

Anti-IgE or Anti-IL5: That Is the Question



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Advances in our understanding of airway inflammation have provided a more precise approach to managing severe asthma. Despite such approaches, the majority of patients remain uncontrolled.^{1,2} With the recognition that airway eosinophils play a role in evoking airway inflammation and asthma exacerbations, and with new therapies targeting IL5, an important eosinophil survival factor, health care providers now face a dilemma in choosing the optimal monoclonal antibody. This conundrum is especially salient because antibodies against IgE are effective therapies in severe disease and the mechanisms of action overlap for anti-IgE and anti-IL5 agents. This discussion uses a case-based approach to illustrate asthma phenotypes that predict therapeutic responses to specific monoclonal antibodies. Each of the cases assumes that adherence has been optimized and that comorbidities have been addressed to the fullest extent possible.³

CASE 1

We present a 45-year-old man with a history of childhood asthma. The patient has been managed on high-dose inhaled corticosteroids (ICS) and long-acting bronchodilators. Despite this therapeutic approach, he annually experienced 2 exacerbations requiring oral prednisone courses. His diagnostic evaluation includes IgE 200 IU/mL, blood eosinophil count 100 cells/ μ L, a positive radioallergen sorbent test (RAST) to house dust mite, and a fractional exhaled nitric oxide level (FeNO) that was 30 ppb. What monoclonal antibody therapy would you choose?

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No funding was received for this work.

Conflicts of interest: R. A. Panettieri has received research support and personal fees from AstraZeneca and Novartis; has received research support from Genentech; and has received personal fees from Teva. E. Israel has received consultancy fees from AstraZeneca, Philips Respironics, Regeneron Pharmaceuticals, Bird Rock Bio, Nuvelution Pharmaceuticals, Vitaeris, Sanofi, and Merck; has received consultancy fees from and is a data safety monitoring board member for Novartis; has received travel support from Research In Real Life; has received consultancy fees and travel support from Teva Specialty Pharmaceuticals; and has received research support from Genentech, Boehringer Ingelheim, GlaxoSmithKline, Merck, Sunovion, Teva, and Sanofi.

Received for publication September 19, 2017; revised October 2, 2017; accepted for publication October 10, 2017.

Available online November 14, 2017.

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2213-2198

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<https://doi.org/10.1016/j.jaip.2017.10.025>

Israel (anti-IgE)

The important points here are as follows. This patient, with uncontrolled asthma despite high-dose ICS/LABA (long-acting beta-agonists), meets all the criteria for anti-IgE therapy. Further, he has a high likelihood of responding to anti-IgE therapy. Lastly, his biomarker levels suggest that he does not have a high likelihood of responding to anti-IL5 therapy. Let us review these points. First, in whom has anti-IgE therapy been shown to be effective? Most of the studies that demonstrated efficacy for anti-IgE therapy examined patients on moderate- to high-dose ICS or on combination therapy who had at least one exacerbation a year.⁴ In addition, these patients had to have an IgE $\geq$ 30 IU/mL and a skin prick test or RAST positive for a perennial allergen. In those patients, the exacerbation rate was cut by 25%, asthma symptoms and control improved, and there was a very small improvement in airway function. Omalizumab had little effect on subjects on oral corticosteroids. So, this patient qualifies for anti-IgE.⁵ Now let us look at his chances of responding. We know from a recent retrospective analysis of the studies conducted in patients on high-dose ICS plus a LABA who qualified for anti-IgE that several biomarkers identified those most likely to respond. The best of these markers was FeNO.⁶ Those with an FeNO $\geq$ 19.5 ppb (while on high-dose ICS/LABA) had a 53% reduction in exacerbations compared with a 16% reduction in those whose FeNO was less than 19.5 ppb.⁶ These patients also had a significant reduction in albuterol use and improvements in their asthma quality-of-life score. Interestingly, patients with a blood eosinophil count $\geq$ 260 cells/ μ L also preferentially responded to anti-IgE with a 32% reduction in exacerbations compared with a 9% reduction in those with blood eosinophil counts that were lower.⁶ However, there was no consistent response in the secondary outcomes in this eosinophilic group. Lastly, will this patient have a high likelihood of responding to anti-IL5? As we will discuss later, a blood eosinophil count of 100 cells/ μ L bodes ill for the likelihood of response. A blood eosinophil count of at least 300, but probably higher, might make this choice a harder one. In this case, anti-IgE is the way to go.

