Transcript Details

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Future-Proofing in HAE: Advances in Long-term Prophylaxis to Prevent Attacks and Improve Quality of Life

Announcer:
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Dr. Riedl:
All right, so let’s jump into a little content here. And, again, we’re going to ultimately focus mostly on preventative therapy, but let’s first talk about HAE in general to provide some context. Many of you are familiar with this condition, but just to, to level-set the conversation, this is a very, a rare medical condition, a genetic condition that causes angioedema without urticaria. And of course, in allergy practices, we most—we see a lot of hives. This is angioedema without hives. We don’t know the exact prevalence of HAE, but most of the epi studies suggest it’s right around 1 in 50,000, and we know, of course, that it affects the skin, the GI tract and the airway.

Now, as I mentioned, this is a genetic condition, and it often, but not always, has a positive family history. It is autosomal dominant, and that’s important because, if you identify a patient, there’s a 50/50 chance that their offspring will inherit this genetic trait, and most patients that inherit the, the gene will be symptomatic. There are rare exceptions of asymptomatic patients. There’s a couple of subtypes of HAE, as you know. HAE Type 1 and 2 are most common and result from either deficient levels of C1 inhibitor or a C1 inhibitor protein that’s dysfunctional because it’s, not folded correctly due to the mutation. Don’t forget there is this very rare condition called HAE with normal C1 inhibitor where the complement labs will all be normal, but the patient has all the signs and symptoms, of HAE, that we’ll talk about. We don’t understand HAE with normal C1 inhibitor very well, and it’s a tough diagnosis to make because we generally lack biomarkers, although there have been some progress in the genetics of HAE normal C1 inhibitor.

Now, HAE recall causes these very severe and, and typically prolonged angioedema symptoms. They, they take generally 12 to 24 hours to hit their peak, and they last, up to five days if they’re not effectively treated. HAE, of course, does not respond to allergy medicines, like antihistamines, corticosteroids or epinephrine, which is pretty much the reason we’re here talking about this. HAE requires a very different set of therapeutics, a different treatment plan from the much more common mast cell mediated swelling that we may see. HAE is terribly unpredictable, and this is one of the major burdens, because patients can’t predict when and where these attacks will occur. There are some known triggers. Estrogen, can trigger HAE attacks. ACE inhibitors, of course, are contraindicated. And we know that trauma, either physical or psychological trauma or stress, can be strong triggers in, in some patients. But most attacks don’t have a clear trigger. They appear to be random. They’re unpredictable. And this is a really a huge burden on patients and their families.

The other issue with HAE is, of course, the variability, and that, that can relate to the frequency of the attacks, the types of attacks that occur. We know that the majority of attacks are either skin or GI, and skin attacks can hit anywhere but the face. The extremities are very common sites. You see genital attacks here. These are actually pretty common. Patients won’t talk about this because it’s embarrassing to them, but if you ask patients, many of them have urogenital involvement when they swell. GI attacks, of course, are very painful, disabling and disruptive. Before we had, treatments or even imaging, many patients historically were taken to the operating

room because the abdominal pain was so severe that the surgeons did exploratory laparotomies, due to the severity of the pain. Airway attacks, fortunately, are, are much less common than these other types but are very serious. The mortality rate for untreated HAE attacks historically has been as high as 30%, and so this is something we worry about. We counsel patients about the, the threat, and the unpredictability of airway events. And there are some prodromal symptoms that can precede the actual swelling. You see them listed here. Erythema marginatum is probably the most specific, the sort of lacy, serpiginous red rash that occurs often a few hours before the actual angioedema. Some patients will mistake this for hives. They'll tell you they have hives, but if you saw it as a clinician, you'd say that, that looks different than urticaria. But at any rate, that, that can be quite specific for HAE attacks. These others tend to be a little more nonspecific and vague and, and maybe not as good of predictors, but some patients have very reliable prodromes, which can be useful in anticipation of, of needing, their acute treatment.

