

Are Macrolides the Pulmonologists' "Statin"?

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In recent years there has been an increasing number of clinical trials, case series and other evidence suggesting that utilization of macrolides can lead to improved outcomes in patients with a variety of lung diseases. There is evidence to support their use in diffuse panbronchiolitis [1], where it changes the course of the disease; bronchiolitis obliterans after lung transplantation, where preventive use can prevent its occurrence and can improve lung function after bronchiolitis obliterans occurrence [2,3]; Chronic Obstructive Pulmonary Disease (COPD), where they have been showed to decrease exacerbations [4,5]; cystic fibrosis, where improved lung function, decreased exacerbation rates and weight gain have been found [6,7]; and non-cystic fibrosis bronchiectasis, where exacerbation rates have improved [8,9]. As a result, macrolides are a common medication in many lung diseases. The majority of trials have studied azithromycin, which has a long half-life and few doses can have a significant effect and be well tolerated. Erythromycin, which has lower cost, is less frequently used because of need of multiple doses, more significant gastrointestinal side effects and medication interactions.

However, with increasing use some concerns have started to arise. A recent retrospective study suggested that azithromycin use for any reason, in a large state Medicaid database led to increased cardiovascular events [10]. Another laboratory investigation suggested that in the presence of azithromycin *Mycobacterium abscessus* can evade the body's immune defenses. In addition, azithromycin is one of the most important medications in the treatment of Nontuberculous Mycobacterial (NTM) [11]. Its use as a standalone medication can lead to macrolide resistance and make successful future treatment of such disease very difficult. In addition, the incidence and prevalence of NTM disease has continued to increase in specific diseases Cystic Fibrosis (CF) and the general population [12]. Finally, chronic antibiotic use will always lead to increased resistance of other pathogens for these patients and possibly in the community.

These issues raise a lot of important questions. First, how should we proceed about starting macrolides in patients that can possibly benefit from their use? Do we need screening for NTM in these patients? Do we need to screen or decide on use based on cardiovascular risk factors? What screening is needed? Sometimes NTM are difficult to grow and many of the patients do not easily expectorate sputum. Second, how long should patients be treated in order to assess effectiveness? What constitutes a "success"? Finally, which macrolide should we use?

It is very difficult to answer these questions, but trying to individualize recommendations based on specific patients is always a good idea. For many of these disease states only azithromycin has been studied, therefore erythromycin cannot be recommended. However, future comparative studies could clarify the utility of the two antibiotics. Erythromycin interacts with many medications and is more likely to create cardiac arrhythmias, so azithromycin might be the medication of choice in such patients. On the other hand, erythromycin does not have a role in the treatment of NTM and it might be a good choice in such patients, while preserving azithromycin for future treatment of NTM (if and when needed). One of the more difficult decisions to make would be defining success. Clinicians and patients should work together prior to starting macrolides in "defining" success, so unnecessary and prolonged use is avoided. Of course, careful selection of patients in the first place can help limit their use in patients where the best evidence of success exists.

In summary, macrolides are another treatment option for many patients with advanced lung disease with medications that have been available for a long time and are not very expensive. However, increased use could lead to many unwanted complications if clinicians are not careful. We are responsible as a community to try and find the best answers for the above questions and achieve the best treatment for our patients.

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