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info@reachmd.com
(866) 423-7849

The Importance of Biomarkers in Asthma Clinical Phenotypes

You're listening to ReachMD XM160, The Channel for Medical Professionals. Welcome to hot topics in allergy presented by the American College of Allergy, Asthma, and Immunology. Your host is Dr. Ketan Sheth, Medical Director of the Lafayette Allergy and Asthma Clinic in Lafayette, Indiana.

More than 20 million Americans have asthma, yet each may have a unique clinical phenotype. How can biomarkers clinically improve the management of asthma in various asthma phenotypes? Joining us to discuss clinical phenotypes in asthma, the importance of biomarkers is Dr. William Calhoun, the Sealy and Smith Distinguished Chair of Internal Medicine and Vice-Chair for research in the Department of Internal Medicine at the University of Texas Medical Branch in Galveston, Texas.

DR. KETAN SHETH:

Welcome, Dr. Calhoun.

DR. WILLIAM CALHOUN:

Thank you very much, Dr. Sheth.

DR. KETAN SHETH:

Well, what are biomarkers?

DR. WILLIAM CALHOUN:

Biomarkers are measurements that can be made in an individual relatively noninvasively, which give us information about an outcome that we are really more interested in knowing. So, for example, a serum cholesterol can be a biomarker for an increased risk of stroke or cardiac disease. The increased cholesterol in an average itself doesn't necessarily cause the stroke immediately. It simply is a biomarker. It's a measurement that easily can be made that predicts some other important clinical consequence.

DR. KETAN SHETH:

Well, what are phenotypes then?

DR. WILLIAM CALHOUN:

Phenotypes are distinct subsets of a particular disease and when we are talking about asthma, for example, asthma is a syndromic disease. It's characterized by obstructive airways disease, by airway hyperresponsiveness and by airway inflammation, but under that broad umbrella, lie a dozen or more different phenotypes of asthma. For example, in asthma we may have exercise-induced asthma or we will have allergic asthma or we can have asthma related to viral infection. We can have asthma related to menses and that is just a few of the phenotypes. So, there are number of phenotypes, a number of discernible categories of disease that likely have different pathogenic mechanisms and also may well respond differently to therapy and that is really from a clinician standpoint what is important to us.

DR. KETAN SHETH:

Is that really the reason or the crux of why it is important to recognize these phenotypes or why should we care about what the phenotypes are for asthma?

DR. WILLIAM CALHOUN:

Well, firstly and most importantly, the phenotype may well associate with therapeutic responsiveness. For example, the severe asthma phenotype is associated with a blunted or even absent response to inhaled corticosteroids. The smoking asthmatic phenotype is another group, which has a blunted responsiveness to inhaled corticosteroids, but beyond that, we may need to understand these phenotypes because they are predictive of certain pathological processes that we can intervene on or they may be associated with an adverse trajectory, that is the population of asthma that has frequent exacerbations and an accelerated loss of lung function. So, phenotype simply helps us as physicians, as clinicians, to recognize subsets of variability within a broader disease category that may have important clinical consequences.

DR. KETAN SHETH:

Coming back to the biomarkers, which ones are being evaluated for asthma?

DR. WILLIAM CALHOUN:

Well, a number of them have been evaluated; probably most interesting right now is the fraction of exhaled nitric oxide in exhaled breath. There is an FDA-approved instrument for measuring exhaled nitric oxide. So, we can do exhaled nitric oxide measurement in our clinic, get a number and interpret that number to help us manage patients. In addition to that, induced sputum has been used, induced sputum is probably the most accurate biomarker we have, but the inconvenience and the difficulty in obtaining good induced sputum and in having it measured and analyzed properly really precludes its use in clinical medicine. Bronchoalveolar lavage has been used and exhaled breath condensates have been used, but neither of those in 2008 are really up to par as a useful biomarker. So, exhaled nitric oxide is probably the best biomarker we got right now and it can be used at least in some cases, as an index of airway inflammation and as a tool for assessing compliance with inhaled corticosteroid therapy.

