

Macrolide therapy for the prevention of acute exacerbations in chronic obstructive pulmonary disease

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KEY WORDS

antibiotic prophylaxis, chronic obstructive pulmonary disease, exacerbation, macrolide

ABSTRACT

Acute exacerbations are a major contributor to health care costs and a leading cause of death in patients with chronic obstructive pulmonary disease (COPD). A reduction in acute exacerbations of COPD (AECOPD) would lead to significant improvements in patient well-being and survival. Bacterial and viral infections cause a majority of AECOPD episodes; however, with the exception of influenza and pneumococcal vaccines, preventative therapies for exacerbations do not directly address these infectious causes of AECOPD. Antibiotics were shown to have marginal benefit in preventing AECOPD several decades ago; however, since then, pathogens and antibiotics have changed substantially. Macrolides display immunomodulatory and anti-inflammatory effects in addition to their direct antibacterial effect. Several studies have examined macrolides in AECOPD prevention, with a recent landmark study by Albert et al. clearly demonstrating the efficacy of azithromycin in preventing AECOPD. Unfortunately, the rate of isolation of macrolide-resistant pathogens does increase with such treatment. Macrolides could also suppress bacterial colonization and thus decrease airway inflammation, thereby interrupting the vicious cycle of inflammation and infection in COPD. COPD patients with two or more exacerbations a year in spite of appropriate standard therapy are potential candidates for this therapeutic approach. However, optimal duration and dosing of macrolide prophylaxis for AECOPD remains uncertain.

Introduction Chronic obstructive pulmonary disease (COPD) is the 5th leading cause of death in the United States (US) and is projected to increase to the 3rd leading cause of death by the end of the decade.^{1,2} Worldwide, COPD is the 4th leading cause of death and nearly 25% of adults older than 40 years of age have COPD.³ COPD has a projected 2010 direct cost of \$29 billion and indirect cost of \$20 billion in the US alone.¹ The European Union spends 38 billion Euros in direct costs for COPD. Undoubtedly, COPD is a major global health care problem.

Contributing substantially to the morbidity and mortality in patients with COPD are episodes of increased respiratory and systemic symptoms characterized as acute exacerbations (AECOPD). Patients with frequent AECOPD have faster lung function decline, prolonged time to recovery, and increased incidence of depression, anxiety, and

a poorer quality of life.⁴⁻⁸ More than 30% of patients discharged from an emergency room visit due to AECOPD will have recurrent symptoms within 14 days and eventually 17% will require hospitalization.^{9,10} Patients requiring 3 or more hospitalizations in a year due to AECOPD have a significantly reduced 5-year survival.¹¹ Because many exacerbations need additional medical care, they are responsible for the consumption of substantial health care resources. For instance, in the US, exacerbations account for 16 million office visits and over 500,000 hospitalizations per year.¹² It has been estimated that AECOPD management is responsible for up to 50% of the overall cost of care of COPD.^{13,14} With improving care of the chronic stage of COPD and potentially improved survival, AECOPD are likely to become a larger health care issue, as typically exacer-

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bations increase in frequency as the severity of underlying COPD worsens.¹⁵

Current methods to prevent exacerbations Guidelines for COPD management, such as the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, have over the years increasingly recognized the importance of exacerbations in the course of COPD.³ In fact, one of the major goals of COPD management in the GOLD guidelines is the “prevention and management of exacerbations”. Reduction of AECOPD has also become a major goal in the development of new therapeutics for COPD. Several aspects of COPD management are supposed to reduce exacerbations, though the evidence to support these effects is variable. The current approaches to the reduction of exacerbations include smoking cessation, vaccination against influenza and pneumococcal infection, long-acting anticholinergics, combination treatment with long-acting β -agonist and inhaled corticosteroids, and pulmonary rehabilitation. However, these strategies at best appear to have been able to reduce AECOPD only by 40%.^{16,17} Data from a recent large observational study in COPD, the ECLIPSE study, also demonstrate the exacerbation reduction in COPD is suboptimal.¹⁸ In this study, 22% of GOLD Stage 2, 33% of GOLD Stage 3, and 47% of GOLD Stage 4 patients had 2 or more exacerbations in the first year of the study, and 7%, 18%, and 33%, respectively, were hospitalized for an exacerbation in the same time period. This happened in spite of the majority of these patients being under specialized care and receiving optimal current long-term treatment for COPD with long-acting bronchodilators and inhaled corticosteroids. Obviously, therapeutic approaches to further safely decrease AECOPD are needed. These would impact not only patient quality of life and survival, but reduce the overall cost of health care of COPD.

