with STAT3 deficiency as first-line therapy (AII).[2, 3] In the absence of bronchiectasis co-trimoxazole prophylaxis is recommended for children with common variable immunodeficiency (CVID) and hyper IgM-syndrome.[2, 3] It is also recommended as a long-term prophylaxis for patients with X-linked agammaglobulinaemia, Wiskott-Aldrich syndrome, and Di George syndrome.[2] The choice of antibiotic prophylaxis should be made depending on the type of the immunodeficiency and severity of the disease, since CVID and Di George syndrome have variable clinical manifestation, and not all cases require antibacterial prophylaxis.[12]

Limitations of use

The main limitation of co-trimoxazole is its high potential for the development of severe adverse effects, such as severe allergic reactions connected with sulfamethoxazole, namely Stevens-Johnson and Lyell's syndromes.[13] Other adverse effects include

neurologic disorders, decreased oxygen-carrying capacity and other hematologic abnormalities, reproductive toxicity, hypoglycemia, and hyperkalemia.[14]

Besides the potential for adverse reactions, another factor contributing to the decrease in the use of co-trimoxazole is the increasing bacterial resistance to this class of antibiotics.[14] The use of sulfonamides for the treatment of nonbacterial infections has been contributing to the development of bacterial resistance to this drug. Thus, a wide use of co-trimoxazole for the prophylaxis of *Pneumocystis* pneumonia increases the number of multidrug-resistant strains of many bacterial species. This can result in the unsuccessful treatment of bacterial infections in immunocompromised, primarily HIV-infected patients. Since Treatment options for the patients with *Pneumocystis* are limited, the use co-trimoxazole for bacterial infection should be restricted.[14]

Azithromycin

Azithromycin Is a nazalide, a type of macrolide antibiotic with bacteriostatic activity. It decreases protein production, stopping bacterial growth. Azithromycin was discovered in 1980, and used in medical practice since 1988.[15] It is active against the most common respiratory bacterial infections (Table 2). It may also be used for intestinal and sexually transmitted infections (caused by chlamydia and gonorrhea).

Table 2. Azithromycin activity spectrum

Gram (+) cocci	*Staphylococcus aureus* (Methicillin-sensitive only) *Streptococcus agalactiae* *Streptococcus pneumoniae* *Streptococcus pyogenes*
Gram (-) cocci	*Moraxella catarrhalis* *Neisseria gonorrhoeae*
Gram (-) coccobacillus	*Haemophilus influenzae* *Haemophilus ducreyi* *Bordetella pertussis* *Legionella pneumophila*
Anaerobic microorganisms	*Peptostreptococcus* species *Prevotella bivia*
Other microorganisms	*Chlamydophila pneumoniae* *Chlamydia trachomatis* *Mycoplasma genitalium* *Mycoplasma pneumoniae* *Ureaplasma urealyticum*

It is one of the most common prescribed antibiotics in many countries due to its relatively broad spectrum, safety, and affordable price.[16] Extensive use of azithromycin has resulted in growing resistance of some pathogens (such as *Streptococcus pneumoniae*).

In recent years, azithromycin was shown to have beneficent immunomodulatory effect in the treatment of many chronic respiratory diseases.[15, 17] This effect has been demonstrated in patients with chronic lung diseases such as cystic fibrosis (CF), bronchiolitis obliterans syndrome, and asthma. Azithromycin slows down the decline of lung function in patients with chronic lung diseases.

Immunomodulatory effect of azithromycin

Azithromycin accumulates in polymorphonuclear neutrophils, and its sputum levels are higher than plasma and blood concentrations.[17] Concentrations of other macrolides are at least 10-fold higher in the epithelial lung fluid than in serum.

Modulation of neutrophil function and circulating inflammatory mediators was reported in a study of healthy human subjects. Chemokine and interleukin-6 serum levels decreased while in apoptosis of neutrophils increased for up to 28 days after the last azithromycin dose.[18] Extended anti-inflammatory activity may reduce harmful inflammation. Azithromycin reduced TNF-α mRNA levels and decreased TNF-α secretion in CF airway epithelial cells.[19] The reducing of lung TNF-α levels was associated with inhibition of neutrophil replacement in the lung of the murine model stimulated with *Pseudomonas*. Inflammatory reaction, neutrophils' activation are pathogenetic mechanismsof lung injury.[20]

Azithromycin affects T-cell regulation by dendritic cells.[17] It was shown to increase the production of IL-10. Azithromycin was also reported to play a role in the stimulationof neutrophil apoptosis, and in the increase of phagocytosis of apoptotic epithelial cells and neutrophils by alveolar macrophages.[21]

In vitro studies demonstrated that azithromycin increased the transepithelial electrical resistance of human airway epithelial cells.[22]

Immunomodulatory effect was described for other 14- and 15-membered macrolides (e.g., erythromycin, clarithromycin, roxithromycin, and azithromycin) meaning they regulate hyperimmunity or hyperinflammation without affecting the normal immune or inflammatory response to infection.[17]

The immunomodulatory effect of macrolides, in particular of azithromycin, is independent

of antimicrobial criterion.[17] This allows using azithromycin for long-term prophylaxis of chronic lung diseases.

