STELLA LEE: Thank you, Dr. Ively. So the topic of my presentation is on these new therapeutic medications, they're called biologics. And I will also talk about some of the other newer therapies that we have been actively involved in for clinical trial work here at UPMC. These are my disclosures. We've been working with several industries for these clinical trials.

So let's start with the prevalence of chronic rhinosinusitis. We know that worldwide there is about a 12% prevalence in the United States, and about 10.9% Europe, and about 7% to 8% in China and Korea, but we still have very little understanding about the prevalence of CRS worldwide.

So the topic of my presentation really is going to focus on biologics. So I wanted to go over briefly what a biologic is. A biologic is a complex structure, it's genetically engineered, and we encounter biologics every day. They're in vaccines, they're in different kinds of gene therapies. But specifically for chronic rhinosinusitis, we're using these medications-- specifically monoclonal antibody therapies as you can see here on this chart, it's down here-- to target very specific inflammatory chemicals, cytokines in particular. But as you can see here on this chart, biologics include insulin. For example, interferons, interleukins, growth factors, et cetera, and vaccines, as I mentioned.

So we know that biologics are at the cutting edge of biomedical research at this point. And the FDA also recognizes that. And that these medications may really offer the most effective means to target and provide personalized therapy to patients who have really difficult illnesses that current therapies are not able to address.

These are the emerging biologics for chronic rhinosinusitis. Specifically, as you can see there are very specific targets. The trials that we are currently doing now are looking at IL 4, 5, and 13, and some of these biologics are already available for asthma.

So as you can see here, dupilumab is one of the biologic therapies I will talk about. But omalizumab has been around for about 14 years or so. So that is another biologic therapy that specifically targets IGE that's responsible for certain types of asthma and chronic rhinosinusitis. Recently, several anti L5 therapies have come into the horizon, and mepulizumab reslizumab, as well as benralizumab have been studied in asthma and now are on the horizon for treatment of polyposis, as well.

So comparison to small molecules. So biologics are very complex molecules, they're very complex drugs that take a lot of effort to manufacture compared to a small molecule drug. A small molecule drug, a good example is, for example, aspirin. So aspirin, a small molecule drug, is relatively simple in chemical structure. It's produced by chemical synthesis whereas biologic drugs are produced in living cell cultures. And they're definitely, as I mentioned, more difficult to produce, but they can be more immunogenic. So those are some differences between small molecule drugs that we're currently aware of compared to biologic drugs.

So next I will talk for a little bit more about omalizumab, which is the most well known biologic right now for the treatment of asthma and potentially CRS. How it works, it binds free circulating IGE and inhibits the binding of the IGE to the receptor. And thereby it helps prevent the downstream inflammatory effects of the IGE binding and the cytokines that are produced. So as a result, there's decrease not only in circulating IGE, but the receptors on the mast cells, basophils, and dendritic cells that ultimately create the inflammatory response in severe allergic asthma and potentially CRS.

There have been two studies in omalizumab. One was very promising, the very rigorous study, but a small number of patients. They did show a decrease in nasal polyp score after 16 weeks of therapy. And there were also improvements in nasal and asthma symptoms scores. And This was a study done out in Belgium.

And just to show you how effective this medication was, this is a CT scan showing before therapy where you can see the frontal sinuses have pacified as well as the maxillary sinuses and after treatment where you have a relative clearing of the inflammatory infiltrate and the opacification.

But there's conflicting data still. The Chicago group showed that there actually wasn't a significant difference between using omalizumab versus placebo in radiographic scores, although symptom scores improved in the treatment group. So still we need more research in this area. And we are embarking on a phase 3 trial for omalizumab here at the University of Pittsburgh in the near future in the next couple of months.