With the exception of the influenza and pneumococcal vaccination, the current strategies in the prevention of AECOPD are not directed at the predominant causes of exacerbation, i.e., respiratory bacterial and viral infections.¹⁹ However, it is firmly established that the use of bronchodilators, especially the long-acting anticholinergic agents, and the use of potent inhaled corticosteroids indeed reduce AECOPD. While improvements in these classes of agents may incrementally improve their ability to reduce exacerbations, alternative approaches that directly address the infectious and inflammatory aspects of exacerbations are more likely to have a significant additional benefit in terms of exacerbation reduction. Vaccines are the optimal approach to prevention of infection. However, significant impediments exist to vaccine development for AECOPD prevention. There are a variety of pathogens that cause exacerbations, and the contribution of an individual pathogen to exacerbations in an unselected population of patients with COPD is likely at most 15%. This creates a practical problem for study design

for vaccine studies in the prevention of AECOPD, as large populations need to be enrolled to show a benefit of reduction in infection with a single pathogen. Blunted immune response to vaccine antigens in elderly and debilitated patients with COPD is another impediment to vaccine development, and has been demonstrated for the current pneumococcal vaccine used in these patients.²⁰ Antigenic diversity among strains of bacteria that cause exacerbations, most notably nontypeable *Haemophilus influenzae*, has also been a problem in developing vaccines that are effective against a wide variety of strains of such pathogens.²¹

Role of macrolides An alternative approach to preventing infectious exacerbations of COPD is the use of antibiotics in a prophylactic manner. Prior to 1970, when the British hypothesis of COPD causation was prevalent, several small trials were conducted with long-term antibiotics to prevent AECOPD. In a Cochrane systematic review of 9 such trials, a small reduction of exacerbations per patient per year was observed with an odds ratio of 0.91 (0.84–0.99) with treatment.²² These studies are now mainly of historical interest. Quality of these trials was inadequate, and antibiotics, bacterial pathogens, and their antibiotic susceptibility have evolved considerably in the past 30 years.

Among the antibiotic classes, macrolides (including erythromycin, azithromycin, and clarithromycin) are especially attractive as prophylactic antibiotics in COPD. In addition to their direct antibacterial effects, they have also been shown to have potentially beneficial immunomodulatory and anti-inflammatory effects.^{23–25} Macrolides have also been used successfully in preventing exacerbations and improving lung function in other airway diseases such as cystic fibrosis and diffuse panbronchiolitis, and their efficacy in these diseases appears to be related more to their nonantibiotic effects.

There are now several published studies of macrolide use in AECOPD prevention. The first study published in 2001 by Suzuki et al.²⁶ was a prospective, open-label, randomized, placebo controlled trial in 109 patients treated with erythromycin 200–400 mg daily for 12 months. There was a significant reduction in common cold episodes and AECOPD and decreased risk of hospitalization due to AECOPD. Though the findings were quite impressive, the open-label nature of the study was a major limitation. The second study came out in 2005, which was a prospective, double-blind, randomized placebo-controlled study of 67 patients with moderately severe COPD with 3 months of clarithromycin 500 mg daily.²⁷ This study failed to meet its primary endpoints of decrease in sputum bacterial colony counts, exacerbation rate, or health status, assessed by the St. George’s Respiratory Questionnaire (SGRQ). However, there was a statistically significant improvement in the symptom domain of the SGRQ in the clarithromycin arm. Though this study was a double-blind placebo-

-controlled study, it was underpowered and the duration of treatment was too short for an exacerbation prevention trial.