Macrolides, including azithromycin, improved survival in patients with chronic lung disease (CF, diffuse panbronchiolitis) associated with *P. aeruginosa* infection.[17] This effect is ensured by inhibition of adherence, inhibition of virulence factors and inhibition of biofilms.

Asthma

Evidence on the efficiency of macrolides in the management of chronic asthma is contradictory. Immunomodulatory effect of macrolides was first described in 1970 for the treatment of patients with asthma.[17]A 2007 assessment of seven chronic asthma studies showed no clinically significant benefit of using macrolides in the management of chronic asthma.[23]A multicenter, randomized, double-blind, placebo-controlled clinical trial (Azithromycin Against Placebo in Exacerbations of Asthma, AZALEA) showed that azithromycin treatment resulted in no statistically or clinically significant benefit.[24] However, other studies showed that eight weeks of intermittent, low-dose administration of azithromycin in patients with mild asthma reduced the severity of bronchial hyperresponsiveness (mean PC20 values significantly increased) and neutrophilic airway inflammation.[25]

Diffuse panbronchiolitis (DPB)

DPB is an inflammatory disease that affects the bronchioles, and is characterized by sputum expectoration and dyspnea.[26] It can result in chronic sinusitis leading to severe obstructive respiratory disorder, bronchiectasis, respiratory failure and death. *Haemophilus influenza* and *Pseudomonas aeruginosa* are commonly detected in the sputum.[26] Long-term treatment with macrolides improved pulmonary function, hypoxemia, and the survival of patients with DPB.[26] Macrolides significantly reduced BALF concentrations of IL-1 beta and IL-8, neutrophil chemotactic activity in BAL fluid and the serum levels of soluble adhesion molecules in DPB patients. Clinical benefits and good tolerance of azithromycin for patients with diffuse panbronchiolitis were also reported.[27]

Cystic Fibrosis

Outlined similarities between CF and diffuse panbronchiolitis (DPB) suggested that long-term azithromycin administration may improve lung function in children with CF.

A prospective randomised double blind, placebo controlled study of adults with CF that were administered 250 mg/day of azithromycin of doses for 3 months reported significantly improved quality of life, reduced CRP levels and the number of respiratory exacerbations, and reduced rate of the decline in lung function.[28]

Long-term use of azithromycin was supported in children with CF not responding to the conventional treatment.[29] A multicenter, randomized, double-blind, placebo-controlled trial of patients with CF and a chronic *P. aeruginosa* infection, conducted at 23 CF care centers in the United States, demonstrated that azithromycin treatment was associated with improvement in clinically relevant points: increase in FEV1, lower exacerbation risk, higher gained weight.[30] Another study showed temporary pulmonary function improvement in the first year after the start of azithromycin therapy, which decreased in the second and third years.[31]

Long-term treatment with azithromycin is recommended by the Cystic Fibrosis Foundation guidelines for CF patients 6 years of age and older, and with *Pseudomonas aeruginosa* persistently present in the cultures of the airways, to improve lung function and to reduce exacerbations.[32] This advice takes into account microbiological, immunomodulatory and anti-inflammatory properties of azithromycin, as well as its capacity to reduce the pathogenic role of *Pseudomonas aeruginosa* by interfering with bacterial metabolism, increasing bacterial susceptibility to antibiotics. Subsequently, the risk of presumably mild viral infections resulting in bacterial pulmonary exacerbations is reduced. The guidelines, however, also note that azithromycin is effective in the first year of administration, but the effect of longer treatment is debated.

In contrast, in children and adolescents with CF, but not infected with *P. aeruginosa,* a 24 week long treatment with azithromycin did not improve pulmonary function.[33]

A Cochrane review supports improved respiratory function after six months of azithromycin.[34] Beyond six months, the data were less clear, although the reduction in pulmonary exacerbation was sustained.

Non-cystic fibrosis bronchiectasis

British Thoracic Society 2010 guidelines for non-CF bronchiectasis point out that macrolides may have disease-modifying activity, but a large randomised controlled trial is needed for a definitive proof.[35] A randomised, double-blind, placebo-controlled trial at three centres in New Zealand showed reduced number of exacerbations in patients 18 years or older with non CF bronchiectasis after a treatment with azithromycin three times a week for 6 months.[36] Decreased pulmonary exacerbations in children with non-cystic-fibrosis bronchiectasis and chronic suppurative lung disease after once-weekly azithromycin for up to 24 months were also reported.[37] However, the long-term treatment was associated by increase in azithromycin-resistant bacteria.