Panettieri (anti-IL5)

This patient manifests uncontrolled asthma given his frequent exacerbations despite maximal inhaled therapies. Presumably, the patient is well informed on the inhaler technique and is adherent to prescribed medication. His workup is remarkable for atopy with sensitivity to perennial allergens and modest increases in blood eosinophilia and in FeNO. Collectively, studies suggest that such a patient would be less likely to respond to an anti-IL5 agent as compared with an anti-IgE agent.⁷⁻⁹ In this instance, an important patient attribute in choosing among the monoclonal antibodies in moderate to severe asthma concerns the relatively low blood eosinophil count. In pivotal trials with anti-IL5 agents,

Abbreviations used

FeNO- Fractional exhaled nitric oxide level

ICS- Inhaled corticosteroids

RAST- Radioallergosorbent test

the greater the blood eosinophil counts (>300 cells/ μ L) the greater clinical response to these agents.⁷

CASE 2

A 55-year-old obese woman was diagnosed 5 years ago with asthma that was associated with sinusitis. The patient was managed with high-dose ICS and long-acting bronchodilators. Despite this therapeutic approach, she annually experienced 3 exacerbations requiring oral prednisone courses. Her diagnostic workup included IgE 10 IU/mL, blood eosinophil count 550 cells/ μ L, negative RAST and skin prick testing to inhalant allergens, and an FeNO that was 45 ppb. What monoclonal antibody therapy would you choose?

Panettieri (anti-IL5)

The salient points in this case include uncontrolled asthma in a patient who developed asthma in mid-life and who likely experiences chronic rhinosinusitis. Further, she is nonatopic but manifests significant eosinophilia and airway inflammation as determined by FeNO that is refractory to high-dose inhaled corticosteroids. Although a few studies suggest that anti-IgE therapy may offer therapeutic value in nonallergic patients with eosinophilia,^{6,10} this patient would be an ideal candidate for an anti-IL5 monoclonal antibody. Compelling evidence suggests that patients with difficult to manage eosinophilic asthma have improved symptoms, lower exacerbation rates, better pulmonary function, and require less oral corticosteroids when managed with anti-IL5 therapy. In fact, as blood eosinophil levels increase, the probability of therapeutic response to anti-IL5 antibodies also increases.^{6-9,11,12} Assessment of response should be determined routinely; however, the duration of treatment required to show improvement in exacerbation rates may require 6 months or longer.⁷

Israel (anti-IgE)

This patient has significant eosinophilia and does not really qualify for anti-IgE because her serum IgE is below 30 IU/mL. T2 inflammation can be suggested by ≥ 300 eosinophils/ μ L and/or FeNO ≥ 19 ppb. She seems to belong to the group of patients with late onset disease and less atopy. Her high eosinophils (≥ 300 cells/ μ L) and her frequent exacerbations suggest that she has a high likelihood of responding to an anti-eosinophilic drug, especially with a reduction in exacerbations. In view of her sinusitis, it would be reasonable to evaluate her for aspirin exacerbated respiratory disease characterized by late onset disease, sinusitis/nasal polyps, eosinophilia, and sensitivity to inhibitors of cyclooxygenase-1 such as aspirin and nonsteroidal anti-inflammatory drugs. This disease is characterized by leukotriene overproduction and may benefit from treatment with leukotriene modifiers, or possibly aspirin desensitization.

CASE 3

A 23-year-old man was diagnosed with asthma 18 years ago. The patient was managed with high-dose ICS and long-acting bronchodilators. Despite this therapeutic approach, he annually

experienced 3 to 5 exacerbations requiring oral prednisone courses. His diagnostic workup included IgE 250 IU/mL; blood eosinophil count 400 cells/ μ L; markedly positive RAST and skin prick testing to grass pollen, house dust mite, cat, dog, and several molds; and an FeNO of 45 ppb. What monoclonal antibody therapy would you choose?

Israel (anti-IgE)

The major points here are uncontrolled asthma since childhood with a strong history of allergic disease, a qualifying IgE, high eosinophils, and a high FeNO. This patient has a high likelihood of responding to both anti-IgE therapy and anti-eosinophil therapy. The high FeNO, on high-dose ICS therapy, suggests that the patient has a high likelihood of experiencing a 50% or greater reduction in exacerbations if treated with anti-IgE because his FeNO is greater than 20 ppb.⁶ If this patient gave a history of seasonal exacerbations or exacerbations with specific allergic triggers, I would especially be inclined to treat with anti-IgE. Further, some data suggest that you might only need to treat "in season" to prevent seasonal exacerbations,¹³ which may mean less necessity for continuous exposure to a biologic.