The next published study was a single-center, randomized, double-blind, placebo-controlled study of twice daily erythromycin 250 mg, administered to 53 patients with moderate-to-severe COPD for 12 months, while 56 patients received placebo.²⁸ The primary outcome measure was exacerbation frequency. Changes in airway and systemic inflammation were also assessed using sputum interleukin (IL)-6, IL-8, and myeloperoxidase, and serum C-reactive protein and IL-6. Changes in sputum bacterial flora were also studied. Erythromycin use was associated with a significant reduction in moderate-to-severe exacerbations, defined by the requirement for antibiotic and/or systemic corticosteroid treatment. Median time to first exacerbation was also significantly increased. Rate of decline of lung function was not changed with macrolide treatment. However, in contrast to the clinical benefits, macrolide treatment was not associated with a reduction in any of the inflammatory markers measured in this study. Erythromycin use was well tolerated with no significant adverse effects. Macrolide resistance was rarely observed with the emergence of one resistant *S. pneumoniae* strain observed

in the treatment arm; however, the number of cultures assessed was inadequate.

Though these studies were generally supportive of long-term macrolide use in COPD to prevent exacerbations, none of them provided definitive evidence to justify macrolide use. In the *New England Journal of Medicine* August 25, 2011 issue, Albert et al.²⁹ report a major study with daily azithromycin for the prevention of exacerbations. In this multi-center, prospective, placebo-controlled, double-blind, randomized trial, the authors examined the use of azithromycin in 570 subjects with COPD compared with placebo in 572 subjects with similar severity of COPD. Subjects were enrolled in 17 sites affiliated with 12 academic medical centers in the US. The daily dose of azithromycin was 250 milligrams orally for 1 year.

The study participants were at least 40 years of age, had a pre-existing diagnosis of COPD, and were at high risk for an exacerbation. High risk for exacerbation was identified by the use of systemic steroids, history of an AECOPD within the previous 12 months (but not within the prior 4 weeks), or by the use of supplemental oxygen. Exclusion criteria were a diagnosis of asthma, a resting heart rate greater than 100 beats/minute, a prolonged corrected QT, the use of medications that increase the QT interval, or a hearing impediment.

