Practical Implications for the Use of Targeted Treatment in Atopic Diseases

A Q&A With Neal Jain, MD

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***AJMC®*: How would you assess the current therapeutic outlook and unmet treatment needs for asthma?**

JAIN: Over the past 2 to 3 decades, we have gone from a point where our understanding of asthma has dramatically changed from it being a disease characterized by hypertrophy and airway hyperresponsiveness to one that we now understand has variable aspects [of] inflammation. If you look back at the literature since the 1950s, we have known there are 2 types of asthma, including those [who] have eosinophilic inflammation that seems to be responsive to steroids. Those [who] did not have that type of inflammation did not respond to steroids. That is what has become new again in our understanding of this idea of type 2 inflammation as a broader pathophysiologic explanation for this eosinophilic phenotype, as well as some of the subcategories under that.

We learned a lot about type 2 inflammation and how that originates in the airway epithelium and how we have therapeutic options that are already available to us or are in the pipeline. What we do not have is a way to assess and identify different non–type 2 asthma phenotypes, and we also have very little available to manage those patients. This is one of the biggest unmet treatment needs.

Steroids remain the mainstay of treatment, but we are learning more about, potentially, the consequences of not only oral steroids or systemic steroids, but also about inhaled steroids when used at high doses. We are learning that a high dose for one individual may not be the same high dose for another individual. There is this idea of the "steroid footprint," or the total burden of steroids and the impact that they may have over time, whereby when you are using steroids plus intranasal steroids plus topical steroids over extended periods of time, there may be negative consequences from that, especially in susceptible individuals. As a result, another unmet need is finding alternatives to steroids that are not so expensive—in other words, not biologics—or unavailable for the majority of patients [who] have type 2 asthma. We are starting to see options such as Janus kinase inhibitors, as well as options that block different mediators to help manage these patients, and these may serve as a bridge for those patients in whom inhaled steroids are not advised or who cannot tolerate them or as add on therapy prior to starting biologic therapy.

***AJMC®*: As we learn more about the disease spectrum affected by type 2 inflammation, what are the implications for treatment?**

JAIN: Type 2 inflammation is an important pathway of inflammation that can impact a variety of disease states. We are starting to learn now that it may actually, for asthma, [begin] in utero, and if you had a mechanism by which you can measure internal type 2 inflammation, even if they do not have asthma, it seems as though type 2 inflammation inflammatory markers, specifically [interleukin] IL-4/IL-13, that are turned on in

pregnancy [are] the biggest predictors of a child going on to have asthma at some point in their life. There are epigenetic changes that occur in utero for these children that lead to the development of other kinds of things. We are seeing that type 2 inflammation has an important role in driving atopic dermatitis, in driving the development of food allergy, and driving the development of rhinitis and chronic rhinitis, chronic rhinosinusitis, sometimes with nasal polyps. So it does seem as though there is this sort of broad spectrum of diseases that type 2 inflammation touches on. Is there a unifying factor that seems to predict the onset of this or cause all of this inflammation? This is an area of active investigation, and a lot of people [favor] this idea of the alteration of the microbiome. Perhaps there are changes that we are seeing in the microbiome that may be resulting from our external influences in what we are seeing regarding antibiotic use, pesticide [exposure], viral infections, damaged epithelium, pollution, etc. We are starting to learn that the microbiome has an influence on our immune system and may allow these abnormalities or [that] changes in the microbiome lead to more of this type 2 inflammation pathway getting turned on. This leads to the development of diseases such as atopic dermatitis and food allergy early on in life and the development of allergic rhinitis and sometimes chronic rhinosinusitis and asthma that we tend to see later in childhood or into adulthood.

> **“The cost implications of the current treatment spectrum must be considered when we start to think about the ability of the healthcare system to pay for these newer biologic therapeutics.”**

***AJMC®*: What are the current challenges and potential opportunities when it comes to the use of biomarkers to differentiate types of inflammation?**

JAIN: I think a really important point is how you identify type 2 inflammation in individuals with asthma. We need to be better, and we need use the tools already available and to have more tools available to us to help identify patients with type 2 inflammation. [Regarding] non–type 2 individuals, one question that clinicians who see patients with asthma need to consider is whether the patient truly has asthma. There are good data to [suggest] that about one-third of patients diagnosed with asthma do not have asthma. As a specialist, one of the first things I look for is the presence of markers of type 2 inflammation; that gives me a proxy idea of their risk for having asthma. There are individuals [who] don't have any markers of type 2 inflammation, such as including comorbid conditions such as a history of atopic dermatitis, chronic rhinosinusitis, nasal polyps, or food allergies.