Some of the side effects that we worry about with biologic therapies are neoplasia. Because it can suppress the immune system, there is the concern that it can potentially allow for malignancies to occur. So there was a very small increase in malignancy in the omalizumab treated group compared to the placebo group, but a prospective-- actually, a study looking at the cohort of patients-- and it was prospectively done study-- showed that the malignancy rates were actually similar between the treated group and the placebo group. Still, however, there is concern. And my patients who are considering biologic therapies, I do let them know about these findings and counsel them appropriately.

Mepolizumab is another medication that we should all be aware of. It has been approved for asthma. It inhibits IL 5, it's a monoclonal antibody. So IL 5 is very important for eosinophils, for activation of maturation. And as a result, inhibiting IL 5 technically should help with the symptoms of asthma as well as potentially CRS.

And so we know that there's a lot of promising research in asthma and has been approved for asthma, but as far as polyps we don't know that yet. There are a couple of studies that show that there is a positive effect of mepolizumab in treating polyps, that it can decrease polyp score. But however, this study done by the same group in Belgium showed that there was no significant difference in symptom scores. So that is a little bit conflicting. And so we need more research in that area, as well.

The most common side effects that have been reported are quite minor as you can see here, headaches, and injection site reactions, and perhaps a slight immunosuppression. So we see herpes zoster occurring and a couple of patients. The most important thing I think for the future for biologic therapies are that we need biomarkers. We need to determine which patients would be good candidates for these drugs. And that means that we need to identify particular perhaps eosinophil counts that can tell us whether a patient would be a good candidate versus a poor candidate. And there have been studies in asthma that show that patients who have high eosinophils, for example, have better outcomes compared to those who have low eosinophils for mepolizumab treatment.

And finally, the dupilumab is, I think, one of the most promising biologics for the treatment of asthma, also atopic dermatitis and chronic rhinosinusitis. We know that IL 4, 5, and 13, as I mentioned, are critical cytokines in the pathogenesis of these diseases, these TH2 type disorders. And IL 4 and 13 are important for the eosinophil trafficking to the sites of local inflammation. And I think that's why blocking these two cytokines have been much more effective, because we know that chronic rhinosinusitis and polyps, for the most part, it is a local process mediated by a systemic immune dysfunction, but the actual blocking of those cytokines at the local level seems to be quite effective.

The way that this medication works, it inhibits IL 4 and 13 by binding to the IL for receptor. And it binds very specifically to the alpha subunit. As a result, it can block both IL 4 and 13 at the same time. So studies that have blocked IL 4 and 13 independently have been disappointing, but you have to block both in order to have the desired effect.

And there have been studies very rigorously done that have showed that dupilumab is very effective for persistent asthma with elevated eosinophils as well as in atopic dermatitis. And dupilumab is actually approved already for atopic dermatitis and probably is going to be approved for asthma in the winter, which is soon.

And the final paper that I really would like to talk about that is I think one of the most important papers for the biologic therapeutic for CRS is this paper on subcutaneous dupilumab and nasal polyps published in JAMA. And our site was one of the key sites, as well, for this phase II study randomized, double blind, placebo controlled trial. And there were 13 sites overall across the US as well as in Europe. And we were able to recruit 60 patients with and without asthma. And they had to have failed nasal corticosteroids and have severe symptoms as well as objective findings of severe polyposis.

So these patients were treated with dupilumab weekly, it's like an allergy injection for 16 weeks. And the primary endpoints, as I described in the other studies with mepolizumab and omalizumab, were looking at polyp scoring as well as symptoms such as loss of smell and as well as overall quality of life. And they met all the primary as well as secondary endpoints. It was quite effective.

So the yellow line is the dupilumab. The other line, the darker line is the placebo. So for nasal polyp score, you can see the dupilumab was significantly effective. This is a peak nasal inspiratory flow, it's showing how much air is flowing through the nose. That the treated group had much better airflow through the nose. SNOT 22 scores the severity of symptoms that dupilumab had significantly decreased SNOt 22 scores, and patients are able to smell again even at the eight week mark for dupilumab compared to placebo.

