The Significance of the Type 2 Inflammatory Spectrum

A Q&A With Mark Boguniewicz, MD

MARK BOGUNIEWICZ, MD

Professor, Division of Pediatric Allergy and Clinical Immunology

Department of Pediatrics

National Jewish Health and University of Colorado School of Medicine

Denver, CO

***AJMC®*: How have perspectives toward atopic diseases, such as atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyps, evolved over the past several years?**

BOGUNIEWICZ: I practice in a unique medical environment at National Jewish Health in Denver, Colorado. We evolved into a center of excellence where patients with a spectrum of allergic, immune, and pulmonary diseases come from all over the country. Often, these are among the most severe [cases, involving] patients who have already seen many excellent physicians locally or regionally. I get to see patients who come to our day hospital for 2-week evaluations. [The model is based on] a complex medical psychosocial model, meaning that for a lot of these patients, the reason things aren't going well is that there is a significant psychological or behavioral component to their illness. Patients and caregivers are often overwhelmed by the chronic or relapsing nature of these diseases. They are also exhausted and sleep-deprived and may be depressed, and some even admit to having suicidal ideation. Patients are often looking for a cure and are not happy with the medications that we prescribe. When I talk to colleagues, who are busy dermatologists, pulmonologists, or allergists, they may only be able to spend minutes with these patients. Some [interventions] aren't working, and part of the problem is that a quick evaluation and recognition that a patient has asthma or atopic dermatitis and then handing them a prescription is not enough. These patients and their families need a lot of hand-holding and education, [along with] addressing various aspects of their quality of life. Our current model of medicine for chronic relapsing diseases with significant sleep impairment doesn't work, because if you haven't slept—not only for days or weeks but for months or years—the information that you're given in a short clinic visit sometimes just does not register. The medications we prescribe may all blur, and [patients may not] know what to put where, when, or how much to use, or they are tired of smearing the same topical steroid on their skin.

[From a health economics perspective,] you can estimate the cost of atopic dermatitis to the economy at [approximately] $5 billion, but asthma surpassed $50 billion. Those are serious numbers that our National Institutes of Health recognizes. They have funded our Atopic Dermatitis Research Network for several funding cycles. Patients with atopic dermatitis, especially those with more severe atopic dermatitis, may go on [to] develop asthma and other allergic disorders. We need to better understand which patients may follow this atopic or allergic march to develop early intervention strategies.

In addition, a number of nonatopic comorbidities are being increasingly recognized. For example, there is an association between atopic dermatitis and propensity for colonization or infection by various microbes that is not seen in other inflammatory skin disorders such as psoriasis. Studies examining the skin microbiome will help us understand the interaction of a diverse microbial world with our immune system, and investigations

are already under way looking to potentially recolonize patients' skin with commensal nonpathogenic bacteria. Studies are also addressing association of atopic dermatitis with different mental health disorders, as well as obesity and cardiovascular diseases, especially given our growing appreciation of atopic dermatitis not just as a skin disease but one with a systemic component.

Atopic dermatitis is a disease that impacts the quality of life of our patients and their families in a profound way. Clearly, not every patient with atopic dermatitis has persistent disease or goes on to develop asthma and allergies. Therefore, it's important to do the science and [identify] patients who maybe deserve systemic targeted intervention early.

***AJMC®*: Can you talk about the concept of type 2 inflammation and how it links these diseases?**

BOGUNIEWICZ: The type 2 inflammation/immunity picture evolved back in the 1980s, when scientists showed that there are different types of T cells—specifically, T-helper cells—and then showed that these cells secrete certain interleukins [ILs], which are a type of cytokine or signaling molecule; then their dysregulation was observed in certain diseases. In 1994, we published a paper that showed the importance of IL-4 in atopic dermatitis and, a year later, another on the role of IL-13, but then it took many years for other scientists to develop monoclonal antibodies that are fully human in a mouse system—which is an amazing feat in itself—that target IL-4 and IL-13, two key type 2 cytokines that are abnormally dysregulated in atopic dermatitis but also in other diseases.

You can find common pathophysiology in atopic dermatitis, asthma, and chronic sinusitis with nasal polyps. While not every patient with asthma, for example, has that classic type 2 inflammation, the majority do. We could start thinking about potentially treating these patients with a single or maybe some combination of targeted therapies, so that's why things have gotten really exciting: We went from using nonspecific "shotgun" therapies like corticosteroids—whether it was for the skin, the lungs, or nasal polyps—to now targeting the abnormal cytokines. I would say we're just at the beginning of this age of biologic therapy in the allergic diseases. Other fields, like rheumatology and, obviously, oncology, have championed effective targeted therapy.