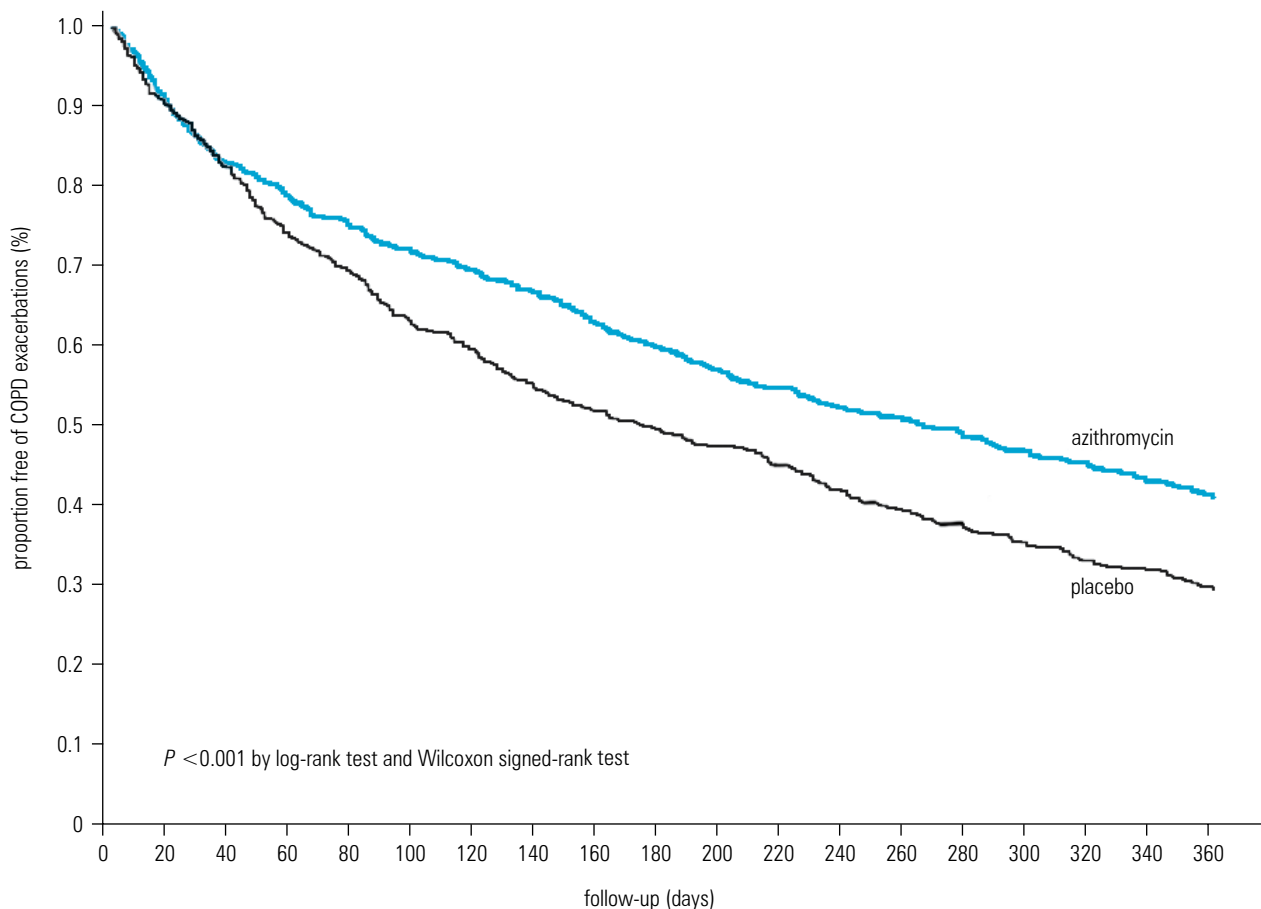


FIGURE 1 Reduction in exacerbations with azithromycin in the study by Albert et al. Reproduced from Albert RK, et al. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med.* 2011; 365: 689-698.²⁹ Abbreviations: COPD – chronic obstructive pulmonary disease

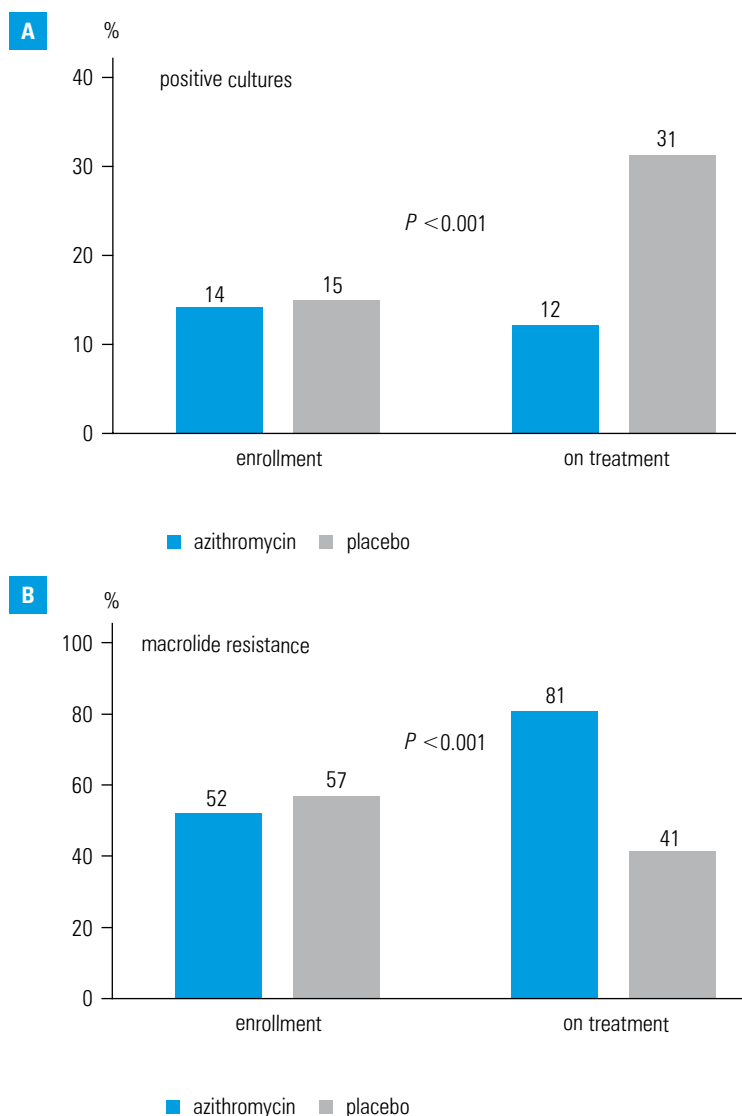


FIGURE 2 Results of nasopharyngeal cultures in the study by Albert et al.²⁹ **A** – proportion of nasopharyngeal cultures positive for potential respiratory bacterial pathogens at enrollment and subsequently on treatment; **B** – rate of macrolide resistance among nasopharyngeal bacterial pathogen isolates at enrollment and subsequently on treatment