And then I'll skip through some of these other slides. But in general, dupilumab has been the most successful as far as that I can tell for the treatment of polyposis, and it might be that IL 4 and 13 are very critical in the pathophysiology of CRS. I'll show you one slide that really says it all. This is one of my patients who had complete blockage of all of his sinuses, had not been able to smell, or taste, or breathe for about 10 years. And after treatment with dupilumab, you can see his post-op-- not post-operative, but actually post-therapy CT scan. And he could-- all of his symptoms went away. He could smell, he could breathe, he could taste, and he hadn't been able to do that for a decade or so.

SPEAKER: So I have to interrupt you there. So what was the duration of time that that treatment required? Because that's dramatic changes on that CT scan. How long did that take?

STELLA LEE: So the patient told me that he could tell the difference even after the first injection. But I think that CT scan was done at the 16 week mark, so it was at the end of the study.

SPEAKER: So four months.

STELLA LEE: About four months.

SPEAKER: That's still dramatic.

STELLA LEE: Right. But even at the eight week mark, you could see that there was a difference. People smelling again, and tasting, and all their symptoms improving.

SPEAKER: Neat.

STELLA LEE: So dupilumab, in conclusion, showed improvement to endoscopic, radiographic, and symptoms scores. And also as we know in the New England Journal paper that it was able to help improve lung function, as well. And there are several other drugs that we're working on that are more small molecule drugs, but I won't go into them in further detail. Just to give you an overview that we are working on other novel therapeutics that can potentially target CRS inflammatory biomarkers and hopefully help improve polyp scores, as well as patients' quality of life.

And this is a medication called dexpramipexole, which is a small molecule drug that shows that it can significantly decrease eosinophils from baseline. But unfortunately, these are the patients, only one patient really had a significant improvement. These are individual patients that we're looking at. This particular patient had a dramatic improvement, and this goes back to why it's so important to understand which patients might be a candidate for a particular drug and some patients might not respond.

And finally, the last drug I wanted to mention is a drug called AK 001, doesn't even have a name yet. But it's a monoclonal antibody directed against siglec 8. So this is a member of a CD 33 related family, it's also called sialic acid binding immunoglobulin like lectin. It's interesting it's restricted to mast cells, and eosinophils, and mature eosinophils specifically. And so the hypothesis is that if we target these particular cells and inhibit mast cells as well deplete eosinophils that we can really get an improvement in patients' quality of life and ability to decrease inflammation.

So as of now, the recruiting has been done for the study. And we have about 70 patients, and we're looking at all of these primary and secondary endpoints. But we are still analyzing the data. Lot of promising-- I think there's a lot of promise in these drugs, and it's in a very exciting time for biologic therapies. But there are these implications for chronic rhinosinusitis therapy. As far as will there be long term side effects, we don't know that yet. And how do we decide whether a patient will benefit from the surgery versus a biologic therapy? That question still needs to be answered. We need to do more comparative effectiveness studies to really delve into those questions. And so which patient populations would most benefit from these drugs?

And finally, as of the current time, we take these patients who have the most refractory disease to surgery and then we treat with topical steroids. But should we be as aggressive in our surgical approaches, we need to really consider the ciliary and olfactory reserves that these patients have. Because when we're doing very ablative surgeries, they may destroy cilia and nerves that can maybe regenerate and potentially be functional with biologic therapies in the future. And biomarkers and patient selection are critical.

And I think understanding the pathophysiology of CRS makes all of this possible, that we really have to do more research to understand which pathways are involved in the inflammatory process, and how we can potentially block those areas that are causing the uncontrolled inflammation, and hopefully provide a better and novel therapeutics with less side effects for patients. And I'd like to acknowledge my collaborators. BJ Ferguson was one of our collaborators here who was really instrumental in helping to bring the biologic trials to the University of Pittsburgh, as well as our collaborators in Belgium and locally. Thank you.