The Clinical Relevance of IL-4/IL-13 Inhibition in Atopic Diseases

A Q&A With Aiden A. Long, MD

AIDEN A. LONG, MD

Associate Professor of Medicine, Harvard Medical School

Clinical Director, Allergy and Clinical Immunology

Chairperson, Clinical Council, Department of Medicine

Massachusetts General Hospital

Boston, MA

***AJMC®*: Can you talk about type 2 inflammation and its broader role in atopic diseases?**

LONG: Type 2 inflammation is very important in allergic diseases. In fact, we used to consider it almost synonymous with allergic inflammation. We also used to call it Th2 inflammation, because we thought that it was created by a certain subset of T-helper cells called Th2. We now realize that while those Th2 cells are important, other sources of type 2 inflammation exist, such as innate lymphoid cells. Histologically, type 2 inflammation is characterized by infiltration of tissues by certain cell types and is not accurately distinguishable from other types of inflammation based on this. More importantly, type 2 inflammation is characterized by the types of cytokines that are involved, such as interleukin (IL)-4, IL-5, IL-9, and IL-13. Inflammation associated with release of those cytokines is called type 2 inflammation. This profile is seen in the inflammation observed in nasal tissues of allergic rhinitis, in nasal polyp tissues, in chronic sinus disease, in allergic asthma, and in acute allergic dermatitis. In chronic atopic dermatitis, the pattern changes a bit, but we are confident that the pathogenesis of atopic dermatitis involves a significant amount of type 2 inflammation. On the flip side, some people with chronic sinus disease with chronic severe asthma don't have type 2 inflammation. Type 2 inflammation is not the only mechanism of those disease types, although it is the dominant one.

***AJMC®*: Can you discuss barrier dysfunction and its role in the type 2 inflammatory process?**

LONG: Barrier dysfunction is fundamentally important in diseases characterized by type 2 inflammation. [Patients with atopic dermatitis] often have a defect in skin barrier function; this results in increased water loss from the skin and possibly also allows easier passage through the skin of allergens or irritants. In some cases, it seems that this primary defect predisposes patients to atopic dermatitis. On the other hand, there is also evidence that type 2 inflammation provokes or actually exacerbates barrier dysfunction. Well-described examples of these are filaggrin gene mutations, which seem to cause a fundamental skin barrier defect in a portion of patients with atopic dermatitis, who then get type 2 inflammation. In turn, cytokines of type 2 inflammation can make the barrier dysfunction worse. In the other type 2 inflammatory diseases, such as asthma, we know there is barrier dysfunction in the airway epithelium. Histochemical studies of airway epithelial biopsies, staining for junctional proteins that bind cells together to form the actual barrier, have shown widespread differences from the normal patterns seen in nonasthmatic airways. The disrupted or dysfunctional barrier that results is felt to play a role in the pathogenesis of airway inflammation in asthma. Interestingly, to what extent the barrier disruption is a primary defect leading to type 2 inflammation or a secondary defect of type 2 inflammation, we don't know.

Other abnormalities within the airway epithelial barrier may be contributory to disease. For example, the epithelial barrier in the bronchial airways has a population of dendritic cells that, in a healthy individual, will have a very brisk response to viruses that get into the airway. The dendritic cells typically make interferons to fight those viruses. However, it seems that in the asthmatic airway, where type 2 inflammation exists, that ability of airway resident dendritic cells to mount antiviral responses is very much reduced. Again, we think that this phenomenon might be secondary to type 2 inflammation rather than primary. Failure to fight viruses in the respiratory tract is a problematic and significant factor in asthma exacerbations. Simply stated, airway barrier dysfunction in large part explains why asthma exacerbations can be caused by viral exposure—defective antiviral response—or by allergen exposure or irritant and pollutant exposure—increased barrier permeability.

The general principle really holds for many type 2 diseases. Barrier dysfunction is an integral part of the disease; in some ways it is primary and in other ways it is secondary, but it is clearly playing a role.

***AJMC®*: What is the significance of comorbidities in type 2 inflammatory conditions?**

LONG: I recently saw a patient who I have been treating for about 10 or 12 years, a gentleman [aged] about 40 [years]. He has atopic dermatitis, severe asthma, chronic sinus disease, and type 1 food allergies that can cause anaphylactic reactions, and he also has eosinophilic esophagitis. These are all type 2 inflammatory diseases. I don't [think it would be] quite appropriate to classify one as his primary disease and the others as comorbidities; these are coexisting primary conditions. That pattern of having multiple manifestations of the allergic diathesis is very common. You can view it in childhood as beginning with atopic dermatitis, then leading to rhinitis, then leading to asthma. Adult patients who come to see me as an allergist typically have 2, 3, or 4 allergic conditions that they need help with. They have food allergies, dermatitis, sinus disease, asthma, rhinitis—these are coexisting diseases. I don't want to call it one primary disease and [secondary] comorbidities. These are all manifestations of the atopic diathesis, all characterized by type 2 inflammation.

A practical upside of the coexistence of different clinical diseases that have the same pathology, possibly the same pathogenesis, is that if you can inhibit type 2 inflammation with systemically available therapies, you may ameliorate several of these conditions simultaneously. Such an approach has great potential. Whether it is real or not remains to be seen.