Haworth C.S. et al. emphasized the need to balance the risks and benefits of macrolide therapy, not only the emergence of bacterial resistance, but also cardiotoxicity and ototoxicity of the drug.[38]

Posttransplantation bronchiolitis obliterans syndrome (BOS)

Posttransplantation BOS isthe leading cause of morbidity and mortality afterlung transplantation. Research supports significant benefits of azithromycin in the treatment of post. lung transplant BOS, such as improvement of lung function and FEV1 after long term treatment.[39, 40] Azithromycin also significantly reduced airway neutrophilia and IL-8 in patients with BOS. The authors suggest that BAL neutrophilia can be a predictor for the FEV(1) response to azithromycin.At the same time, long-term azithromycin treatment failed to reverse post lung transplant BOS, while slowing progression of the disease.[41]

Chronic obstructive pulmonary disease (COPD)

Long-term treatment with azithromycin demonstrated safety and effectivenessin severe COPD patients with tracheostomy, reducing exacerbations, hospitalizations, and improving quality of life.[42] No serious adverse events were reported.

A randomised, double-blind, placebo-controlled, single-center trial in the Netherlands demonstrated that azithromycin significantly decreased the rate of exacerbations, and recommended its use in patients with COPD who have the frequent exacerbations and are refractory to standard care.[43] In this study the most common adverse event was diarrhea.

A meta-analysis also demonstrated benefits of azithromycin in reducing frequency of exacerbations in patients with COPD, while the treatment also increased adverse events and produced macrolide resistance.[44]

HIV infection

Enhanced antimicrobial prophylaxis, consisting of continuous trimethoprim-sulfamethoxazole plus isoniazid-pyridoxine and fluconazole, 5 days of azithromycin, and a single dose of albendazole, was compared to a standard prophylaxis (trimethoprim-sulfamethoxazole alone) in HIV-infected patients in Africa receiving ART with advanced immunosuppression. It resulted in reduced rates of death at both 24 weeks and 48 weeks without compromising viral suppression or increasing toxic effects.[45]A multicentre (Malawi and Zimbabwe), double-blind, randomised controlled trial of weekly azithromycin for 12-month for the treatment of HIV-associated chronic lung disease in children and adolescents (BREATHE trial) started in 2017.[46]

Primary immunodeficiency

Azithromycinin the dose of 10 mg/kg and in combination with inhaled tobramycin was suggested for common variable immunodeficiency and bronchiectasis in patients with hyper IgE-syndrome.[2, 47]A two week prophylaxis with azithromycin in the dose of 10 mg/kg three times per week is recommended for patients with ataxia-teleangiectasia.[2,48]

Bronchiectasis is one of the most severe recurrent respiratory infection complications in patients with hypogammaglobulinaemia.[2] British Thoracic Society 2010 guidelines for non-CF bronchiectasis underline PID, especially antibody deficiency as a frequent course of bronchiectasis.[35] Long-term oral antibiotics should be considered for patients having ≥3 exacerbations per year or for patients with fewer exacerbations if these cause significant morbidity.[35] Macrolides can be an antibiotic of choice, as they have disease-modifying activity, although a large randomized controlled trial is needed to evaluate this particular group of drugs.

French National Reference Center for PIDs issued recommendations for anti-infectious prophylaxis in the most common PIDs, which underline macrolides as an alternative for a long-term therapy in cases of bronchiectasis in patients with agammaglobulinemia.[3] These recommendations are based on the macrolides anti-inflammatory effect in addition to their antibacterial activity. Azithromycin is a commonly used macrolide for this purpose.

Limitation of use

Given the anti-inflammatory impact of azithromycin,it is widely used for treating chronic lung diseases, including in patients with PID. However, long-term prophylaxis may cause adverse events.

First of all, long-term antibiotics use may result in development of antibiotic resistance.[17,35] In patients with chronic lung diseases receiving long-term azithromycin the risk of bacterial resistance increased 2.7-fold at the same time as the risk of bacterial colonization decreased.[49]

The risk of bacterial resistance increases proportionately to the duration of macrolide use. In a study of 3 year-long course of macrolide prophylaxis, staphylococcal resistance to azithromycin increased over time, from 10% at the baseline to 83% in the first year, 97% in the second and 100% in the third year.[31]

Secondly, the increased risk of hearing impairment was reported in patients receiving long-term azithromycin therapy.[49] Another adverse effect, QTc interval prolongation, torsade de pointe, is connected with increased the risk of death, especially in patients with heart problems.[50]

However, the use of antibiotic prophylaxis in patients with PID is a common practiceworldwide; it has mostly been extrapolated from the data of immune competent patients with chronic lung diseases.[7]We have not found any publications regarding the low adherence of patients to long-term antibacterialprophylaxis, as reported for other diseases[51, 52].There are no controlled trials on the use of prophylactic antibiotics in patients with primary immunodeficiency disorders.[2,49]

Conclusions

Both co-trimoxazole and azithromycin, are used for the long-term treatment and prophylaxis of primary immunodeficiencies due to their different antibacterial effects.

Co-trimoxazole is a widely used antimicrobial agent for pneumocystosis prophylaxis in immunocompromised patients, including patients with primary cellular immunodeficiency.

Antiinflammatory effect of azithromycin made it a drug of choice in the management of chronic lung diseases in the patients with primary immunodeficiencies, especially in those with antibody deficiencies.

Further randomised controlled studies are needed to define the optimal agent for all types of primary immunodeficiencies, its dose, duration of treatment, benefits and safety of long-term use. A recommendation for the prophylactic use of long-term therapy should consider the balance between benefits and risks of the adverse events.

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