**Transcript Details**
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/medical-industry-feature/thinking-allergic-asthma-first/14917/

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Thinking Allergic Asthma First

**Announcer:**

Welcome to ReachMD.

This medical industry feature, titled “Thinking Allergic Asthma First,” is sponsored by Genentech and Novartis. This program is intended for healthcare professionals. Guests have been compensated for their participation.

Here’s your host, Dr Jennifer Caudle.

**Dr Caudle:**

Approximately 60% of asthma is allergic—and its prevalence has increased every year between 1996 and 2016. This is ReachMD, and I’m your host, Dr Jennifer Caudle.

Joining me to discuss allergic asthma in patients and strategies for identifying it are my guests, Wanda Phipatanakul, MD, MS, and William Calhoun, MD. Dr Phipatanakul is an allergist who is the S. Jean Emans Professor of Pediatrics at Harvard Medical School, as well as the Director of the Asthma, Allergy, Immunology, Dermatology, and Rheumatology Research Center at Boston Children's Hospital. Dr Phipatanakul, thank you so much for being here today.

**Dr Phipatanakul:**

It’s a pleasure to be here!

**Dr Caudle:**

And Dr Calhoun is an allergist and pulmonologist who is the Professor and Vice Chair for Research in the Department of Medicine at University of Texas Medical Branch. He's also the Nelda C HJ Lutcher Stark Distinguished Chair in Internal Medicine. Dr Calhoun, it’s great to have you with us.

**Dr Calhoun:**

Thank you very much for having me!

**Dr Caudle:**

And before we begin, let’s take a moment to review some Important Safety Information for XOLAIR® (omalizumab).

**Announcer:**

**INDICATION**

XOLAIR® (omalizumab) is indicated for adults and pediatric patients 6 years of age and older with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.

Limitations of Use: XOLAIR is not indicated for the relief of acute bronchospasm or status asthmaticus.

**IMPORTANT SAFETY INFORMATION**

**WARNING: Anaphylaxis**

**Anaphylaxis presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of XOLAIR. Anaphylaxis has occurred as early as after the first dose of XOLAIR, but also has occurred beyond 1 year after beginning regularly administered treatment. Because of the risk of anaphylaxis, initiate XOLAIR therapy in a healthcare setting and closely observe patients for an appropriate period of time after XOLAIR administration. Health care providers administering XOLAIR should be prepared to manage anaphylaxis which can be life-threatening. Inform patients of the signs and symptoms of anaphylaxis and instruct them to seek immediate medical care should symptoms occur. Selection of patients for self-administration of XOLAIR should be based on criteria to mitigate risk from anaphylaxis.**

Additional important safety information to follow.

**Dr Caudle:**

Now, let's dive right in starting with you, Dr Calhoun. What do you look for when you think allergic asthma may be affecting your patients? And how do you differentiate that from other types of asthma?

**Dr Calhoun:**

It's very important to personalize treatment, and in my own practice I strive to customize plans based on what's driving disease in my patients. I've seen some pulmonologists who prefer to focus exclusively on lab values.

But I do think that we should be considering our patients holistically—and that includes thinking about their home situation and what could be driving their exacerbations. There is no one-size-fits-all approach.

**Dr Caudle:**

So, Dr Phipatanakul, can you describe any particular examples of the drivers you see triggering an allergic response in your patients, even in small amounts?

**Dr Phipatanakul:**

Well, for instance, the antibody immunoglobulin E, or IgE, is a key driver of inflammation in allergic asthma. But IgE levels alone may not paint the entire picture of the allergic asthma patient—allergic asthma may be diagnosed in patients whose IgE levels are not considered very high.

Even in small amounts, IgE can trigger an allergic response. In cases like this, for patients with moderate to severe persistent asthma, I consider choosing a treatment such as XOLAIR®, which is designed to target IgE and inhibit IgE-mediated inflammation in allergic asthma. It's actually the first biologic treatment that is designed to do so.

**Dr Caudle:**

Now let's zero in on IgE for a moment, Dr Calhoun. What else should we know about IgE in relation to allergic asthma?

**Dr Calhoun:**

What I've learned is that IgE affects eosinophils and other Type 2 inflammatory mediators, like Interleukin-4, Interleukin-5, and Interleukin-13. Sometimes I see patients with allergic asthma whose symptoms are not controlled, even when they're taking an inhaled corticosteroid.

If I've confirmed this information—and I know that the results of my IgE tests show that perennial allergens are a trigger—then I know that these patients have different treatment needs than my nonallergic asthma patients. And that's when I start to consider a treatment like XOLAIR as a potential option.