Panettieri (anti-IL5)

The salient points in this case include uncontrolled asthma in a patient who developed asthma in early childhood and who likely has allergic asthma, eosinophilia, and airway inflammation. The characteristics of this patient's asthma suggest that he would be a candidate for either anti-IgE or anti-IL5 therapy.⁷ Although either monoclonal antibody may be an appropriate treatment, I favor initially anti-IL5 treatment. Given that eosinophilia can be easily followed longitudinally, anti-IL5 therapy will markedly diminish blood eosinophils and this outcome can at least serve as a target engagement biomarker. The pharmacological indicator suggests therapeutic target engagement but not necessarily improved clinical outcomes. Such biomarkers are not available for anti-IgE therapy. If engagement of IL5 with a monoclonal antibody markedly decreases blood eosinophils but has little effect on clinical outcomes, then these results provide evidence that the patient's asthma is unlikely eosinophil dependent. Such an outcome also provides a rationale for switching to an anti-IgE antibody to manage allergic asthma. Other evidence shows that therapies that decrease blood eosinophils swiftly improve pulmonary function often within 1 month, which is not typically observed with anti-IgE antibodies.^{7,8,11,12} The benefit in improving pulmonary function quickly may provide patients with improved symptom control and foster better adherence. Whether such benefits only exist for anti-IL5 therapy as compared with those of anti-IgE remains to be proven and will require comparative efficacy trials.

CASE 4

We present an 8-year-old boy with asthma on high-dose ICS/LABA. He was a full-term baby. He has had 3 exacerbations in the past year. Two of these exacerbations were in the Fall. His serum IgE is 200 IU/mL and his blood eosinophil count is 350 cells/ μ L; he has a positive RAST to pollens, house dust mite, and *Alternaria*. His FeNO was not measured.

Israel (anti-IgE)

Let us talk about what makes this case easy in terms of a choice between anti-IgE and anti-IL5. Currently, anti-IL5 therapy is not

licensed below age 12, whereas in the USA, anti-IgE is approved down to 6 years of age. However, separate from the logistics, should you treat this boy with anti-IgE therapy? There are several aspects to this case that suggest that you should. First, as mentioned in the list in the answer to question number 1, he qualifies. But that is not a reason to treat him. More importantly, there are studies that show that treating such patients will reduce their rate of exacerbations. The Inner-City Anti-IgE Therapy for Asthma (ICATA) study showed that treating young patients who met the anti-IgE criteria and had recurrent exacerbations reduced asthma exacerbations, particularly in the Spring and the Fall.¹⁴ Most interestingly, a follow-up study examined whether treatment just before the Fall and discontinued in the winter reduced exacerbations.¹³ Thus, this patient might be eligible for a shortened yearly course of therapy. Lastly, there is another good reason to consider anti-IgE in this patient. He is a young child on high-dose ICS, and the data do suggest that there is a small effect on the growth of high-dose ICS.¹⁵

Panettieri (anti-IL5)

This child clearly manifests severe, uncontrolled disease given his frequent exacerbations. Further the patient is atopic but also has significant blood eosinophils. Arguably, if anti-IL5 and anti-IgE agents were available, then the provider would have a choice. To date, only anti-IgE therapy is approved in children of this age. An important observation was his frequent Fall exacerbations that could be related to seasonal sensitivities to allergens and/or viral-induced asthma flares. The ICATA study suggests that modulating IgE-dependent responses improves exacerbations potentially to allergen- and to viral-mediated triggers.¹² Whether anti-IL5 therapy will offer similar benefits remains unclear. The interplay of the adaptive and innate immune system affects asthma exacerbations and conveys an important clinical message that may provide insight into the identification of novel therapeutic targets to treat difficult-to-control asthma.

SUMMARY

The advent of biologics targeting type 2 “allergic” inflammation provides new avenues of treatment for patients who fail step V asthma therapy. Our “debate” provides points to consider based on currently available data with emphasis on allergic history and testing, level of eosinophils, number of exacerbations, and level of exhaled nitric oxide as useful markers in guiding decisions. Regardless of the clinician’s choice, it probably makes

sense to try the initial therapy for 3 to 6 months before switching to an alternative (if the patient qualifies for both). Well-done randomized head-to-head studies will be helpful in clarifying these decisions. It is important to remember that up to half of patients with severe asthma may not have evidence of high grade type 2 disease as defined by eosinophils or FeNO on step V therapy and those patients are not very likely to respond to either of these therapies.

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