Hi, my name is Paula Busse. I am an Associate Professor at the Icahn School of Medicine at Mount Sinai in New York City. Today's presentation is going to be highlights of several of the abstracts that were presented on hereditary angioedema, which I will refer to as HAE, at the 2022 American Academy of Allergy, Asthma, and Immunology (AAAAI) annual meeting.

Before I start the presentation today, I'd like to give a little background about hereditary angioedema, or HAE. It is a rare autosomal dominant disorder and it presents with recurrent and unpredictable episodes of angioedema or swelling. The swelling can be in different parts of the body, the extremities, abdomen. It also can occur in the airway, which can be potentially life-threatening if not treated.

As you can well imagine, these episodes of swelling have a significant impact on patient's quality of life. HAE can be divided into several subtypes. HAE, type one and type two, are due to a dysfunction in the C1-inhibitor protein. The C1-inhibitor protein is important to prevent the development or the production of bradykinin, which produces vascular endothelial leak and swelling.

There is another subtype of HAE, which is called HAE with normal C1-inhibitor. We are learning some of the underlying genetic features of this disease, but we also believe that in some patients it involves excessive bradykinin production, and in other patients with HAE with normal C1-inhibitor disposed, normal C1-inhibitor endothelial dysfunction.

Over the past 10 years there has been significant improvement in both the treatment of acute attacks, as well as prophylaxis to prevent attacks. The abstracts I'm going to present were presented at the 2022 AAAAI meeting, which occurred February 25th through 28th in Phoenix, Arizona.

The abstracts have been published in the Journal of Allergy and Clinical Immunology. I've grouped these abstracts into several different categories.

The first category is about updates on newly approved medications. Four abstracts of the AAAAI on Lanadelumab. Three were based upon the EMPOWER observational study and one was based upon an open label extension of the original HELP Phase 3 study.

As a background, Lanadelumab is a subcutaneous plasma kallikrein inhibitor, which has been approved by the FDA for prophylaxis of HAE attack. It was approved by the FDA based upon the pivotal HELP Phase 3 phase double blind placebo control study, in which the primary outcome was the reduction in monthly attack rates. The FDA approved the medication, or Lanadelumab, at 300 milligrams every two weeks. And if patients were doing well after six months, they have the option to extend to every four weeks.

There were three abstracts discussing the EMPOWER observational study. The background of this study is that there are, to date, 93 participants in the US and Canada, and they are patients with type I and type II HAE. Patients were categorized into two populations. One described as new users of Lanadelumab. At the time of enrollment, they had used fewer than four doses, and these were 15 participants.

The other group of patients were established users who had used more than four doses at enrollment, and there were 78 participants in this group. Outcomes are collected every six months. The outcomes that are collected are the rates of attack, the AE qual, which is a measure of angioedema associated quality of life, treatment satisfaction and the characteristics of patient's comorbidities. At the AAAAI data was presented on some of the interim data collected at the 12-month period. These are the findings.

So as I mentioned before, the EMPOWER study is an world. So for the patients, prior to starting Lanadelumab, many of the patients used plasma drive C1-inhibitor for prophylaxis, nearly 50% in the new users, and about 11.5% in established users.

Of note, less than 3% of established users used androgens prior to starting Lanadelumab. The treatment intervals, as I had mentioned previously, the FDA has approved Lanadelumab every two weeks with the option to extend to every four weeks, 100% of the new users, and 81.8% of established users, at this time point were using land every two weeks. The remainder of the established users were using it every four weeks. Six of the established users discontinued Lanadelumab, but none due to adverse events.

Other results, which were published at the AAAAI meeting from the EMPOWER observational study, is saying that many of the data which have been reported in the EMPOWER study are similar to what was found in the pivotal health study. The most common AEs have been infections. 2% of patients have reported serious adverse events, and none have been related to Lanadelumab. The mean attack rate has been a reduction in about 83.3% of monthly attacks from starting therapy at baseline to the time of collection of data.

Also, many of the data which was reported was based upon patient reported outcomes. Patients, similar to the pivotal trial, the HELP study patients have reported better quality of life based upon the AE qual, which is the angioedema associated quality of life. Patients also have been reporting improved angioedema control and improved satisfaction with treatment. Again, this data is similar to what has repeated before and is mentioning what's happening in the real world.

The last abstract that was presented on Lanadelumab was based upon the HELP and the HELP open label extension post-hoc analysis. In this abstract, they looked at patients who had previously taken androgens for prophylaxis compared to the larger study population. As a background, androgens many years were used for preventative therapy that really have fallen out of favor because of the adverse side effects that they pose and, also, that they don't tend to be all that effective. What this study is reporting is that regardless if patients have started on androgens or were on other prophylactics, they had a similar reduction in their HAE attacks after starting lanadelumab.

The next group of abstracts were focused on berotralstat. First, I'd like to give a little background of the medication. This medication is a oral plasma kallikrein inhibitor, which has been approved for prevention of HAE attacks. And this was based upon the Apex 2 study. In this study, patients from week zero to 24 took either two doses, either 110 milligrams or 150 milligrams every day or placebo.

And, at week 24 to 48, the placebo patients were randomized to either 110 or 150 of the study drug, whereas the other actively treated patients were continued on their original therapy. As I mentioned before, it was approved by the FDA. This was a novel therapy because this is an oral preventative therapy and although the androgens are oral, this has many fewer side effects. The most common side effects tend to be abdominal pain, vomiting, diarrhea, back pain and reflux disease.

There were three abstracts presented at the AAAAI on the extension of the Apex 2 study at the 96 weeks, so from week 48 to 96. This slide demonstrates here the background of the study showing the data were presented at the AAAAI. And these were a total of 21 patients who received 150 milligrams of study medication. This is the dose which has been approved by the FDA.