**Dr Caudle:**

For those of you who are just joining us, you're listening to ReachMD. I'm your host, Dr Jennifer Caudle, and today I'm speaking with Dr Wanda Phipatanakul and Dr William Calhoun about patients who present with allergic asthma.

So coming back to you, Dr Phipatanakul. Now that we've briefly talked about considerations for treating our patients with XOLAIR, let's dive a bit deeper into this therapy. How may XOLAIR help treat allergic asthma?

**Dr Phipatanakul:**

Well, when XOLAIR was approved in 2003, it was the first approved biologic for moderate to severe allergic asthma uncontrolled on inhaled corticosteroids in patients 12 years and older, and also the first biologic approved to treat patients aged 6 years and older. Going

back to that IgE conversation briefly, XOLAIR is the first FDA-approved biologic designed to target and block IgE.

Decreases in exacerbations with XOLAIR were seen in two studies of 1071 patients aged 12 and older with moderate to severe asthma who were evaluated for 28 weeks. At 16 weeks during the inhaled corticosteroid-stable phase, Study 1 showed a 33 percent decrease in exacerbations versus control, while Study 2 showed up to a 75% decrease in exacerbations versus control.

And in the inhaled corticosteroid-reduction phase at 28 weeks, Study 1 showed up to a 50 percent decrease in exacerbations versus control, while Study 2 saw a 33 percent decrease in exacerbations versus control. In the inhaled corticosteroid-stable phase of Studies 1 and 2, 85.8 percent and 87.6 percent of patients experienced zero exacerbations, respectively, compared to 76.7 percent and 69.9 percent of patients in the control group.

In the inhaled corticosteroid-reduction phase, Studies 1 and 2 saw 78.7 percent and 83.9 percent of patients experienced zero exacerbations, respectively, compared to 67.7 percent and 70.2 percent of patients in the control group.

And a third trial evaluated 341 patients aged 12 and older with severe allergic asthma for 32 weeks. This number of exacerbations in the XOLAIR group was similar to that in the control group.

The absence of an observed treatment effect may be related to differences in patient population compared with Studies 1 and 2, study sample size, or other factors. Reduction in exacerbations was not observed in XOLAIR-treated patients who had FEV1 >80% predicted at time of randomization or in patients who required oral corticosteroids as maintenance therapy.

**Dr Caudle:**

And, Dr Calhoun, can you explain the safety and efficacy of XOLAIR?

**Dr Calhoun:**

Yes. The safety and efficacy of XOLAIR have been studied in patients aged 12 and older, as well as in a diverse range of pediatric patients aged six to less than 12 years. And it's important to note that XOLAIR has a boxed warning for anaphylaxis. Additional important safety information will follow.

In clinical studies, up to eight percent of adult and adolescent patients who took XOLAIR experienced adverse reactions like arthralgia and general pain. For pediatric patients aged six to less than 12 years, nasopharyngitis (23.6% vs 23.2% in control) and headache (20.7% vs 19.5% in control) were among the most common adverse reactions.

**Dr Caudle:**

Thank you for that, Dr Calhoun. And before we end our discussion today, Dr Phipatanakul, is there anything else you would like to share with our audience?

**Dr Phipatanakul:**

We've been discussing the role of IgE when it comes to treating allergic asthma a bit today. And I'd just like to say one more thing on that topic related to the pharmacodynamics of XOLAIR. As we mentioned, IgE levels are a key driver of inflammation in allergic asthma.

In clinical studies for XOLAIR, serum free IgE levels were reduced in a dose-dependent manner within one hour following the first dose and maintained between doses. When XOLAIR was used at recommended doses, serum free IgE levels decreased by an average of over 96 percent. Although we should keep in mind, this is pharmacodynamic data.

**Dr Caudle:**

Excellent, those are great takeaways as we come to the end of today's program. And I'd like to thank my guests, Dr Phipatanakul and Dr Calhoun, for helping us better understand how to identify and treat patients with moderate to severe allergic asthma.

Dr Phipatanakul and Dr Calhoun, thank you so much both for being here today. It was great speaking with you.

**Dr Calhoun:**

Thank you for having me!

**Dr Phipatanakul:**

Thank you for this opportunity!

**Dr Caudle:**

And before we close, let's take a moment to review some Important Safety Information related to XOLAIR.

**Announcer:**

**Important Safety Information (cont'd)**

**CONTRAINDICATIONS**

XOLAIR is contraindicated in patients with a severe hypersensitivity reaction to XOLAIR or to any ingredient of XOLAIR.