DR. KETAN SHETH:

Do you think it is practical to use these, in addition to some of the other things that we do to measure asthma such as lung function?

DR. WILLIAM CALHOUN:

The question is a good one indicating the question of whether the biomarker adds value is an important one. There are some data that suggest that adding exhaled nitric oxide measurements to standard clinical measurement does improve asthma outcomes or allows asthma outcomes to be maintained at a lower dose of an inhaled steroid. As you know, we are part of the NIH-funded Asthma Clinical Research Network and one of our current trials in ACRN is specifically designed to evaluate the added benefit of measuring exhaled nitric oxide in the ongoing management of patients with mild-to-moderate asthma. So, in the next 18 to 24 months, we should have definitive information on the added value that nitric oxide does or does not give in the management of asthma.

DR. KETAN SHETH:

As we talk about measuring exhaled nitric oxide, certainly some recent studies have suggested that maybe it doesn't add anything. I know you are talking about some studies, which you are doing with the new clinical research network, we don't have that data yet, are we going to get an answer in one way or another or are these different patient populations and when we are back to these phenotypes, we don't know what we are studying.

DR. WILLIAM CALHOUN:

My guess is that, as you intimated, there will be some patients for whom ongoing measurements of exhaled nitric oxide will be important and for others, it may not be particularly helpful. What we need to do is to identify that subset of patients that phenotype of patients for whom the ongoing or periodic measurement of exhaled nitric oxide actually has added benefit. In some patients, the absence of an inhaled corticosteroid dose within the past couple of weeks is associated with a dramatic rise in exhaled nitric oxide. So, if your patient comes in and they have very high nitric oxide, you can sit down and have the conversation with them. Are you really taking your inhaled steroids? Are you taking it as I prescribed? Are you getting it every day? Are you getting it twice a day? You can have that conversation with him on the basis of the data that you generate in your office.

DR. KETAN SHETH:

Let's turn us around a little bit. Can the biomarkers themselves help the clinicians recognize the important clinical phenotypes?

DR. WILLIAM CALHOUN:

That's another key question and in many fields of medicine, the answer to that is "yes." In oncology, for example, there are number of

biomarkers that inform the selection of appropriate therapy in breast cancer, for example, the presence of high expression of estrogen receptors or progesterone receptors strongly informs the choice of appropriate chemotherapy for that particular patient that is a biomarker that informs treatment. In asthma, we are almost to that point. Is there a specific biomarker that we can measure that tells us that a particular drug is the proper treatment? No, we are not quite to that point yet. My guess is that over the next 12 to 36 months, some of these biomarkers will actually come into the clinical arena.

DR. KETAN SHETH:

If you are just tuning in, you are listening to hot topics in allergy on ReachMD.com at XM160, The Channel for Medical Professionals. I am your host, Dr. Ketan Sheth and joining me to discuss clinical phenotypes in asthma, the importance of biomarkers is Dr. William Calhoun, The Sealy and Smith Distinguished Chair of Internal Medicine and Vice-Chair for research in the Department Of Internal Medicine at the University of Texas Medical Branch in Galveston, Texas.

Dr. Calhoun, you talked about exhaled nitric oxide. Do you think that is the best validated biomarker in 2008?

DR. WILLIAM CALHOUN:

In 2008, it probably is the best practical validated biomarker. As we talked a little bit ago, induced sputum, the measurement of eosinophils in induced sputum in particular, has very nice predicted value for a variety of very important asthma outcomes. However, it's not a technique that most of us as clinicians can get and that's even in academic medical centers. So, although induced sputum is reasonably well validated and has good predicted value for a number of important asthma outcomes, it is not practical. So as a practical biomarker, exhaled nitric oxide probably rises to the top of the list.

DR. KETAN SHETH:

I will ask you a loaded question here and I know lot of your research was in bronchoalveolar lavage and its use as markers and finding that. Is that a good validated biomarker that helps us in research questions?