Patients where in this group were categorized based upon whether they had their attack reduction was less than 50% in the initial portion from weeks zero to 24, over 50% in the weeks zero to 24. And in those patients who had more than a 50% reduction in attacks, those were sub-classified into patients who had more than 70%.

This is the data which was presented at 96 weeks. As you can see in the figure to the right, the Group A is the patients who had a little bit of a slower onset on reduction of symptoms at the initial baseline to week 24. And then you can see in the green and the orange lines, the patients that had more than a 50% reduction at the initial study onset, and those patients in the green who had more than a 70%.

The findings of this study from 48 to 98 weeks was that, regardless of the onset of improved symptoms, at week 96 patients had similar reduction in symptoms. So this was regardless of the baseline frequency of attacks. A third abstract focused upon the long-term treatment upon the quality of life. Again, similar to this prior studies, from week 48 to 96 medication continued to improve quality of life.

The next group of abstracts focused upon pipeline therapies for hereditary angioedema. The first, there were two abstracts presented on donidalorsen. The background of this medication is that it's an antisense oligonucleotide targeted to reduce the hepatic or liver production of prekallikrein, which is a precursor to bradykinin. There were two abstracts presented on the phase 2 study results, which have recently been published in the New England Journal of Medicine as a full manuscript.

The study design is that patients were randomized to the one to receive 80 milligrams of study medication for placebo. Participants received study medication or placebo every four weeks for a total of 12 weeks. Participants were diagnosed with hereditary angioedema with dysfunctional C1-inhibitor. The results of the study demonstrated that the study medication was rapidly absorbed into systemic circulation. As plasma bradykinin is difficult to measure, they measured surrogate markers to demonstrate that plasma bradykinin was significantly reduced. It was significantly reduced after two weeks of the first injection.

It peaked at day 85. The markers that were used were the PKK, PPA and cleaved high molecular weight kininogen. From day 85 onward, no HAE attacks were reported by participants receiving study medication. Of note, those patients who received study medication also had a significantly improved quality of life using the validated AE qual.

In a third abstract focused on this novel therapy, was based upon a smaller study of three participants with HAE with normal C1-inhibitor. This is novel also because few studies have focused on this subgroup of patients with HAE. Much like the other study design, patients received 80 milligrams of study medication. There was no placebo. What was reported was the mean decrease in monthly attack rate from baseline to treatment of over 75%. The study medication was well-tolerated without severe adverse events.

This next pipeline therapy, which it was reported at the meeting, was the KVD900. There were two abstracts presented on the phase 2 clinical trial, which were presented based upon data studied in patients with HAE type one and type two. As a background, KVD900 is an oral plasma kallikrein inhibitor for treatment of acute attacks. The prior study we talked about was a prophylactic.

This, the study design, was there were two parts. Participants received a single dose of 600 milligrams in clinic and PK values reflected. Then participants went to a double blind placebo control crossover study, where they used study medication or placebo in a blinded fashion to treat acute attacks.

The results of the study are as follows. The plasma, there was rapid absorption of the oral medication. The plasma prekallikrein activity was inhibited more than 50% within 15 minutes of administration. There was near complete inhibition of plasma kallikrein activity within one hour. This inhibition was maintained for over four hours after dosing.

In terms of how the medication impacted attacks, this was studied by time to symptom relief, measured by the patient global impression of change, as well as a BAS score for completed attack resolution. And again, there was significant improvement in time to symptom relief with the study medication compared to placebo.

Clinical pearls, or summary of what was presented. In regards to medication which has been approved by the FDA, Lanadelumab is a background. It's a subcutaneous prophylactic therapy. In the observational study the mean decrease in attack rate in the real world was similar to patients newly starting Lanadelumab compared to established patients. And this was similar decrease in attack, which was

found in the original pivotal trial. Similar to the pivotal trial in the real world, the quality of life improved with treatment. And again, regardless of what patients were taking prior to Lanadelumab, particularly if they were taking androgens, the improvement in symptoms with Lanadelumab was the same.

Berotralstat is an oral prophylactic treatment for HAE. In the studies, the initial studies were studied up to week 48. At the AAAAI, data was presented from 48 to 96 weeks. What was notable was that those participants who may have had a slower onset to improvement of their symptoms, by 96 weeks had similar reduction of symptoms as other subjects who had a faster onset to symptom relief.

This long-term prophylactic treatment also continued to improve quality of life in HAE patients. The pearl from this is that initially, if you have patients that don't respond quickly to this new medication, they may need additional time to achieve full benefit.

The next group of abstracts were on novel therapies. One is the donidalorsen, which is a phase 2 study, which is a prophylactic sub-q antisense oligonucleotide to inhibit the liver production of prekallikrein. It is administered every four weeks. In this study in patients with HAE with C1-inhibitor, there was significant reduction of bradykinin expression as measured by several surrogate markers of bradykinin. By day 85, no participants received active medication had attacks. This was also associated with a significant improvement in angioedema associated quality of life.

There was a third abstract that was an open label study of patients with HAE with normal C1-inhibitor, which also demonstrated a 76% reduction in attacks and was well-tolerated. This study was novel in that it was looking at participants with HAE with normal C1-inhibitor.

The other pipeline therapy, the KVD900, it is a phase 2 study. It is an oral plasma kallikrein inhibitor for acute attacks. This is novel as we don't have any FDA-approved medications for acute attacks, which are oral.

In the studies that were presented, it demonstrated a rapid plasma kallikrein. In addition, and this was associated with early reduction of symptom attacks as assessed by the patient global impression of change and CAS. The patient global impression of change was also demonstrated to be effective tool to monitor prediction to response of the study medication.

Thank you again for participating in the CME approved activity. I hope that you found this information interesting and applicable to your clinical practice.

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