Now, not surprisingly to any of you, HAE has a huge impact on health-related quality of life, and there are many studies showing this. This is just a single study of, of 90-some patients using a validated, tool, the EQ-5D-5L, which is, of course, a health-related quality of life, a snapshot in time of their, of their health, quality of life. And you can see, between attacks, this population was pretty comparable to the normal population in the US, but, if you look at when they have swelling, you see this dramatic decrease, not surprisingly due to the pain and disability of these episodes. And of course, the more severe the attack is, the more it impacts their quality of life. So this just shows that, these attacks do have a huge impact on, on people, and in fact, there's some association with poorer outcomes if you delay that on-demand therapy, which is why there's a huge emphasis in the, in the guidelines to treat attacks early, with an effective, HAE-specific medication.

Lots of data and studies showing that HAE, at least historically, has been associated with anxiety and depression. We're hoping this changes as we manage it better, but this is, in fact, reality up until this point that these threat of, constant threat of unpredictable symptoms really weigh on people. It's a huge emotional burden. It affects their work. It causes social isolation. People, in fact, miss work, they miss school, and, and it has been shown to have a negative impact on their, career trajectory, on their educational attainment. These studies here, you can see, look at anxiety severity or depression anxiety. I'm sorry, depression severity. And what I'll point out is that, of course, the more severe your anxiety or depression, the more impaired you are when it comes to work, productivity and activity impairment. But it's not just missing work. You see absenteeism is affected a little bit, but the other domains—activity, work productivity, presenteeism. So you can show up to your job or your school, but you don't get much done, and you're not very productive. And again, this is sort of a constant, even outside of the attacks, a, a chronic issue that HAE patients have, have dealt with. It, of course, affects their ability to travel and do other things, other activities, with their family as well.

And so recognizing there's this burden, a lot of focus is on our—with our therapies has been, can we reduce the burden of HAE? And we have made progress. Some of these measures have been built into clinical trials, and we're extremely grateful for the progress that's been made. However, as recently as 2023, this is some data presented by Stephen Betschel at the European Academy of Allergy meeting showing that as recently as a couple of years ago, patients still had, issues. They still, had burden on their daily activities despite having HAE on demand and prophylactic therapy. And you can see here, over 90% of patients alter their plans after an attack. Over 90% don't feel like themselves due to their HAE, and over half had their travel, work, and social activities, affected by the condition. So while there's been a huge amount of progress, we're not quite there yet. We haven't truly normalized people's lives, with—even with the advances we currently have in our toolbox to manage the condition.

So let's revisit one of our questions. Which patient-reported concern is most commonly cited as a primary contributor to decreased quality of life in individuals with HAE? Same answers as before: is a concern over the genetic transmission of disease, fear of spontaneous attacks interfering with activities, dissatisfaction with prophy medication adverse effects, or the financial burden of diagnostic testing. Would you answer this the same or differently from your previous response? And we'll have a look at the answers. Great. And I do think this is the best answer. I think most of you answered this to begin with, but this is really—of these concerns, this is the one we hear over and over in the research looking at, at patient concerns. If we just kind of look at these answers quickly—again, as I've said a couple of times now—it's this unpredictability that, that really drives the anxiety, the depression, the interference with work, school and other activities.

Now, A is absolutely true. Patients are worried about transmitting this to their kids. It's one of the things we, we haven't been able to fix with—even with our therapeutic advances. It's still a genetic condition that can be passed on. The dissatisfaction with prophy medicines, fortunately, these medicines have been quite safe in general. There are some side effects that we'll see when we go through the clinical trials. And some patients may be dissatisfied with that, but that's not been probably the major concern. And then financial burden is always a concern, probably not so much related to diagnostic testing, but certainly when we talk about management, the cost of medications and so forth, that does become a, a major issue for, for many patients. So probably not so much in the testing—could be—but more with the therapies that we are using to manage, HAE.

All right. So let's talk a little bit about now the treatment strategies. And, and, and of course, we'll try to keep this patient-centered because we have to work with our patients to develop the best plan, for each of them. As you will recall, we have kind of these three strategies that we use to manage hereditary angioedema, and first and foremost, on-demand therapy. This is medication, of course, used to stop an attack at the time it occurs, and this is necessary for all patients. We have a rule at our center. No one that has a new diagnosis leaves the office without a plan and a prescription for a rescue medicine, because again, you just don't know when and where these attacks will hit, and they can be life-threatening. The guidelines recommend that patients have enough medication to treat at least two, HAE attacks, so on-demand therapy for everyone.

