Xolair Advisory Committee Meeting Comments
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Mister Chairman, Members of the Committee, my name is Dr. Stuart Stoloff. I am a Clinical Professor in the Department of Family and Community Medicine of the University of Nevada School of Medicine. In addition, I am a Member of both the Expert Panel II of the NHLBI "Guidelines for the Diagnosis and Management of Asthma" and the NIH, NHLBI Science Based Committee for Monitoring World Asthma Research Literature. I very much appreciate the opportunity to share my perspectives on issues of importance to your consideration of the approvability of Xolair for the treatment of moderate to severe asthma.

From the outset, I want to make it clear that I am not here to advocate a specific position on whether this particular agent should be approved or not, but to highlight the significant need for an accurate diagnosis before such drugs are administered. Furthermore, I would like to note that any drug that can reduce the symptoms of moderate to severe asthma and improve patient functioning and well-being are greatly welcomed.

For the record, I would like to state that I have no conflicts with respect to the approvability of Xolair. I neither own stock in Genentech or its competitors, nor do I consult for them. My appearance today, however, has been supported by Pharmacia Diagnostics, which markets a highly specific FDA approved *in vitro* diagnostic test that

allows physicians to accurately assess a patient's sensitivity to a specific allergen to tailor therapy appropriately.

As is clear to this Committee, asthma is a disease of staggering proportions, affecting over 26 million Americans and having significant individual and societal impact, and alarmingly, the prevalence of this disease is increasing. Unfortunately, as identified in numerous studies, asthma morbidity and severity disproportionately affects socially disadvantaged populations, including African Americans and residents of low-income inner-city neighborhoods. This reality highlights the importance of cost effective strategies for reducing the burden of this disease, and the need for identifying those who could benefit from costly therapeutic intervention before their initiation.

Asthma is a multi-factorial disease with numerous triggers. The association of asthma and allergy has long been recognized. Inhaled allergens, such as pet dander, dust mites, cockroach allergens, molds and pollens, to which a patient is sensitive, are known to increase asthma symptoms and severity and to precipitate asthma exacerbations. Demonstrating a patient's relevant sensitivity to inhalant allergens will guide the clinician in implementing therapeutic interventions, including the recommendation of specific environmental controls to reduce exposures.

In July of 1997, the National Institutes of Health National Heart, Lung, and Blood Institute (NHLBI) published Guidelines for the Diagnosis and Management of Asthma. I

had the honor of serving on the expert panel that promulgated these guidelines, as well as the panel that updated these guidelines last year. Importantly, the clinical practice guidelines specifically note that for at least those patients with persistent asthma on daily medications, the clinician should:

1. Identify allergen exposures
2. Use the patient's history to assess sensitivity to seasonal allergens
3. Use skin testing or *in vitro* testing to assess sensitivity to perennial indoor allergens
4. Assess the significance of positive tests in the context of patient's medical history

The Guidelines also specify the importance of an accurate diagnosis, as many conditions present with similar symptoms. For instance non-allergic symptoms that present as allergy, such as rhinitis, sinusitis and gastrointestinal reflux should be ruled out and managed appropriately.

Unfortunately, today, almost 7 years since the guidelines were published, their implementation remains woefully inadequate. This lack of adherence to the Guidelines relates to the under diagnosis of the severity of the condition, and hence the perceived need for testing, the difficulty in obtaining a referral to a specialist and the perception that allergy testing is difficult to do. It is also likely that patients seeking a "quick fix" are enamored by the promise of new pharmacotherapeutic approaches, and as such are not

even aware that avoidance of the agent they are sensitive to may be the best therapeutic approach.

Primary Care Physicians manage over 65 percent of allergy and asthma in the US and often do so with minimal objective evidence of underlying etiology. Only a very small, single-digit percentage, of allergy patients seen by such physicians are actually tested for allergen-specific IgE antibodies, resulting in many being misdiagnosed and therefore mistreated. A proper work-up, including allergy testing, will not only enhance diagnostic certainty, and determine appropriate management, but will have significant cost saving advantages as well. This is particularly relevant for a drug that is expected to cost patients and providers over $10,000 per year.

It is my belief that it is imperative for all patients to have an appropriate work-up, including allergy testing before consideration of initiation of Xolair, or other drugs for managing patients with moderate to severe asthma because there may be factors that can be treated that could diminish the need for such treatment. Conversely, such an evaluation could identify patients who could best benefit from treatment.

Both allergy skin testing and allergy blood tests are equally reliable in determining sensitivity and one or the other of these approaches should therefore be routinely employed when evaluating patients with persistent asthma. The choice as to which diagnostic test to use should be based on the clinical setting and abilities of the treating

physician. In the primary care setting, the necessity for training on both the procedure and interpretation of the result will in most cases preclude primary care physicians from performing skin testing. *In vitro* testing does not require knowledge of the "art" of skin testing, does not require availability of allergen extracts, can be performed on patients who are taking allergy medications or who have eczema, and is not associated with systemic reactions or increased risks.

There is increasing evidence that there is a significant under classification of asthma disease severity by treating physicians, which may in part, underlie why testing is not occurring to the extent it should. A study published this year by Wolfenden, et al in the January 2003 issue of the Archives of Internal Medicine demonstrates the significance of physician under estimates of underlying disease severity on treatment outcomes. It found that regardless of the physician group, patients' perception of disease severity was greater than that of the physician, resulting in asthma care that was inconsistent with national guidelines and associated with poor patient outcomes, including underutilization of effective measures and more frequent ER visits and hospitalizations.

Halterman and colleagues published findings of an underestimation of asthma severity among urban children with asthma. This study published in February, 2002, in the Archives of Pediatric and Adolescent Medicine, found that only one-third of children in the sample received the recommended daily therapy for their level of asthma severity.

Many have postulated that difficulties experienced by both patients and physicians in recognizing asthma severity and subsequent under treatment may be a reason for the high level of asthma burden in this country. This is best exemplified by the finding of Fuhlbrigge, et al in a recent publication in the American Journal of Respiratory and Critical Care Medicine (Oct. 2002) that found that when patients are appropriately classified, over 70% of patients have moderate to severe persistent asthma. The fact that many of these patients were considered by their physician to have mild intermittent asthma resulted in the failure of appropriate treatment modalities to be instituted.

I am concerned, that as new therapeutic approaches, such as Xolair, are approved that patients and physicians will view them as a panacea. This will result in many more patients being treated with pharmacologic approaches without an adequate diagnostic work up. This will not only potentially expose them to unneeded therapies, but also prevent them from having the necessary knowledge to practice avoidance. I think this is particularly important for an agent with an anti IgE mechanism, as many will think that it adequately addresses symptoms of an allergic nature. Such an outcome, I fear would further enhance the underdiagnosis and mistreatment that is rampant in asthma care.

I would encourage the Committee to consider that the labeling for Xolair stipulate that diagnostic evidence of an allergic (IgE) etiology be established if this therapy is to be appropriately initiated. The routine utilization of diagnostic testing in evaluating patients

with persistent asthma would identify the appropriateness of treatment for the patient and diminish symptoms.

Improving the diagnosis and classification of asthma severity will improve patient outcomes and have a positive effect on overall public health. Enhancing the ability of the primary care physician to effectively assess whether an allergic etiology underlies a patient's asthma symptoms should help to ensure the rational selection of therapeutic modalities and result in improvement in quality of life for both the patient and their family.

I appreciate that opportunity to offer these comments and would be happy to answer any questions you might have.

References:

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