The time to the first AECOPD requiring treatment with antibiotics and/or systemic steroids was the primary outcome. The median time to the first AECOPD was 266 days in the azithromycin group vs. 174 days in the placebo group, which was significantly different (FIGURE 1). The authors also noted an exacerbation frequency of 1.48 exacerbations per patient-year in the group receiving azithromycin vs. 1.83 exacerbations per patient-year in the placebo group, with a hazard ratio of 0.73 (95% confidence interval, 0.63–0.84; *P* < 0.001). There was no significant difference in death or major adverse events; however, the incidence of a decrease in hearing in the group receiving azithromycin was greater than those receiving placebo (25% vs. 20%). Otherwise the medication was well tolerated.

A major concern with chronic antibiotic use is the emergence of antibiotic resistance. In the Albert study, antibiotic resistance was monitored in nasopharyngeal swabs performed at baseline and

then with periodic sampling during the study. Sputum sampling was initially included in the study protocol, but the low yield of adequate spontaneous sputum samples led to a discontinuation of sputum monitoring in this study. Sputum induction could have provided a larger number of adequate samples; unfortunately, it was not pursued in this study. Two important observations were made with the nasopharyngeal culture results (FIGURE 2). There was a significant decrease in the incidence of positive cultures for bacterial pathogens in the macrolide group; however, there was a significant increase in the proportion of macrolide-resistant bacterial strains in the azithromycin group vs. the placebo group. It is difficult to interpret the significance of nasopharyngeal bacterial colonization as it is not a validated surrogate for sputum or bronchoalveolar lavage culture. Though there was no association between nasopharyngeal colonization and AECOPD occurrence, there were inadequate details provided about the microbiology at the time of AECOPD to exclude increased incidence of exacerbations with macrolide-resistant pathogens in patients on azithromycin.

The exact mechanism by which macrolides prevent exacerbations in COPD is not clear. In the studies with low-dose erythromycin, the systemic drug levels achieved with these low doses is below the minimal inhibitory concentrations for common respiratory pathogens. Therefore, the speculation is that anti-inflammatory or immunomodulatory effects of erythromycin may be more important than its antimicrobial action in its benefits in COPD. Interestingly, there was no decrease in inflammatory markers in sputum or serum in these studies.²⁶⁻²⁸ Though direct antimicrobial effects are unlikely at low-dose macrolides, indirect effects, such as altered biofilm synthesis or enhanced phagocytosis and bacterial clearance by alveolar macrophages, could provide an alternative antimicrobial action with low-dose macrolides.³⁰ Azithromycin given at a dose of 250 mg daily is a therapeutic dose, should provide direct antimicrobial activity, and be accompanied by considerable intracellular drug accumulation over time. Therefore, with azithromycin dosed on a daily basis, at least some of the benefits are likely related to direct antimicrobial activity. The reduction in nasopharyngeal colonization by potential bacterial pathogens in the azithromycin arm is consistent with this concept.

Inhaled steroids and phosphodiesterase inhibitors reduce exacerbations of COPD and the effect appears to be related to their anti-inflammatory actions. Whether the anti-inflammatory effects of macrolides are responsible for exacerbation reduction in COPD is unknown. Though reduction in inflammation was not seen when examined in the earlier studies, inflammation in COPD is complex, and the assessment of inflammation in these studies may have not been comprehensive enough to capture differences. Biomarker assessment is planned in the Albert study and the results are eagerly awaited. However, they will only have data for systemic inflammation as sputum samples were not collected.