We won't spend a lot of time on short-term prophylaxis, but recognize this is important to mention to patients because this is short-term treatment used, before an event or a timespan where we might expect a high risk of attacks. Most commonly, we talk about surgical procedures, intubation, dental procedures, because we know, that can trigger HAE symptoms. Sometimes, though, we're talking about situational prophylaxis, which kind of refers more to life events, and this could be, you're getting married; you have a, a big final exam; you have a vacation that, that you don't want to have screwed up by an attack. And so there may be short periods where we use prophylaxis but not necessarily for medical procedures, and so that, that's important to recognize. But we need our patients to know about this so they inform us about these important either procedures or events, and we can help them, get through that, hopefully minimizing the risk of HAE.

And then long-term prophylaxis, which is just what it sounds like, this is medicine, of course, taken regularly to decrease the frequency and the severity of these attacks, ideally prevent them entirely, although that's certainly not true for all treatments and all patients. But a lot of our efforts in recent years have been in this long-term prophylactic domain, because it can potentially, get the patient closest to, to normalizing their life, to putting HAE kind of in the background. May not be used in every patient, but increasingly we're seeing patients migrate to preventative treatment, and I think that makes sense. That's sort of the evolution of medicine. Why, why wait to get sick if you can prevent the condition from making you ill in the first place? And as we walk through this, just remember, we have some choices now, so individualization has become a buzzword, like it is for a lot of the things we treat, trying to tailor the treatment plan for each, individual patient.

Now, as we choose therapies and, and make decisions with our patients and their families, there's a lot of factors to consider. You see attack data on here a lot, attack frequency, location severity, and absolutely that's important. It's what we've always focused on because that's the major symptoms of the, of the condition, these attacks that we're trying to navigate or prevent, but recognize, as we've evolved, there are other factors. It's not just about attacks. It's about quality of life, as we've talked about. It's about the patient preference and, and what's going to work best for their goals and their life. It's about resource availability. So while attacks are important, I would say we don't want to exclusively focus on that. Don't forget about these other important considerations as we put together management plans.

And we've gotten better at measuring some of these other factors. There's actually a slew of, of tools now that have been validated. You see some of them here. And of course, you're not expected to read this fine print, but some of these look at the activity of the angioedema attacks. Many of them incorporate quality of life measures. And I just draw your attention to that third, panel over. That's the Angioedema Control Test. It's four questions. It's very quick and easy for patients to fill out before they see you, while they're waiting to see you, and it's analogous to the Asthma Control Test that many of us are familiar with, but it's been validated. If you score 10 or higher, that's considered to be well controlled. If it's lower than that, we have some work to do. And so it provides another angle, another snapshot that we can look at and use as we have visits with our patients. Do we need to make changes, or are we accomplishing our goal in terms of controlling the angioedema condition?

Just a few words about on-demand therapy and short-term prophylaxis, and then we're going to turn to long-term prophylaxis. So again, on-demand therapy, can never overlook this because we don't have perfect preventative measures yet. The recommended effective HAE meds are listed here: Icatibant, ecallantide, IV C1 inhibitor. Many of you know there was an oral on-demand HAE medicine, FDA approved a few months ago, sebetralstat. If you don't have access to those or patients don't have access to those, you can consider some of these second and third-line therapies, recognizing they have not been proven to be as effective or as safe, as those first-line treatments. And just a reminder again, ideally, patients have enough medicine to treat at least two attacks because these are unpredictable and because they may have a second attack before they get their medicine refilled after treating an attack.

Short-term prophylaxis I mentioned. Again, mostly, we, we need to hear from our patients when they're going to have procedures that can trigger attacks. IV plasma-derived C1 inhibitor is considered first line. This is based on retrospective data. We do not have, rigorous prospective data, but the retrospective data we have points to IV, C1 inhibitor being the, the most protective or the most effective for short-term prophylaxis. Again, you see some second-line agents there, recombinant C1 inhibitor, FFP, androgens, which could also be used and, and are likely to be beneficial in terms of preventing attacks, during procedures or other events that may trigger HAE.