**WARNINGS AND PRECAUTIONS**

**Anaphylaxis:** Anaphylaxis has been reported to occur after administration of XOLAIR in premarketing clinical trials and in postmarketing spontaneous reports. In premarketing clinical trials in patients with asthma, anaphylaxis was reported in 3 of 3507 (0.1%) patients. Anaphylaxis occurred with the first dose of XOLAIR in two patients and with the fourth dose in one patient. The time to onset of anaphylaxis was 90 minutes after administration in two patients and 2 hours after administration in one patient.

A case-control study in asthma patients showed that, among XOLAIR users, patients with a history of anaphylaxis to foods, medications, or other causes were at increased risk of anaphylaxis associated with XOLAIR, compared to those with no prior history of anaphylaxis.

In postmarketing spontaneous reports, the frequency of anaphylaxis attributed to XOLAIR use was estimated to be at least 0.2% of patients based on an estimated exposure of about 57,300 patients from June 2003 through December 2006. Approximately 60% to 70% of anaphylaxis cases have been reported to occur within the first three doses of XOLAIR, with additional cases occurring sporadically beyond the third dose.

Initiate XOLAIR only in a healthcare setting equipped to manage anaphylaxis which can be life-threatening. Observe patients closely for an appropriate period of time after administration of XOLAIR, taking into account the time to onset of anaphylaxis seen in premarketing clinical trials and postmarketing spontaneous reports. Inform patients of the signs and symptoms of anaphylaxis, and instruct them to seek immediate medical care should signs or symptoms occur.

Once XOLAIR therapy has been established, administration of XOLAIR prefilled syringe or autoinjector outside of a healthcare setting by a patient or a caregiver may be appropriate for selected patients. Patient selection, determined by the healthcare provider in consultation with the patient, should take into account the pattern of anaphylaxis events seen in premarketing clinical trials and postmarketing spontaneous reports, as well as individual patient risk factors (e.g. prior history of anaphylaxis), ability to recognize signs and symptoms of anaphylaxis, and ability to perform subcutaneous injections with XOLAIR prefilled syringe or autoinjector with proper technique according to the prescribed dosing regimen and Instructions for Use.

Discontinue XOLAIR in patients who experience a severe hypersensitivity reaction.

**Malignancy**: Malignant neoplasms were observed in 20 of 4127 (0.5%) XOLAIR-treated patients compared with 5 of 2236 (0.2%) control patients in clinical studies of adults and adolescents (≥12 years of age) with asthma and other allergic disorders. The observed malignancies in XOLAIR-treated patients were a variety of types, with breast, non-melanoma skin, prostate, melanoma, and parotid occurring more than once, and five other types occurring once each. The majority of patients were observed for less than 1 year. The impact of longer exposure to XOLAIR or use in patients at higher risk for malignancy (e.g., elderly, current smokers) is not known.

A subsequent 5-year observational study of 5007 XOLAIR-treated and 2829 non-XOLAIR-treated adolescent and adult patients with moderate to severe persistent asthma and a positive skin test reaction or in vitro reactivity to a perennial aeroallergen found that the incidence rates of primary malignancies (per 1000 patient years) were similar in both groups (12.3 vs 13.0, respectively). Study limitations which include the observational study design, the bias introduced by allowing enrollment of patients previously exposed to XOLAIR (88%), enrollment of patients (56%) while a history of cancer or a premalignant condition were study exclusion criteria, and the high study discontinuation rate (44%) preclude definitively ruling out a malignancy risk with XOLAIR.

**Acute Asthma Symptoms and Deteriorating Disease:** XOLAIR has not been shown to alleviate asthma exacerbations acutely. Do not use XOLAIR to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with XOLAIR.

**Corticosteroid Reduction:** Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of XOLAIR therapy for asthma. Decrease corticosteroids gradually under the direct supervision of a physician.

**Eosinophilic Conditions:** In rare cases, patients with asthma on therapy with XOLAIR may present with serious systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome. These events usually, but not always,

have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between XOLAIR and these underlying conditions has not been established.

**Fever, Arthralgia, and Rash:** In post-approval use, some patients have experienced a constellation of signs and symptoms, including arthritis/arthralgia, rash, fever, and lymphadenopathy with an onset 1 to 5 days after the first or subsequent injections of XOLAIR. These signs and symptoms have recurred after additional doses in some patients. Physicians should stop XOLAIR if a patient develops this constellation of signs and symptoms.

**Parasitic (Helminth) Infection:** Monitor patients at high risk of geohelminth infection while on XOLAIR therapy. Insufficient data are available to determine the length of monitoring required for geohelminth infections after stopping XOLAIR treatment.