Although biomarkers can be used, there is no perfect biomarker that exists, and there likely will never be one. The biomarkers we have available to us are somewhat fuzzy or hazy biomarkers that give us a general idea of what is going on; those would include eosinophil levels, peripheral levels in blood, and fractional exhaled nitric oxide [FeNO], which I think is a vastly underutilized and underappreciated biomarker [because of] its ability to identify the presence or absence of the type 2 inflammation in the airway. It is important to emphasize that the underuse of FeNO is in part related to a lack of coverage by many payers and in part related to a lack of understanding about the utility of this tool despite multiple guidelines recommending its use. It is an important marker that can identify the likelihood of response to inhaled and oral steroids, as well as to certain biologic therapies. Immunoglobulin E is an even dirtier measure of activation of this pathway. Although none are perfect, the absence of any of these markers should make a practitioner question the diagnosis of asthma or, at the very least, the utility of treatments targeting type 2 inflammation.

There are other measures or biomarkers that I think we should be looking at, one of which is exacerbations. Patients that have type 2 inflammation have exacerbations, and if you do not have type 2 inflammation, you are less likely to have exacerbations. Then, if you look at the different biologics available, patients who respond the best to biologics are the patients [who] have the most exacerbation history and have the highest rate of exacerbation. Lung function is also a measure of proxy. We know that loss of lung function is also a result from those exacerbations that tend to occur.

Other biomarkers are certainly in the works and that we'll start to look at. As we start to get more sophisticated and more technologies become available to us, it is likely that one day, blood analysis for epigenetic markers or activation of certain cytokine pathways may

be possible. As the future unfolds, [stakeholders] will need to start thinking about how we're going to match therapies to the right patients. We certainly do not want to put patients [who] will not benefit from these therapies on those medications

AJMC®: What are the challenges and opportunities associated with the use of targeted agents, such as interleukin inhibitors, for conditions marked by type 2 inflammation?

JAIN: There are some of the challenges with IL-4, IL-5, and IL-13 inhibitors. I think, first and foremost, [the most important question is]: How do you choose the right therapy for the right patient? It is clear, at least when you look at IL-5 agents, that they really ought to be used in patients [who] have severe disease, because patients who are exacerbation prone often respond. If you look at those therapies in patients [who] have milder disease and tend to have not as many exacerbations, those patients just did not seem to have enough of an effect.

Dupilumab, an inhibitor of IL-4 and IL-13, is an interesting therapeutic option, both from the standpoint of if you think about where IL-4 and IL-13 touch in the inflammatory pathways of type 2 inflammation and when you think about the spectrum of diseases that are associated with these cytokines' activity. Along with that, dupilumab has a broader indication that includes moderate to severe disease, as well as patients who are oral-steroid dependent.

When you think about these biologic agents, it is a dilemma as to whether we should put patients with moderate disease on biologic agents such as dupilumab or omalizumab, as they are costly and it's hard to separate out in whom [they are] truly justified. If an individual has moderate uncontrolled asthma, and chronic rhinosinusitis with nasal polyps and food allergy or eosinophilic esophagitis—in other words, multiple type 2 high [risk] conditions—and their steroid footprint is high, is that an individual who deserves biologic therapy, despite not having severe disease or meeting criteria set by payers for each individual condition? The question will likely become: At what point do we draw the line and say that this is a person who is appropriate for this therapy and the cost associated with it may justify the benefits that are achieved with it?

Approximately 8% of the US population has asthma, which is about 26 million individuals. According to the GINA [Global Initiative for Asthma] severe asthma guide that was published in November 2018, the percentage of individuals with severe uncontrolled asthma is somewhere between 3% to 5%, and the data from Europe suggest that is right around 4%, translating roughly to 1 million individuals who have severe disease that is uncontrolled. If you look at the severe population of asthmatics, the true severe asthmatics are defined [as] patients who are adherent to a medium to high dose of inhaled steroids plus long-acting beta agonists [LABAs]. They remain uncontrolled with symptoms, typically have exacerbations, and they tend to be the patients [who] have this type 2 inflammation. In 1 million individuals, what is the cost of putting that full million, that full cohort of patients, on a biologic therapy? Are we at the right price point, and do these costs have to come down? I think that's one of the big questions. Ultimately, then you start to say about some of the medications, if you use these medications earlier, would you have an impact on the natural history of the disease down the road? What does that cost-benefit analysis look like?

Other logistical questions include: Should these agents be administered in the office versus at home, and what are the caveats of administering at home in a population of severe patients? Will patients fall off therapy? Will falling off therapy lead to other adverse outcomes, such as nonresponsiveness to the medication down the road, because you could have a situation in which you take the medicine for period of time and then you stop taking it because you feel good and then it loses effect upon recapture when you put someone on it? Do you see exacerbations leading to hospitalizations with these medications if [patients] are nonadherent and they are getting them at home? Also, what is the value to the physician who's prescribing or administering these medications? It takes a lot of time, staff, and money for us to take care of patients with severe disease, and the cost to practitioners is high to take care of these patients without any real monetary benefit by putting patients on these therapies. In fact, in the era of managed and capitated care, if we are high prescribers of these therapeutics, we may be at a disadvantage for taking care of these patients. Reimbursements could go down and practitioners could be penalized by virtue of the fact that we are seeing a higher population of patients with severe disease who require these costly therapies.