Let's turn to long-term prophylaxis, or LTP, now. And as I mentioned, there's been a lot of action in this area in recent years, primarily because it is best suited to reach this goal, that's listed in pretty much every evidence-based guideline, that goal of disease control and, and aiming to normalize patient quality of life. As I noted, perhaps not every patient, needs or elects to go on long-term prophylaxis, but we are seeing more and more patients move in that direction. Certainly, the more frequently patients swell, the more severe attacks they have, the more complications they have. That's a patient where we need to strongly be considering prophylactic therapy, but we have to tailor it to our individual patients.

And as I already mentioned, we've got effective options. I'm going to show you the data on our current options for LTP, but there continues to be work going on in this area because, as we already talked about, there are even very recent studies showing that patients are still not quite, meeting their goals, or the treatment that they're on is burdensome. There is a burden of treatment that's actually interfering with their, life or their quality of life, and so I think we'll continue to see some evolution in advances in the coming years. And I'll show you a little bit of data on what's in the pipeline, that might help us to, to better reach these goals, reduce the burden of HAE, but also hopefully reduce the burden of treatment.

So let's very quickly—it's going to be a whirlwind—but let's talk about some of our options for long-term prophylaxis. This is data on C1 inhibitor for LTP of HAE attacks, and as you know, C1 inhibitor has been around for many years, approved in 2008 as an IV, prophylactic treatment, and then a significant advance in 2017 with subcutaneous, C1 inhibitor approved, for long-term prophylaxis. And as you can imagine, we've really, really moved towards the subcutaneous route, not only because of the advantages of, of how it's administered, but the efficacy data is—looks better for subQ C1 inhibitor. And you see these studies. I'll draw your attention to this box, in the middle of the chart, which shows the mean reduction in HAE attack rate, 84% compared to placebo for the subQ C1 inhibitor, 50% in the pivotal trial for IV C1 inhibitor, so these are effective therapies, have generally been very safe. You can see there are some AEs listed there. These are generally, infrequent, and so this is a very effective and has historically been a very safe option for patients.

A significant advance in 2018 when lanadelumab as a monoclonal antibody that targets plasma kallikrein was, was approved in the United States. This is, as you know, administered subcutaneously, generally started at 300 mg every two weeks, but can be shifted to 300 mg every four weeks if patients have an excellent response to the treatment. I'll just point your attention here to the right column in the orange. This is the starting dose, the highest dose of 300 mg every two weeks. You don't have the percentage here, but this was about a, about a 70, I'm sorry, about an 87% reduction, in, mean reduction in attack rate compared to the placebo, so again, a highly effective, medication now given every, two to four weeks.

These are the safety data from the pivotal trial and again, this has generally been a very safe medication, no serious AEs. You can see the most common, adverse effects, were injection site pain or reactions, somewhat higher compared to the placebo, but otherwise a, a very favorable safety profile for lanadelumab.

And here's some, real world efficacy data. This is a phase 4 trial data where patients were treated for up to 36 months, just to show that this efficacy is maintained, and you can see this 85%, mean reduction in HAE attack rate, over this very prolonged treatment period of about three years. About half of the patients reported some, some AEs, but most were mild or moderate, and so evidence of a durable efficacy for this treatment in preventing attacks.

The next advance came along in 2020, and this was berotralstat, which was an oral, targeted drug, an oral plasma kallikrein inhibitor. There's been considerable interest in, specific oral medications in HAE. And this pivotal trial on the left showed at the highest dose of 150 mg once a day, a 44% reduction in the mean attack rate. So in the population, not quite as high as we're seeing with the subcutaneous drugs, but much more variability. And there are patients in—if you look at the, the subset of the responder analysis, there are patients where this, drug is, is very effective. That was also seen in a significant reduction in HAE attacks that required, treatment with this once-daily oral medicine. Again, this has been a very safe medicine. We had long-term efficacy and safety, data from this, open-label, study. And, and again, you can see here out to 96 weeks this significant reduction in HAE attack rate. This study over 96 weeks also demonstrated the safety of the medication with no major safety concerns.

I will point out, there, is—there was diarrhea in about 15% of patients, and this has been something we discuss with patients because, a subset of them will develop, um, some GI side effects. These are usually mild to moderate and manageable. It's been fairly rare for people to discontinue due to that. It generally, decreases over time, but, but this is, a little bit of a unique, adverse effect in a subset of patients with the oral medications that we should certainly be, discussing and helping our patients manage through if, if they elect this as their long-term prophylactic therapy.

