MARCiE FAQs - Macrolides for Asthma: Registry of Clinical Experience

What is MARCiE?

MARCiE is an Internet-based, human subjects committee-approved registry into which practicing clinicians can enter prospective, de-identified data on adolescent and adult patients with (1) severe, refractory asthma, (2) new-onset asthma, and (3) other asthma for whom they have chosen to prescribe long-term (≥3 months) azithromycin treatment (or other selected antibiotic(s)). The purpose is to document the proportions of these patients who will benefit from the antibiotic treatment in "real world" settings and under usual care conditions.

What is the evidence for antibiotic treatment for asthma?

Macrolide treatment for severe, refractory asthma has Strength of Recommendation (SOR) grade B level evidence. Macrolide treatment for new-onset asthma has SOR C level evidence. An **Evidence Review** presents the existing evidence and can be accessed at https://www.fammed.wisc.edu/wren/resources/macrolides-for-asthma. There is insufficient evidence to apply an SOR grade to other asthma. (Other asthma patients who have sought out macrolide treatment include (i) some with uncontrolled asthma who cannot be classified as refractory and (ii) some with well-controlled asthma who desire to lower or eliminate steroid treatment.)

What is the definition of severe, refractory asthma?

The definition of severe, refractory asthma is asthma that does not respond to conventional guideline asthma medications. The working definition adopted for MARCiE is: Severe, refractory asthma is defined as asthma that remains severely uncontrolled (Asthma Control Test [ACT] score of 15 or less) despite taking high dose inhaled corticosteroid-LABA or LAMA combination inhaled therapy.

What if my patient also has some COPD in addition to their asthma? Are they still a candidate?

Yes, patients who also have some COPD are candidates. It is common in primary care to have patients with diagnoses of both asthma and COPD (called the "overlap syndrome"). Chronic lung infection with *Chlamydia pneumoniae* (a potential etiologic agent identified in asthma) is associated with severe asthma. Severe asthma is associated with the development of the overlap syndrome. There is SOR A level evidence to support the use of azithromycin in patients with smoking-associated COPD without co-existing asthma. Overlap syndrome patients have not been studied, so any information about clinical response to azithromycin in patients with the overlap syndrome is desirable.

What are the alternatives for treating severe, refractory asthma?

Treatment options include adding or increasing doses of oral steroids or adding biologic agents (e.g., anti-IL5R for severe eosinophilic asthma) in selected subgroups. Macrolides, particularly azithromycin, represent an alternate approach that avoids the side effects of increasing doses of corticosteroids, and the costs and limited application of biologics. The AMAZES trial found that azithromycin benefit applied equally to eosinophilic and to non-eosinophilic severe asthma.

What is the definition of new-onset asthma?

The definition of new-onset asthma adopted for MARCiE is: First asthma symptoms (e.g., cough, wheeze, chest tightness, shortness of breath) began within the past 2 years. Primary care studies have reported that new-onset asthma symptoms first began after an acute lower respiratory tract illness, such as acute bronchitis or pneumonia, in almost half of patients.

What are the alternatives for treating new-onset asthma?

Current expert opinion guidelines recommend a step-care approach to treatment with anti-inflammatory medications that is familiar to most clinicians. A limited amount of published evidence suggests that an undetermined amount of new-onset asthma is infectious in etiology and potentially curable. One specific aim of MARCiE is to determine what proportion of new-onset asthma will benefit from antibiotic treatment.

What antibiotic is most recommended?

Azithromycin has the best evidence to support its use for severe, refractory asthma. There are some clinician and patient reports of success using a tetracycline (e.g. doxycycline, minocycline) after azithromycin was not found beneficial.

What azithromycin dosing schedule do you recommend?

The AMAZES trial showing efficacy for azithromycin in severe, refractory asthma used a dose of 500 milligrams three times weekly (1500 milligrams weekly) for one year, without a post-treatment observation period to see if benefits continued after treatment ended. Observations from the AZMATICS trial, and extensive clinical experience of the MARCiE administrator indicate that a weekly dose of 750 milligrams for three months can yield equivalent results in patients with severely uncontrolled asthma. AZMATICS also had a post-treatment observation period that documented continued benefit up to one year after treatment in this group of patients.

If my patient responds well to three-month treatment with azithromycin but then relapses, what should I do?

Clinical experience suggests that an additional three-month treatment may result in a more prolonged improvement or remission. Consider continuous azithromycin treatment only for those patients who benefit on treatment but who continue to relapse off treatment. Patients with the overlap syndrome may ultimately require continuous treatment.