Infection and inflammation in COPD have been characterized as comorbid conditions in COPD, with each one perpetuating the other worse in a vicious circle.³¹ There is increasing evidence that chronic bacterial colonization of the lower airways perpetuates inflammation and contributes to the progression of COPD.¹⁹ Furthermore, excessive inflammation as seen in COPD is detrimental to lung defense mechanisms making it more susceptible to infections, both acute and chronic. Macrolides, by their direct and indirect anti-infective effects, could suppress bacterial colonization, with a subsequent decrease in airway and systemic inflammation. A primary reduction in airway inflammation in COPD by macrolides could strengthen lung defense mechanisms and reduce infection. This would make it difficult to distinguish the beneficial anti-infective and anti-inflammatory actions of macrolides in COPD.

Irrespective of mechanisms, do we have adequate evidence to use macrolides in the prevention of AECOPD? The Albert study with the supporting evidence from the previous erythromycin studies clearly indicates that exacerbations can be reduced with chronic macrolide use. Whether a daily dose of azithromycin is necessary or a 3 times weekly dose as used in cystic fibrosis is adequate, is an unresolved issue. Identifying the appropriate patient for such treatment is also crucial. Patients with 2 or more exacerbations per year (frequent exacerbators) in spite of appropriate bronchodilator and anti-inflammatory treatment, who do not have any contraindication to the use of macrolides are potentially appropriate for such intervention. Exacerbations while on macrolide prophylaxis that are clinically bacterial and need antibiotics should be treated with nonmacrolide antibiotics, e.g., fluoroquinolones, as the possibility of infection with a macrolide-resistant strain definitely exists. The duration of treatment is also unclear. At least several months are required to assess effectiveness. However, whether treatment should be continued indefinitely, used seasonally or with drug-free holidays, are all important unanswered questions. The societal impact in terms of emergence and spread of macrolide-resistant bacterial strains with widespread macrolide use in the prevention of AECOPD remains a concern. There are clearly several questions that need to be answered about the appropriate use of macrolides in COPD; however, large studies to answer those questions do not appear to be in consideration. Ideally, the development of effective vaccines, targeted anti-inflammatory agents, or therapies that improve lung antimicrobial defense and thus decrease exacerbations will be available in the future. In the interim, judicious use of macrolides in selected patients should be considered.

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Makrolidy w zapobieganiu nagłym zaostrzeniom przewlekłej obturacyjnej choroby płuc

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leczenie antybiotykami, makrolidy, przewlekła obturacyjna choroba płuc, zaostrzenia

STRESZCZENIE

Nagłe zaostrzenia są głównym składnikiem kosztów opieki zdrowotnej i najważniejszą przyczyną zgonów u chorych na przewlekłą obturacyjną chorobę płuc (POChP). Zmniejszenie częstości nagłych zaostrzeń doprowadziłoby do istotnej poprawy jakości życia chorych oraz do wydłużenia przeżycia. Przyczyną większości zaostrzeń są zakażenia bakteryjne i wirusowe, ale działania prewencyjne nie są skierowane bezpośrednio przeciwko tym zakażeniom (z wyjątkiem szczepionek przeciwko grypie i pneumokokom). Kilka lat temu wykazano graniczną korzyść ze stosowania antybiotyków w zapobieganiu nagłym zaostrzeniom POChP, ale od tego czasu odpowiedzialne za nie drobnoustroje i antybiotyki uległy znacznej zmianie. Oprócz działania przeciwbakteryjnego makrolidy mają dodatkowo właściwości immunomodulujące i przeciwzapalne. W kilku badaniach oceniono skuteczność makrolidów w zapobieganiu nagłym zaostrzeniom POChP (m.in. w niedawnym badaniu Alberta i wsp., w którym wyraźnie wykazano skuteczność azytromycyny pod tym względem). Niestety takie leczenie wiąże się ze zwiększeniem częstości izolowania drobnoustrojów opornych na azytromycynę. Makrolidy mogą także hamować kolonizację bakteryjną i w ten sposób zmniejszać nasilenie zapalenia dróg oddechowych, przerywając tym samym błędne koło zapalenia i zakażenia w POChP. Potencjalnymi kandydatami do takiego leczenia są chorzy na POChP z co najmniej 2 zaostrzeniami rocznie pomimo właściwego standardowego leczenia. Optymalny czas stosowania makrolidu i jego dawka w profilaktyce nagłych zaostrzeń POChP pozostają jednak nieznanymi.

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