

between groups became more significant, probably due to the dramatic loss of variance (Figure 1, B).

Finally, Dreborg expressed his concern about the drug concentrations used in the test. Drugs do not activate basophils to the same degree as other allergens. Thus, optimal drug concentrations are generally much higher and effective ranges are much smaller,³ making dose-response curves mandatory to select the drug concentrations able to induce the response *in vitro* without cytotoxic effects. In our study, we have used drug concentrations that gave optimal results in dose-response curves produced previously.⁷

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Biologic Targeted Therapies for the Phenotypes of Type-2 High Severe Asthma



To the Editor:

We read with great interest the Pro/Con Review of Israel and Panettieri.¹ The authors clearly discussed and proposed the most appropriate phenotype-based mAb (anti-IgE or anti-IL-5) for 4 different cases with type-2 high severe asthma. We would like to share our clinical experience and opinions on this subject.

Indeed, despite all current knowledge, there is no consensus or algorithm to decide which mAb should be used as first-line therapy or an alternative therapy, or whether they could be used in combination.^{2,3} We recently shared our “in-house”

classification of asthma phenotypes and decision-making protocol that involves first-choice mAbs or potential alternative mAbs in severe asthma phenotypes particularly.⁴ One review² has proposed omalizumab for patients with an allergic phenotype regardless of their blood eosinophil count, and anti-IL-5 as an alternative in allergic patients with blood eosinophilia in whom omalizumab has failed. This article also recommended anti-IL-5 for patients with an eosinophilic phenotype and omalizumab as an alternative in patients in whom anti-IL-5 fails and IgE level is more than 30 IU/mL.² A good response is expected when mAbs are given to a correct asthma phenotype. If it is not working, an mAb used for another asthma phenotype should not be preferred as an alternative treatment option in my opinion. For example, benefit from anti-IgE treatment is expected in a patient with pure allergic rhinitis and atopic asthma, whether there is eosinophilia or not, because the allergic reaction in this asthma phenotype is based on early and delayed-type allergic inflammatory responses by allergen-specific IgEs and mast cell degranulation. If anti-IgE does not work in this phenotype (it would work if it is pure atopic asthma), alternative anti-IL-5 treatment would also not necessarily work just because there is eosinophilia. Thus, I think that possible alternative mAbs for this group of patients should include dupilumab. Cytokines such as IL-4, IL-5, and IL-13 have a major role in the pathophysiology of allergic inflammation in atopic asthma. IL-4 and IL-13 are the most important cytokines in specific IgE production. On the other hand, in eosinophilic asthma with chronic nasal polyposis, the most appropriate mAb would be an anti-IL-5 because the main mechanisms are leukotriene synthesis dysregulation and chronic epithelial activation (eg, superantigens and environmental pollutants) with expression of thymic stromal lymphopoietin, IL-25, and IL-33, which stimulate type 2 innate lymphoid cell activation and overproduction of IL-5.⁵⁻⁷ Therefore, anti-IgE treatment cannot be a good alternative in case of anti-IL-5 therapy failure, even if there is atopy, in this severe asthma phenotype. In eosinophilic asthma with chronic nasal polyposis and atopy, if there is partial response with anti-IL-5 therapy, instead of switching to anti-IgE and blocking only 1 mediator, combining these 2 mAbs would be expected to lead to better outcomes. Unfortunately, neither comparative efficacy or effectiveness trials of these 2 monotherapies nor trials of combination therapy with anti-IgE and anti-IL-5 are available, and these would be very valuable to support appropriate decision making in patients with asthma who require biologic therapy.

In conclusion, current or future biological mAbs for type-2 high severe asthma should be chosen wisely according to the most suitable phenotype. Although some logical recommendations can be made currently on the basis of mechanisms of action of the drugs and the underlying pathophysiology of various asthma phenotypes and endotypes, further studies are needed to support or refute these preliminary recommendations.