I have a severe asthma clinic, and I may be perceived by payers as a high prescriber of biologics because I take care of patients with severe disease. That may affect my reimbursements and my overall ability to continue to provide quality care to these individuals. How does that coexist in a healthcare system as it is structured right now, in which many practitioners and specialists do not work for hospital systems or integrated health systems, whereby you have contained costs and you can afford to do that. That is a big

question that we just don't know the answer to. It is unfortunate that there are already practices who discourage practitioners' prescribing of therapies that are costly from an administrative standpoint or alternatively may have concerns about payers grading the practice as a high utilizer of such therapies and in turn leading to decreased reimbursements due to capitation and risk-sharing strategies.

***AJMC®*: Can you talk about evolving treatment guidelines and the managed care implications of a growing treatment spectrum?**

JAIN: Treatment guidelines often take a pure clinical approach or science approach, without taking into account costs. As we move beyond the simple paradigm of inhaled steroids, inhaled steroids with long-acting beta agonists, to therapies that are new and target type 2 inflammation but do not fall into the categories that we currently have, a question that must be answered is where do we put these in the our guidelines, and how do we use them? One important aspect is to consider cost, in addition to efficacy. Including managed care stakeholders in the process may make sense. We are unlikely to have head-to-head clinical trials to help answer the questions, and we don't have the science or resources to know the long-term ramifications of choosing different therapies over other therapies. Where do you intervene with a biologic versus other therapeutics, and how does this work from the standpoint of reimbursements, not only for the therapeutics, but also for the physicians who are caring for these patients? It is a big question.

***AJMC®*: How do you see the treatment landscape evolving over the next 5 years, and what would you like to see emphasized among various stakeholders?**

JAIN: There are several factors that are sometimes moving together and sometimes moving in opposite directions that are going to better shape how we use these therapeutics in the future. Amongst those are obviously the managed care side of things, as well as the flip side of that. Where does the pharmaceutical industry see this going? Obviously, from trying to maximize profits and penetration into the market, pushing the fee, does this work in different populations with different comorbid conditions? Does this work in a milder population, and when is it appropriate to use expensive therapeutics, such as biologics, in a more moderate or even mild population? I think that the other question becomes, do you use these earlier in the course of disease with the hopes of impacting the natural history and long-term outcomes associated with this disease in patients [who] have, not only severe disease, but also more moderate disease? Then, are we going to also see increasing step therapy, as other small-molecule therapeutics become available to manage this condition over time? The closest we have come in the past, after the use of inhaled corticosteroids [ICS], and ICS/LABAs, was montelukast, which unfortunately did not have as significant an impact as we initially hoped. There are other therapeutics that are coming down the pipeline that are going to have potential for limited side effects and high efficacy that are significantly different from what we have now. How these will fit in to the equation will be interesting to see and will largely depend on how the ongoing trials evaluating the efficacy of these agents turn out.

***AJMC®*: What are the practical implications of the current treatment spectrum, particularly when it comes to access?**

JAIN: The cost implications of the current treatment spectrum must be considered when we start to think about the ability of the healthcare system to pay for these newer biologic therapeutics. The recent *GINA Pocket Guide to the Identification and Management of Difficult-to-Treat and Severe Asthma* nicely outlines when biologic therapy should be considered and instituted. Patients [who] require high-dose ICS/LABA therapy or oral steroids to maintain control or who are uncontrolled despite such therapy should be considered as candidates for biologic add-on therapy. Certainly, when you get to a point where you have systemic effects from steroids that are unintended consequences and sometimes underappreciated, you should start to think about implementing biologic therapy. In these individuals, the unintended and underappreciated consequences have a lot of long-term negative cost consequences associated with them. I have seen patients [who] come in [who] are resigned to the fact that they have bad asthma; they are on their high-dose ICS/LABA agents plus their oral steroid 3 times a year. Some of these patients have had cataract surgery, have osteoporosis, or uncontrolled diabetes, hypertension, and other unintended consequences that may, in part, result from their chronic asthma therapy. We, as practitioners, need to consider these potential consequences when making decisions about simply continuing their therapies or instituting biologic therapies.

Another aspect of this, of course, is the overutilization of these therapies in individuals who do not really require or will not benefit from such therapies. This is where we really need better education of our patients about the importance of being adherent with prescribed therapies, as well as utilization of diagnostic tools, such as biomarkers, to identify the appropriate patients for such therapies. ◆