All right, now we're up to the present year, 2025, and we've seen a, a couple of additional long-term prophylactic options, approved by the FDA, one of those being garadacimab. This is a monoclonal antibody targeted at Factor XIIa. And recall, Factor XIIa sits up top of the contact system, the kallikrein-bradykinin system, and so this has been a useful target for HAE prophylaxis. You can see in this

phase 3 study of, of garadacimab given subcutaneously now once a month, that there's this significant reduction, 87%, mean, reduction in the mean monthly attack rate, and so very strong efficacy. On the right you see a responder analysis, and I'll point out here, the far right, the orange bar, 62% of the patients receiving the active treatment were attack-free, during this, six-month study where only 8% of the placebo were attack-free. This attack-free status is something we're thinking about more often. Again, can we completely, prevent attacks? It's not attainable in all patients but increasingly being looked at in studies as, an outcome, and so, that was, interesting to see in this particular trial.

Again, if we turn to safety, garadacimab has been, quite safe and tolerable. You can see some of the side effects here in, in low numbers of patients. And in fact, the injection site reactions were quite low, in this particular trial. You see over here AEs of special interest. Because Factor XII has a role in the coagulation system, there's been a very close eye on things like, bleeding or clotting, and fortunately, there have not been any signal, or events of, of concern, for these, areas of special interest, so that's, been reassuring both in the pivotal trial and now in, in open-label extension studies. And here is some of that open-label efficacy and safety data. Again, for patients that were on, 12 months of treatment, you can see this consistent efficacy, a responder analysis showing somewhere between 50 and 63% of patients were attack-free, during this open-label trial. And again, the safety data set is fairly reassuring. You can see the injection site reactions are a bit higher, though we don't have a comparator group in this open-label trial, and then low levels of things like headache, and nasopharyngitis.

And, and this is some quality of life data. Again, as you probably know, this has been integrated into most of the, the clinical, development, programs now because we, we want to measure that. We want to know that these medications not just prevent attacks but improve quality of life. What's interesting about this is you can see, in these cohorts, so attack free, and one or more attack during the study period, in, in groups that were either naive to garadacimab or had previously been on garadacimab. And what I'll point out is lower is better here for AE-QoL scores. You can see the significant difference from baseline to treatment. The minimally clinically important difference here is six points, so you can see it far exceeds that from baseline to treatment, but there's also a difference in patients who are attack free compared to just even having one attack. And so, you know, 23 down to 8, that's, far more than 6, and same over here, 19, down to 8; so again, this idea that being attack-free does have benefits, when you measure quality of life, even to having a rare attack, here and there, and that's something we continue to kind of look at in trials.

All right, the other major advance this, this year, has been the approval of donidalorsen, and donidalorsen has a unique mechanism of action. It's not unique in medicine. It's been used in other areas, but it's unique to our field. This is an antisense oligonucleotide, so it's actually very precisely targeted at messenger RNA, in this case, in hepatocytes. This is a medication that hones into hepatocytes, very precisely, degrades mRNA for a very specific protein, and in this case it's plasma prekallikrein. If you reduce the amount of plasma prekallikrein coming out of the liver, you don't have substrate to make bradykinin, and, and this is the strategy for preventing attacks. You can see in this phase 3 study that looked at either every-four-week subcutaneous dosing or every-eight-week subcutaneous dosing, there is this, significant reduction in attack rate. If we jump over to the table, with the every-eight-week, it was an 81% reduction in mean attack rates and 55% for every-eight-week dosing. If you look at, attacks that were required treatment, it was 92% reduction for the every-four-week dosing. So again we're seeing these dramatic reductions. And what's interesting here, you see the every-eight-week dosing. The further you go out, out to 25 weeks, these lines start to converge, so based on the labeling, this is a medicine that might make sense. You, you can decide with your patients, but it might make sense to start it every four weeks and then move out eventually to every eight weeks if they're doing very well, so less-frequent dosing, less burden of treatment.