**Laboratory Tests:** Due to formation of XOLAIR:IgE complexes, serum total IgE levels increase following administration of XOLAIR and may remain elevated for up to 1 year following discontinuation of XOLAIR. Do not use serum total IgE levels obtained less than 1 year following discontinuation to reassess the dosing regimen for asthma patients, because these levels may not reflect steady state free IgE levels.

**Potential Medication Error Related to Emergency Treatment of Anaphylaxis**
XOLAIR should not be used for the emergency treatment of allergic reactions, including anaphylaxis. In studies to simulate use, some patients and caregivers did not understand that XOLAIR is not intended for the emergency treatment of allergic reactions, including anaphylaxis. The safety and effectiveness of XOLAIR for emergency treatment of allergic reactions, including anaphylaxis, have not been established. Instruct patients that XOLAIR is for maintenance use to reduce allergic reactions, including anaphylaxis, while avoiding food allergens.

## ADVERSE REACTIONS

**Asthma:** In patients ≥12 years of age, the most common adverse reactions (≥1% more frequent in XOLAIR-treated patients) were: arthralgia (8%), pain (general) (7%), leg pain (4%), fatigue (3%), dizziness (3%), fracture (2%), arm pain (2%), pruritus (2%), dermatitis (2%), and earache (2%). In pediatric patients 6 to <12 years of age, the most commonly observed adverse reactions (≥3% more frequent in XOLAIR-treated pediatric patients) were: nasopharyngitis, headache, pyrexia, upper abdominal pain, pharyngitis streptococcal, otitis media, viral gastroenteritis, arthropod bite, and epistaxis.

**Injection Site Reactions:** In adults and adolescents with asthma, injection site reactions of any severity occurred at a rate of 45% in XOLAIR-treated patients compared with 43% in placebo-treated patients. Severe injection site reactions occurred more frequently in XOLAIR-treated patients compared with patients in the placebo group (12% vs 9%, respectively). The types of injection site reactions in asthma studies included: bruising, redness, warmth, burning, stinging, itching, hive formation, pain, indurations, mass, and inflammation.

**Injection Site Reactions in Healthy Adults:** In an open label trial in healthy adults, in which the 300 mg/2 mL autoinjector was compared to the 300 mg/2 mL prefilled syringe, injection site reactions (e.g., induration, pain, erythema, hemorrhage, swelling, discomfort, bruising, hypoesthesia, edema, pruritus) were observed in 24% (16/66) of subjects treated with the autoinjector compared with 14% (9/64) of subjects treated with the prefilled syringe.

**Cardiovascular and Cerebrovascular Events from Clinical Studies in Patients with Asthma:** A 5-year observational study was conducted in 5007 XOLAIR-treated and 2829 non-XOLAIR-treated patients ≥12 years of age with moderate to severe persistent asthma and a positive skin test reaction to a perennial aeroallergen to evaluate the long term safety of XOLAIR, including the risk of malignancy. Similar percentages of patients in both cohorts were current (5%) or former smokers (29%). Patients had a mean age of 45 years and were followed for a mean of 3.7 years. More XOLAIR-treated patients were diagnosed with severe asthma (50%) compared to the non-XOLAIR-treated patients (23%). A higher incidence rate (per 1000 patient-years) of overall cardiovascular and cerebrovascular serious adverse events (SAEs) was observed in XOLAIR-treated patients (13.4) compared to non-XOLAIR-treated patients (8.1). Increases in rates were observed for transient ischemic attack (0.7 vs 0.1), myocardial infarction (2.1 vs 0.8), pulmonary hypertension (0.5 vs 0), pulmonary embolism/venous thrombosis (3.2 vs 1.5), and unstable angina (2.2 vs 1.4), while the rates observed for ischemic stroke and cardiovascular death were similar among both study cohorts. The results suggest a potential increased risk of serious cardiovascular and cerebrovascular events in patients treated with XOLAIR, however the observational study design, the inclusion of patients previously exposed to XOLAIR (88% for a mean of 8 months), baseline imbalances in cardiovascular risk factors between the treatment groups, an inability to adjust for unmeasured risk factors, and the high study discontinuation rate (44%) limit the ability to quantify the magnitude of the risk.

**Pregnancy:** Data with XOLAIR use in pregnant women are insufficient to inform on drug associated risk.

Please see full Prescribing Information, including Boxed WARNING and Medication Guide, for additional Important Safety Information.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555 or Novartis Pharmaceuticals Corporation at (888) 669-6682.

This program was sponsored by Genentech and Novartis. If you missed any part of this discussion, visit ReachMD dot com slash industry feature. This is ReachMD. Be Part of the Knowledge.