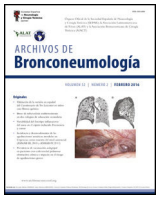
Arch Bronconeumol. 2018;54(2):61–62

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE Bronconeumología

www.archbronconeumol.org



Editorial

Bronchiectasis and azithromycin☆

Bronquiectasias y azitromicina

F. Casas-Maldonado

Unidad de Gestión Clínica de Neumología, Hospital Universitario San Cecilio, Granada, Spain

Bronchiectasis is defined as abnormal and irreversible dilation of the bronchi, and is the final outcome of several diseases that have a common pathophysiology.[1] Changes in local defense mechanisms or the immune response make it harder for the body to eliminate potentially pathogenic microorganisms, and trigger an inflammatory and cytotoxic cascade that damages the epithelium of the airway, completing the vicious circle of obstruction-inflammation-infection that forms the pathogenic axis of bronchiectasis.[2,3] Bronchiectasis is generally classified as cystic fibrosis-related (CF) or non-CF-related (non-CF). Non-CF has different causes and affects a more heterogeneous population. Interest in bronchiectasis has been growing in recent years, due to an increased prevalence, a greater diagnostic capacity offered by high-resolution computed tomography, the increasing identification of diseases associated with bronchiectasis (asthma, COPD, autoimmune diseases, etc.), and the development of new treatments.[4]

Bronchiectasis is a chronic, progressive disease, and its prognosis is associated with the underlying disease, the extent of the lesions, the impact on lung function, and the frequency and severity of exacerbations. In patients with chronic obstructive pulmonary disease (COPD), bronchiectasis is related with a greater number and greater severity of exacerbations and increased mortality.[5] For this reason, the severity of the bronchiectasis must be evaluated, and prevention, diagnosis, and early treatment of exacerbations are essential.[6] Potentially pathogenic microorganisms usually isolated in the sputum of bronchiectasis patients include *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* (PsA).[7,8] However, not all potentially pathogenic microorganisms affect bronchiectasis patients in the same way. Chronic PsA colonization, generally observed in patients with more severe obstruction, is associated to an increase in healthcare costs generated by hospital admissions and inhaled antibiotic treatment,[4] and has been defined as a predictor of mortality.[9]

Macrolide antibiotics, such as azithromycin, exhibit bacteriostatic activity by altering the 50S ribosomal subunit, with the subsequent interruption and inhibition of protein synthesis. Important characteristics of azithromycin are that it achieves high intracellular concentrations, particularly in phagocytes, and reduces the biofilm growth of bacteria such as PsA by interfering with quorum sensing detection signals. It also has powerful immunomodulatory activity that initially reduces acute inflammation, and at a later stage helps resolve chronic inflammation by promoting long-term repair and healing.[10] Because of these properties, azithromycin has been used in the treatment of a variety of chronic pulmonary diseases, including COPD, bronchiolitis obliterans, diffuse panbronchiolitis, asthma, and non-CF and CF bronchiectasis.[10] Azithromycin has been used successfully in the treatment of chronic PsA bronchial infection in patients with CF bronchiectasis, and its use has subsequently been extended to non-CF bronchiectasis. The use of azithromycin for the prevention of exacerbations in patients with non-CF bronchiectasis and a history of at least one exacerbation in the previous year has been supported in several studies and systematic reviews.[11,12] However, in standard practice it is generally used in patients who have had 3 or more exacerbations,[13] in patients with chronic PsA infection, and in patients with fewer exacerbations but poor quality of life despite optimal treatment. Although the optimal dose (duration, dose, frequency) has not yet been established, doses of 250 or 500 mg (body weight < or ≥40 kg, respectively) 3 days a week for periods of 3–6 months have been shown to be potentially beneficial in non-CF bronchiectasis patients with frequent exacerbations. No studies are available to demonstrate efficacy and safety over periods of more than 12 months. Thus, a reasonable option may be to start treatment with azithromycin for 3 or 6 months and then determine the effect on exacerbations and other events. If the results are unsatisfactory, treatment should be discontinued. If the results are good and the compound is well tolerated, treatment may continue, with monitoring for side effects.[14]

Before starting azithromycin, non-tuberculous mycobacterial infection must be ruled out in any patient with clinical or radiological suspicion. If non-tuberculous mycobacteria are isolated, azithromycin should not be indicated, because this would constitute monotherapy.[14] Prolonged treatment with macrolides has been shown to increase resistance to *Haemophilus influenzae*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*, and this phenomenon should be evaluated in future studies.