***AJMC®*: Now that targeted agents appear to be effective across various type 2 inflammatory diseases, what are the practical implications for the treatment of these conditions?**

BOGUNIEWICZ: I think that we need to recognize the importance of this group of diseases really as a global health problem and that this prevalence would resonate with people who know someone with asthma, allergic rhinitis, food allergy, atopic dermatitis, and so on. So, this would be meaningful in a personal way.

Maybe it's going to take advocacy on the part of patients and their representative organizations, like the National Lung Association or National Eczema Association, where they have a unified voice. We would need to prove definitively that taking care of atopic dermatitis early would not only have an outcome on their quality of life [but also mean] fewer infections and fewer comorbidities that [a payer] would wind up paying for down the road. [Payers would likely require] more convincing evidence, not just epidemiologic associations, such as seeing higher rates of cardiovascular disease in adults with persistent atopic dermatitis; a comorbidity might be more related to a patient's lifestyle and not chronic inflammation. We need innovative science to gain a better understanding of these diseases, and I think this will require funding by both our government agencies and our biopharmaceutical colleagues.

***AJMC®*: How do you see the research spectrum developing over the next several years, given the promise of targeting IL-4 and IL-13?**

BOGUNIEWICZ: For our adult and adolescent patients, it was clear that the FDA recognized the value of a targeted therapy like dupilumab, and now we're studying it in patients 6 to 11 years old in severe atopic dermatitis. There is always the question of "Wouldn't it be great to intervene early and maybe show that early treatment with a systemic therapy might prevent the persistence of atopic dermatitis or the progression to other atopic diseases, like asthma?" That sounds great, but if you look at it more critically, you need to consider: "How do we identify those young patients at risk for these different diseases or for persistence?" We need to find biomarkers that could help us identify at-risk patients. Such biomarkers could also help us evaluate a patient's disease and response to treatment.

One of the problems associated with chronic or relapsing diseases that affects payers is the issue of treatment duration. We haven't done the studies yet to know when it would be appropriate to step down, decrease frequency, or hold the treatment. For some patients it could be a lifelong problem, but certainly not for every patient. It's easier to continue patients on chronic therapy if they're the ones that have had the disease for most of their lifetime and have already been on everything else. When you look at systemic treatments [other

than dupilumab that are] used to treat atopic dermatitis, [none of them], including immunosuppressive drugs like cyclosporine, methotrexate, azathioprine and mycophenolate, have been approved for use in atopic dermatitis in any age in this country.

The irony is that oral/systemic steroids are approved treatments, but our guidelines strongly advocate against using them. While they can be a quick fix, systemic steroids are not a long-term solution, and eventually their side effects are worse than the disease that they are treating. Against that group of immunosuppressive systemic therapies, it was easy for dupilumab to look great—both the safe and effective choice—but as we get into much younger patients, we need to know who the right patients are to start on biologic therapy, when, and for how long. Hopefully, that is where our research will be directed in the coming years.

***AJMC®*: What take-home messages would could you offer as the research and treatment spectrum for type 2 inflammatory conditions expands?**

BOGUNIEWICZ: In our 6- to 11-year-old patients with atopic dermatitis, we're going after the severe population. We recognize that as a practical matter, the milder a patient is, the less likely a parent—who is ultimately making the decision for the child—is going to want them on an injectable therapy. In our severe atopic dermatitis children, injectable therapy has not been a significant obstacle, especially [because] it is administered subcutaneously every 2 weeks and can be given at home. At our current understanding of the disease, we're making decisions based on severity scoring of signs and symptoms, as well as body surface area involved and impact on quality of life. Ideally, especially as you treat younger patients, you would like to have better understanding of different disease trajectories. We're learning about unique clinical subphenotypes, but ultimately, we want to be able to classify patients by unique endotypes; that is, based on a defined disease mechanism that could be uniquely targeted. That would be the goal of a precision medicine approach and, hopefully, where the science will take us.

If payers could appreciate the importance of allergic diseases as a global health problem, it might impact their view of our newest systemic therapy. Sometimes, all of our scientific discussions could be trumped by 1 patient telling their story of how they contemplated suicide because of the relentless pruritus and sleep disruption and their inability to interact socially, attend school, or hold a job. Those kinds of stories are powerful and instructive, and even though I've listened to them for 30 years, I'm always moved by them. We now recognize that patient-reported outcome measures should be an important part of evaluating patients, including in atopic dermatitis. Unfortunately, for busy clinicians, that whole aspect of the patient's illness was often missed, because in a limited time, they were focused only on skin lesions or how a patient's lungs sounded or what their nose looked like, and they didn't have time to stop and ask, "What has life been like? Are you sleeping? Do you have a social life? Are you able to go to school or work?" There are some new validated tools that should help our patients and their caregivers communicate these important topics to their healthcare providers in an efficient and timely manner. ◆