This is the side effect profile or the safety data from the, the pivotal trial, and again, very reassuring overall. You can see again the most common, adverse event reported was injection site reactions in a small subset of patients. Otherwise, AEs were, were mild or moderate, and, and generally, not much difference from placebo overall for both the every-four-week and every-eight-week dosing. And again, quality of life, important to have a look at this. You can see these significant improvements in quality of life if you look at the AE-QoL data. Again, most prominent for things like functioning, which is very important, compared to placebo. And working productivity and activity, impairment, again, these very significant reductions, most prominent for the every-four-week dosing in this pivotal trial, so people getting back to work, getting back to school, compared to those, that were, on, placebo.

Now, having said all of that, we have these, really, generally very effective tools. We have choices. How do we put together a plan for our patients? And, and this was an interesting study looking at adherence, for patients because, as it turns out, these medicines only work if our patients take them, if they only stick to the recommended schedule that, that's been shown effective. So, this is, PDC-1 is, product coverage. It basically is a measure of do you have enough medicine for the number of days that you're supposed to be treating? And it looked at EMR or EHR claims data for prescriptions. They did two different analyses in this study, so that's the one and the two. But generally, people, at least most of them, fill enough medicine for the number of days that we're trying to treat them for. You can see, depending on how you look at the data, it's either better than 90% or better than 60%. But what's interesting is it doesn't really matter if it's oral medicine or if it's subcutaneous medicine or how frequently it's dosed, which I think speaks to the fact that our patients have

different preferences in what they're willing to do or would like to do for their treatment.

If you look at persistence here, and this is did patients keep refilling their prophylactic medicine up to 12 months, and we're not surprised there's some fall-off. You start, you know, over around 70% or 80%, and by 12 months, we're 50% to 60%. But again, you don't see dramatic differences based on the actual medicine that's being prescribed, and, and so I think this speaks a little bit to the complexity of decision-making, matching a medicine to our patients' preferences. You can see here they also asked about patient factors, what was most important to them. No surprise that cost and insurance coverage is right at the top of that list, but things like convenience, administration route, and safety are very important to our patients, and so I think we need to be asking about these things because this is—adherence is so critically important. And if we make good matches with our patients, we can get most of them, to stick with their treatment and, and reap the benefits of that.

So that, that sort of brings up this concept of shared decision-making. Again, this isn't new, to those of you that, that are in clinical practice, but it's really applicable to HAE because it's so—such a variable condition, and because we have, some choices now in, in the treatments that we may prescribe. And this all starts, as you know, with discovery, listening to our patients, asking about their needs, their goals, making sure that they know that they have options. And then I think where we as specialists come in your discussion. We know the data. We know the efficacy. We know the side effects, the safety concerns. Making sure our patients have reliable evidence-based data, to match up and, and make decisions with their specific goals and preferences. And, I say I'm notoriously bad at predicting what a given patient will, will choose to do, and that's part of this conversation. I know the data, but I don't know exactly where they're coming from or how HAE may affect them.

And then, of course, we make decisions based on these conversations, and we go round and round. This is, of course, not a static condition. The, the symptoms may change, the attacks may change, life changes with things like pregnancy and work and travel and family life, and so we need to follow up with our patients and make sure that whatever plan is in place, it's actually working as designed. And, and as treatments change, we may want to adapt or adjust the treatment plan as new options become available.

So this is just kind of a conceptual wrap-up slide of this section. I think we've continued to kind of move the goalposts with HAE. When I started specializing in HAE, we just wanted to keep people alive. That was the goal. And we put them in the hospital, in the ICU. That's still the goal, of course, and occasionally, it comes to that, putting someone in the hospital, reducing their pain, reducing the mortality or preventing the mortality, but we're aiming for much more than that, reducing the disability and ultimately that goal of, of reaching a life without HAE interference.

And on the right, these are just some questions I try to ask my patients: Do you feel in control of the condition? What are the concerns you have about your medicine? Yeah, it may be working sort of good enough, but can we improve on, on the efficacy, on the side effects, on the burden of treatment in some way? And then my favorite question is, What are you not doing or not doing well because of HAE? And, I leave that open because I'm always surprised at the responses. Of course, you hear about work and relationships and travel, but certain hobbies, certain family issues, what are they struggling with? So I think leaving that latitude for patients to kind of fill in the blank and then working backwards from there, can we make a change in treatment that will allow them to pursue those goals, without HAE perhaps getting in the way or being constantly on their mind?