DR. WILLIAM CALHOUN:

Bronchoalveolar lavage is invasive, bronchoalveolar lavage is expensive, and bronchoalveolar lavage confers some risk to the volunteer or to the patient and so as a biomarker, it fails the test of ease of use and it fails the test of low expense. What we have learned however, from bronchoalveolar lavage is that the inflammation in the airway can allow us to predict clinical phenotypes and it is a testable hypothesis that other ways of getting samples of the airway such as exhaled breath condensate perhaps a simple sputum not a hypertonic saline-induced sputum or perhaps even a simple sputum may give us the same kind of information. Those are future directions for biomedical research and biomarkers at this point. What we can learn from bronchoalveolar lavage is the pathogenic mechanisms, we can establish that there is biologic plausibility and from the standpoint of the sample itself, it is a pretty clean sample. The next step, of course, and drawing that into the clinical arena is taking that information we have obtained from bronchoalveolar lavage and moving it into a sample regime that is clinically applicable. I think, exhaled breath condensate is probably one of those samples that there is evaluation in that regard.

DR. KETAN SHETH:

Can you tell us a little bit more about exhaled breath condensate? Why do you think that's tying all of these together, at least what I thought I heard you say?

DR. WILLIAM CALHOUN:

Well. Exhaled breath condensate in 2008 is not yet ready for prime time, but considered that exhaled air that comes out through the vocal cords produces a micro-aerosolization of the fluids in the airway, across the vocal cords from the trachea, etc., etc. So we are not just looking at condensed water coming out of the exhaled breath, we are actually looking at micro-aerosolization of material from the upper airway. It is then not a logical lead to suggest that that material could have very important biological information. Exhaled breath condensates can be done in the course of about 10 minutes. They are essentially noninvasive. The patient simply breathes into a tube for a few minutes and the material collects in a sample tube and then it can be analyzed in the laboratory. So, exhaled breath condensate has certain limitations, of course. But, I think, it does have the promise of having biologic possibility, sampling the upper airway being relatively quick, relatively inexpensive, and being noninvasive.

DR. KETAN SHETH:

Well, given your obvious expertise in using these biomarkers, what are the things has your lab discovered in using biomarkers in the research that you have done?

DR. WILLIAM CALHOUN:

Using bronchoalveolar lavage, my colleagues and I at the University of Texas, have found that the cytokine patterns in bronchoalveolar lavage fluid can define 4 different subsets of asthma and we were encouraged to find that one of those subsets corresponded strongly to the severe asthma phenotype that we were studying in our NIH-funded Severe Asthma Research Program. What we didn't expect and were surprised to find and certainly interesting for us to pursue is that those patients who had clinically indistinguishable mild-to-moderate asthma. Had 3 different molecular phenotypes. It is our postulate, our hypothesis, that those 3 molecular phenotypes have a different underlying pathogenesis. May have different responses to therapy and in fact, may have a different trajectory. They may have a different pathway of loss of lung function overtime. Those are all testable hypothesis that were at this point evaluated.

DR. KETAN SHETH:

We have seen some recent data that there may be some genetic abnormalities that lead to some asthmatic exposure smoking earlier. Does this play in to this exact different type of clinical phenotype that we have to prevent exposure in certain people, those types of things?

DR. WILLIAM CALHOUN:

Yeah, absolutely, I think, the role of genotyping in clinical medicine would only enlarge. Obviously, there are some concerns that are legitimately raised about the advent of genotyping and genetic information being rolled into your clinical medical record, but there are very good bioethicists who are working on this problem and I think that the safeguards will be put in place to prevent the genetic information from being used inappropriately.

DR. KETAN SHETH:

I would like to thank my guest from the University of Texas Medical Branch in Galveston, Texas, Dr. William Calhoun. Dr. Calhoun, thank you for being our guest this week on hot topics in allergy.

DR. WILLIAM CALHOUN:

My pleasure, thank you Dr. Sheth.

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