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Examining the Role of Biologics in the Eosinophilic Asthma Treatment Landscape

**Announcer:**
You're listening to *Clinicians Roundtable* on ReachMD, and this episode is sponsored by GlaxoSmithKline. Here's your host, Dr. Charles Turck.

**Dr. Turck:**
Welcome to *Clinicians Roundtable* on ReachMD. I'm Dr. Charles Turck. And joining me to discuss the role of biologics in the eosinophilic asthma treatment landscape is Dr. Ian Pavord, who's a Professor of Respiratory Medicine at the University of Oxford. Dr. Pavord, thanks for being here today.

**Dr. Pavord:**
Oh, thank you for the invitation. Delighted.

**Dr. Turck:**
To start us off, Dr. Pavord, would you give us an overview of the current treatment landscape for eosinophilic asthma?

**Dr. Pavord:**
Well, it's a rapidly changing field with new treatments arriving on a regular basis, but type 2 cytokine targeted biologics are the main sort of new offering that we have. We have biologics, humanized monoclonal antibodies that target IL-5, or block the effects of IL-5 by targeting the IL-5 receptor alpha. We have a biologic that targets the IL-4 receptor alpha and blocks the effects of IL-4 and IL-13, both key cytokines in the pathogenesis of type 2 inflammation in the airway and elsewhere. We've had for nearly 20 years now a monoclonal antibody that targets IgE. And may be particularly effective in more allergen-driven asthma. So yeah, it's a growing field. We've got a lot of treatment options for our patients that have this key treatable trait.

**Dr. Turck:**
And if we zero in on a few of the conventional treatment options, in particular, what are some of the collateral impacts when a patient has an inadequate response to maintenance therapy with high-dose inhaled corticosteroids, oral corticosteroids, or bronchodilators?

**Dr. Pavord:**
Yeah, so the standard approach, which would be a reasonable dose of an inhaled steroid, in combination with a long-acting beta agonist has failed to achieve control in patients that are suitable for biologics. And many of these patients have recurrent asthma attacks. These are episodes of airflow limitation that are not responsive to their salbutamol inhaler and need treating with oral corticosteroids, which come with fairly significant dose-related and treatment, duration-related side effects that will be familiar to many of your viewers, including, osteoporosis, weight gain, thinning of the skin, mental health issues, depression, anxiety.

So, you know, the burden of uncontrolled asthma is not only due to the asthma itself, but also the treatment that's needed to treat asthma attacks particularly. And it can get complicated in the clinic in severe asthma because you've got problems linked to the asthma itself, you've got problems linked to comorbid conditions that might be due to type 2 airway inflammation elsewhere in the body. And you've got problems linked to the treatment that the patient needs to take for for their asthma attacks. And some patients need regular oral corticosteroids to control their asthma, which has a particularly high potential to cause side effects.

**Dr. Turck:**
With that background in mind, Dr. Pavord, let's turn our attention back to biologics. You'd mentioned targeting interleukins and IgE. How else do they work to treat eosinophilic asthma?

**Dr. Pavord:**
Well, the patient with severe eosinophilic asthma who is failing to respond to an inhaled steroid, you have to utilize other strategies to reduce eosinophilic airway inflammation. So, the anti-IL-5 and the anti-IL-5 receptor alpha drugs mepolizumab, benralizumab, reslizumab, they deplete circulating eosinophils to very low levels, typically under 50 cells per microliter. So, there are no eosinophils to be recruited towards the airway epithelium. The reservoir of eosinophils is empty. So that's how they work.

Dupilumab, which targets the IL-4 receptor alpha probably works more in the airway mucosal side by switching off the chemotactic signal that recruits eosinophils towards the epithelium.

The anti-TSLP which is a recently available biologic approach, which is very proximally in the type 2 inflammation cascade and switches off type 2 cell cytokine production and has quite broad inhibitory effects on type 2 inflammation.

I think anti-IgE, we really don't know how it works if I'm quite honest. That's still a mystery 20 years ago, its impact seemed to be largest in patients with type 2 airway inflammation. But exactly how it works is unclear. We know that sputum eosinophils and exhaled nitric oxide are reduced by treatment with omalizumab, so it's probably inhibiting type 2 airway inflammation.

**Dr. Turck:**
For those just tuning in, you're listening to *Clinicians Roundtable* on ReachMD. I'm Dr. Charles Turck. And I'm speaking with Dr. Ian Pavord, about the role of biologics in the eosinophilic asthma treatment landscape.

So, Dr. Pavord, now I'd like to take a look at the use of biologics in clinical practice. You'd touched on this a little bit before but which of our patients with eosinophilic asthma should be prescribed biologics? And when?

**Dr. Pavord:**
Well, the first thing to say is they've had a massive impact in the five or six years that we've been able to use them. I mean, I've been working in severe asthma for 20 or 30 years. And really, our job was about watching an orderly decline that the patient's problems linked to the asthma itself, but also problems linked to the treatment. And then, this landscape has been transformed by the biologics. And we're achieving extraordinary outcomes in some patients.