Contraindications for azithromycin treatment include severe liver disease, severe kidney disease, and a prolonged QT interval, so an electrocardiogram is advisable. As the most common side effects are gastrointestinal (nausea, diarrhea), elevated

☆ Please cite this article as: Casas-Maldonado F. Bronquiectasias y azitromicina. Arch Bronconeumol. 2018;54:61–62.

E-mail address: franciscocasas@neumosur.net

transaminases, and hearing loss, liver function tests should be performed during the first weeks of treatment and at 6-monthly intervals, and an audiometry should be performed annually.[14]

Strategies aimed at improving bronchiectasis diagnosis and preventing exacerbations are of great interest and should have a significant clinical impact. Results from different studies are encouraging, and azithromycin is clearly positioned as a strategy for preventing and reducing the number and severity of exacerbations in patients with non-CF bronchiectasis. However, it is important to determine the types of bronchiectasis patients in whom azithromycin is indicated, and more studies are needed to define the most appropriate doses and dosing regimens, and long-term safety.[15] Other macrolides such as clarithromycin or erythromycin have also been used in non-CF bronchiectasis, but this discussion lies outside the scope of this review, and would require more space than is available here. Several studies have reported on the development of new macrolides with minimal antibacterial activity and a clearly immunomodulatory profile, and these compounds may offer a beneficial effect without inducing bacterial resistance. It seems likely that we will witness their development and application in daily clinical practice in the future.[16]

References

1. Vendrell M, de Gracia J, Olveira C, Martínez MA, Girón R, Máiz L, et al. Diagnóstico y tratamiento de las bronquiectasias. Arch Bronconeumol. 2008;44:629–40.
2. Cole PJ. Inflammation: a two edged-sword-the model of bronchiectasis. Eur J Respir Dis Suppl. 1986;147:6–15.
3. Whitters D, Stockley R. Inmunity and bacterial colonisation in bronchiectasis. Thorax. 2012;67:1006–13.
4. De la Rosa Carrillo D, Prados Sánchez C, Quirós Fernández S. Epidemiología actual y costes de las bronquiectasias. Monogr Arch Bronconeumol. 2016;3:1–9.
5. Martínez-García MA, de la Rosa Carrillo D, Soler-Cataluña JJ, Donat-Sanz Y, Serra PC, Lerma MA, et al. Prognostic value of bronchiectasis in patients with moderate-to-severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2013;187:823–31.
6. Chang AB, Bilton D. Exacerbations – 4 non-CF bronchiectasis. Thorax. 2008;63:269–76.
7. Angrill J, Agustí C, de Celis R, Filella X, Rano A, Elena M, et al. Bronchial inflammation and colonization in patients with clinically stable bronchiectasis. Am J Respir Crit Care Med. 2001;164:1628–32.
8. Alanin MC, Nielsen KG, von Buchwald C, Skov M, Aanaes K, Høiby N, et al. A longitudinal study of lung bacterial pathogens in patients with primary ciliary dyskinesia. Clin Microbiol Infect. 2015;21:1093e1–7e.
9. Loebinger MR, Wells AU, Hansell DM, Chinyanganya N, Devaraj A, Meister M, et al. Mortality in bronchiectasis: a long-term study assessing the factors influencing survival. Eur Respir J. 2009;34:843–9.
10. Cramer CL, Patterson A, Alchakaki A, Soubani AO. Immunomodulatory indications of azithromycin in respiratory disease: a concise review for the clinician. Postgrad Med. 2017;1:1–7.
11. Wong C, Jayaram L, Karalus N, Eaton T, Tong C, Hockey H, et al. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. Lancet. 2012;380:660–7.
12. Fan LC, Lu HW, Wei P, Ji XB, Liang S, Xu JF. Effects of longterm use of macrolides in patients with non-cystic fibrosis bronchiectasis: a meta-analysis of randomized controlled trials. BMC Infect Dis. 2015;15:160.
13. Altenburg J, de Graaff CS, Stienstra Y, Sloos JH, Van Haren EH, Koppers RJ, et al. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non cystic fibrosis bronchiectasis: the BAT randomized controlled trial. JAMA. 2013;309:1251–9.
14. Girón Moreno R, Gómez González C, Máiz Carro L. Tratamiento de las bronquiectasias. Monogr Arch Bronconeumol. 2016;3:30–44.
15. Haworth CS, Bilton D, Elborn JS. Long-term macrolide maintenance therapy in non-CF bronchiectasis: evidence and questions. Respir Med. 2014;108:1397–408.
16. Hodge S, Tran HB, Hamon R, Roscioli E, Hodge G, Jersmann H, et al. Nonantibiotic macrolides restore airway macrophage phagocytic function with potential anti-inflammatory effects in chronic lung diseases. Am J Physiol Lung Cell Mol Physiol. 2017;312:L678–87.