***AJMC®*: Can you talk about the role of IL inhibitors in type 2 inflammatory diseases, particularly in asthma?**

LONG: It is very important to first understand the history of the anti–IL-5 agents. IL-5 is a very important cytokine in eosinophil growth, in its development, and in trafficking it out of the bone marrow into the bloodstream. These processes are under the influence of IL-5 and IL-3. Mepolizumab, the first of the anti–IL-5 agents, was first studied in asthma in the 1990s. Its clinical use showed a profound reduction in peripheral blood eosinophils but no impact whatsoever on asthma. In the early 2000s, anti–IL-5 agents were further tested in asthma but were found to be disappointing failures in terms of improving outcomes for asthmatic patients. However, benefit was clearly shown later, when the agents were studied in a highly selected patient population with a very specific type of asthma. In [this type], despite treatment with high doses of inhaled steroids, or oral steroids, the [patients still had] multiple asthma exacerbations per year, high levels of airway reversibility when tested, and evidence of elevated numbers of eosinophils in the blood or in the airway. This small subset of asthma patients appears to improve with mepolizumab. Similar results were shown subsequently for reslizumab, also an anti–IL-5 agent, and subsequently for the anti–IL-5 receptor antagonist benralizumab. These patients don't represent a broad group of asthmatics; they needed to be carefully selected to identify the benefit of these drugs. In my opinion, these agents are not a broadly effective category of antiasthma drug.

The anti–IL-5 agents have been studied in conditions like nasal polyposis and found to have mildly beneficial effects. They have also been studied, in high doses, in hypereosinophilic syndromes, which are conditions characterized by abnormally high levels of eosinophils in the blood; the eosinophils are considered "bad actors" that cause tissue damage. Benefit has been demonstrated in these disorders, albeit with doses higher than those used in asthma. Thus, the anti–IL-5 agents are beneficial to a certain well characterized type of patient population.

Contrast that, then, with a drug like dupilumab, which targets the IL-4 alpha receptor. The IL-4 alpha receptor is shared by cytokines IL-4 and IL-13 and seems to have a broader impact on diseases characterized by type 2 inflammation, whether in the lung, skin, or nasal polyps, or in eosinophilic esophagitis. What's intriguing is that anti–IL-4 agents alone and anti–IL-13 agents alone, when they were studied,

> **Something appears unique about targeting IL-4 and IL-13 jointly that does not manifest by targeting them individually. When targeted together, [as dupilumab does, the process] seems to quite effectively ameliorate the symptoms caused by type 2 inflammation in the many different tissues.**

primarily in asthma, both failed in late-phase clinical trials. Something appears unique about targeting IL-4 and IL-13 jointly that does not manifest by targeting them individually. When targeted together, [as dupilumab does, the process] seems to quite effectively ameliorate the symptoms caused by type 2 inflammation in the many different tissues: in the airways for asthma, in the sinuses in the nasal polyps, in the skin with atopic dermatitis, and, based on early clinical results, in [the esophagus in] eosinophilic esophagitis.

Based on the clinical data from studies of the anti–IL-5 agents on the one hand and of the anti–IL-4 alpha receptor on the other, I view these as widely different categories of clinical responses.

***AJMC®*: Now that the IL-4/IL-13 pathway has been identified as one of great significance in asthma, what do you think the next steps should be and will be regarding research and development of this specific pathway?**

LONG: IL-4/IL-13 has proven to be a very clinically important pathway, and it's not entirely clear why. As I mentioned, the individual targets of IL-4 and IL-13 separately were not effective targets, whereas together they are. Why that is, we don't fully understand yet. In addition to asthma and atopic dermatitis, dupilumab is being investigated in nasal polyposis, and the studies are going into other atopic conditions as well, such eosinophilic esophagitis. I would make 2 points regarding dupilumab. First, since it's effective in so many clinical areas—and a typical patient, who we described earlier, has several manifestations of type 2 inflammation—it's possible that many of those manifestations will improve with exposure to this type of drug. Second, given the proof of concept that is being demonstrated, other drugs targeting the IL-4/IL-13 pathway with monoclonal antibodies or small molecule inhibitors in the same pathway be the focus of further research.

In my career, which spans close to 40 years now, we have had no real effective treatment for atopic dermatitis other than steroids and calcineurin inhibitors. These are mildly but not hugely effective, and, in the case of steroids, are limited by adverse effects. In contrast, dupilumab is often clinically transformational for that condition. I've had patients who have suffered from atopic dermatitis for decades who appear to have cleared up within weeks of beginning dupilumab. It can be very powerful. I don't personally have as much experience with this drug in asthma, but the clinical trials are very promising.

This pathway is fundamentally important, and future research should be in finding other drugs that target this pathway.

***AJMC®*: What are the broader treatment implications of the availability of a drug that is so effective in type 2 inflammatory conditions?**

LONG: In asthma, the use of IL inhibitors is limited mainly by cost and the perceived cost-effectiveness. The ICER study that came out last fall suggested that these drugs would need to have cost reductions of about 60% to 70% to be cost-effective. Additionally, many physicians are forced to buy and bill a lot of these drugs, and the practices may actually lose money by doing that.

Lack of cost-effectiveness, reported by independent analysis, is limiting for these agents as a class. [Yet] atopic dermatitis is a chronic debilitating skin disease. It causes a very much impaired quality of life. I don't quite know how one can optimally assess that from a cost-effectiveness standpoint. I do know that in my entire career, we haven't had much to treat atopic dermatitis very effectively, and now we have a drug that offers dramatic results. As an individual prescriber, you feel very positively about trying to help your patients that way.

IL-4/IL-13 agents may be extremely beneficial in interrupting these diseases early, preventing the consequences of poorly treated disease. Scientifically, it makes sense to use these drugs very broadly. They could change the whole paradigm by which we treat type 2 diseases if cost were not in the equation, but unfortunately it is. As a physician, I know there's a financial risk to me prescribing these, under current coverage and reimbursement arrangements. ◆