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Recurrent acute rhinosinusitis prevention by azithromycin in children with nonallergic rhinitis—don't extrapolate



The study by Veskitful et al¹ examined the benefit of azithromycin in preventing recurrent acute sinusitis in a select group of children. Specifically, allergic rhinitis was excluded from the study, and 80% of the children had low immunoglobulin subclasses. They describe fewer reports of rhinosinusitis exacerbations among the 20 randomly assigned to receive azithromycin than were seen in the placebo group.

I have 2 concerns regarding this study. First, rhinosinusitis exacerbations were defined as: (1) symptoms of an upper respiratory infection (URI) lasting more than 10 but less than 30 days, (2) worsening symptoms of a URI after initial improvement, or (3) severe symptoms at onset defined as purulent nasal discharge for 3 to 4 days with high fever. Symptoms identified as being from a URI were not defined. Moreover, there is a substantial difference in clinical concern between exacerbations characterized by definitions 1 and 3. Which of the specific symptoms indicating an exacerbation were present, and which were noted to differ between the treated and placebo patients?

A second concern is the unusual characteristics of the patient population studied. Why were immunoglobulin subtypes examined in these patients, and what are the implications of those findings in 80% of the patients? Further immune evaluation appears to be indicated in those patients.

There is already a reason for concern regarding overuse of antibiotics for acute rhinosinusitis by well-intentioned physicians following what they perceive as current guidelines.² It is imperative that the current study should not be used to encourage the use of azithromycin for prevention of recurrent rhinosinusitis in children without addressing the specific concerns described above.

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Reply



To the Editor:

We appreciate the comments by Professor Weinberger¹ regarding our study titled "Recurrent acute rhinosinusitis prevention by azithromycin in children with nonallergic rhinitis."²

In our present study, the diagnosis of acute rhinosinusitis (ARS) was defined by the American Academy of Pediatrics' criteria as follows: persistent symptoms of an acute upper respiratory tract infection (URI), worsening symptoms of a URI, or severe symptoms.^{3,4} Recurrent acute rhinosinusitis (RARS) was defined as 3 episodes of ARS in 6 months or 4 episodes in 12 months, each lasting <30 days and separated by intervals of ≥10 days during which the patient was asymptomatic.^{3,4} In this study, the presenting symptoms of RARS in azithromycin versus placebo group were purulent nasal discharge 100% versus 100%, nasal congestion 100% versus 95%, postnasal drainage 70% versus 45%, and facial pain 0% versus 10%, $P > .05$. The criteria used to diagnose ARS in azithromycin versus placebo group were persistent symptoms 55.9% versus 51.3%, worsening symptoms 35.3% versus 35.9%, and severe symptoms 8.8% versus 12.8%, $P > .05$.

RARS and chronic rhinosinusitis (CRS) are uncommon conditions in healthy children. The investigations for underlying causes such as allergic rhinitis, immunologic workup, and computed tomography scan of the sinus are suggested.⁵ Shapiro et al⁶ studied 61 children with CRS referred to an allergist for allergy and immunology workup. They found that 36% of subjects had a positive skin test result to inhalant allergen and 56% had low IgG or a poor antibody response to a polysaccharide vaccine or both.⁶ Veskitkul et al⁷ found that the most common predisposing factor for RARS in children was a deficiency in an IgG subclass (78.7%), followed by nonallergic rhinitis (64.9%) and allergic rhinitis (35.1%). In our present study, most patients had a deficiency in an IgG subclass that did not justify monthly use of intravenous immunoglobulin.² The practice parameter for the diagnosis and management of primary immunodeficiency suggests that milder antibody deficiencies (eg, selective deficiency of IgA, deficiency of an IgG subclass, deficiency of a specific antibody, or transient hypogammaglobulinemia of infancy) can be treated with antibiotic prophylaxis.⁸

We agree that antibiotics should be used judiciously in children with RARS. The underlying causes should be identified and specific treatment should be done before starting antibiotic

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