But the patients we're really looking for have a number of features. Firstly, recurrent asthma attacks. And I'm particularly interested in how the patient feels when they take prednisolone. The typical type 2 high eosinophilic asthma patient will say that prednisolone is really helpful. And it works very quickly. That's always an important aspect of the history that I ask about. We want the patient to be on a reasonable dose of inhalers so at least moderate dose ICS, and we want, you know, good evidence that they're taking it. You know, asthma can be uncontrolled because patients are not adherent with their treatment. And those are not patients that are attractive candidates for biologics. Our much better option is to try and work with them to improve treatment adherence.

And the other thing we're looking for is evidence of type 2 airway inflammation. And this is an assessment that's based on measurement of biomarkers. And there are two biomarkers that are particularly helpful; the blood eosinophil count, which is typically raised in people with eosinophilic asthma, certainly above 150, and usually above 300 cells per microliter. And broadly speaking, the higher the blood eosinophil count, the better the patient is likely to respond to biologics, particularly the anti-IL-5 biologics.

The other biomarker that's really helpful is exhaled nitric oxide or FeNO, which is increased in exhaled air in severe eosinophilic asthma because of IL-13 induced nitric oxide production by the airway epithelium. So, it's a great biomarker of IL-13 effects. And a raised FeNO is proved to be a very good way of identifying patients who are going to respond well to dupilumab, a treatment that targets IL-4 and IL-13.

Yeah, so these biomarkers are not always done in clinical practice. They're not part of routine clinical practice, certainly a non-specialist's care. And we've got work to do to sort of raise awareness of that. But all other things being equal, if you see a patient with asthma who has a high FeNO and a high blood eosinophil count, they are at risk. So, there's good evidence now that they're at risk of asthma attacks, maybe have a four to five-fold increased risk of asthma attacks, compared to the equivalent least severe patient who has low biomarkers. And they are the patients that are likely to have the really good responses to the biologics that we talked about.

**Dr. Turck:**
Is there a memorable patient case involving biologics that you could share with us?

**Dr. Pavord:**
Yes, there is some, and it's one of the earlier patients that I treated. And we were involved in the first proof of concept study of mepolizumab back in 2009. But the patient that sticks in my mind participated in the subsequent, phase 3 study, the MENSA study. A0nd she was young. She had three kids under the age of five, and her asthma had completely ruined her life. She had horrendous problems recurrent asthma attacks, including one that nearly killed her, so she was on ITU with a severe asthma attack. And she

required high-dose maintenance treatment, including most significantly for her prednisolone at around 20 milligrams a day. And she had had awful side effects, depression, menstrual disturbance a major weight gain, she'd put on 30 or 40 kilograms in weight, unable to work her sort of home life was very difficult, her husband had left her. And it was a very complex situation. But the one feature of her case was that she had red hot biomarkers. So, her blood eosinophil count was very high, until she had started on regular oral steroids, when there was some suppression. And she had a very high FeNO. So, she was you know, a hot, hot patient with very high risk. But also, a very high likelihood of responding to biologics. She was randomized to mepolizumab in the phase 3 MENSA study. And the treatment effects - and she was fortunate to be able to continue with treatment open label in the extension study. But there was a game changer for her. She had a terrific airway response, improvement in lung function, stopped having asthma attacks stopped requiring maintenance of steroids. And that all the side effects melted away really indicating that eosinophilic airway inflammation was the dominant treatable trait in her, and that all the other problems she had were secondary to that.

And I remember bumping into her in the hospital corridor, and I didn't recognize her because she'd lost so much weight, and you look so well. And she had to stop me and say, 'It's me! You know, I've had a great response to whatever you're giving me, you know, and it's really changed my life.'

**Dr. Turck:**
Thank you so much for sharing that story with us. And we're almost out of time, Dr. Pavord. But before we close, is there anything else you'd like to share with our audience about biologics or the treatment of eosinophilic asthma?

**Dr. Pavord:**
Yeah, so look out for patients who are having recurrent asthma attacks, who need prednisolone frequently, and when they take it, they notice a good response. And do look at the blood eosinophil count and invest in a FeNO machine. These are two simple biomarkers, and they really asked simple, that tell you a lot about the risk of asthma attacks. And that's something you really do want to know about. But crucially, they tell you about a patient that has a risk of asthma attacks that you can modify with treatment. And it's very clear that the biologics that we've been talking about work particularly well in patients with high biomarkers. So that's something that you need to go away and maybe plan for, you know, how can I incorporate these measurements into my clinical assessment of patients? And if you've got a patient who's got hot biomarkers, recurrent asthma attacks, appears to be taking reasonable inhaled treatment, and biologics could be a game changer for them.

**Dr. Turck:**
Well, those are great comments for us to consider as we come to the end of today's program. And I want to thank my guest, Dr. Ian Pavord, for joining me to discuss the impact of biologics and the treatment of eosinophilic asthma. Dr. Pavord, it was great having you on the program.

**Dr. Pavord:**
Thank you. It's a real pleasure. And thank you for the invitation.

**Announcer:**
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