All right, so we're moving towards the last section here. Here's a, a, a second post-test question. You recall our 45-year-old gentleman. He's got HAE. It's generally well-controlled on lanadelumab every two weeks, but he's honest with you that he's missing some doses, sort of tired of doing these injections every two weeks. He does have some baseline GI symptoms due to IBS, and he's asking you for your recommendations. What's the most appropriate next step to improve his acceptance and adherence to an LTP strategy? So our options are encourage him to remain on his current treatment due to the favorable efficacy and safety; consider a subcutaneous long-term prophy treatment option with less frequent dosing, like every four to eight weeks; consider oral long-term treatment options; or discontinue LTP and just go with on-demand since his HAE episodes have decreased. Which one do you think is, the best advice?

All right, let's see what you think. Okay, great. And, and again, I don't know that there's necessarily a right or wrong here. I would probably favor #2, like most of you. I think he's obviously willing. He's done subcutaneous, treatments. The frequency is what seems to be wearing on him. And I showed you a couple of options, one of them being, donidalorsen, which could be dosed every four weeks, perhaps even every eight weeks. There are other treatment options that are dosed less frequently, so that might make— be the place to start. The oral treatment also would be a, I think, a good consideration. The only concern about the oral treatment is that it does sometimes have these adverse GI side effects. He's already got some chronic GI issues, and so you'd at least want to have that conversation. He might do fine on it, but that would be something you'd have to navigate as a side effect with the oral, medication that we have available currently. And finally, you know, I think discontinuing LTP might be a little misguided. You could try that, but for—he needed to be on LTP before, and generally, these people sort of go back to their baseline frequency and severity, so just going with on-demand treatment might be a little bit, anxiety-provoking. However, there, there are, you know, the new oral—the, the oral on-demand

treatment option, you know, might change the math for him somehow. So anyway, I think B is the best answer, but this sort of demonstrates we've got options. You sort of have to walk through these options with individual patients.

All right, for the last few minutes before we move to some question and answer, let me show you what's happening, in the, the pipeline, because I don't think we're done yet. I don't think we've quite arrived. We've come a long way, but a lot of efforts continue to see, can we prevent attacks either more effectively or, with less burden of treatment? And you see some of the goals here: less frequent administrations, easier ways to administer medicine, fewer side effects, or just simply taking less time out of life to deal with your HAE treatment plan. These are all goals of some of the, emerging therapies or investigational therapies, and, and this is a map, again, of the, of the contact system. Everything that we've been talking about is predicated on this understanding of, prekallikrein, kallikrein-producing bradykinin, and bradykinin, of course, causing the symptoms, the swelling of HAE.

So we've gone over some, a number of these medicines that we already have approved for use. What's emerging still are—come in different categories, and they're color-coded here. So there's a monoclonal antibody, navenibart, that has a prolonged half-life that's being developed targeting kallikrein. We have other, RNA-targeted therapies and specifically a program with siRNA. The advantage there being that you might be able to dose that once every three months, every six months, maybe even less than every six months and still, prevent attacks by preventing prekallikrein production. There are other oral medications. The one that's furthest along is deucrictibant, which is an oral B2 receptor antagonist. That's being looked at for both prophylactic treatment, but also to treat attacks. And finally, there is a, gene therapy program in human studies, CRISPR-Cas9 technology, that, that basically reduces, prekallikrein production from the liver by targeting the KLKB1, gene with a single dose, ideally having long-term preventative effects.

So let me very quickly show you some of the data so you know what's coming along. This is deucrictibant, the oral B2 receptor antagonist. This is the, preventative, long-term preventative, phase 2 study, the so-called CHAPTER-1 trial. And this is an oral medicine that in the trial was given twice a day. They now have a long-acting, formulation. So in the phase 3 study that's going on, it's dosed only once a day. But you can see this B2 receptor antagonism was very effective at preventing attacks when taken daily, and you can see an 85, mean, 85% reduction in the mean monthly attack rate compared to placebo, so right there in the ballpark for what we're seeing with the subcutaneous drugs but this time with an oral medication. Now, it's a phase 2 study. It's, it's a small group of people, and so we'll have to wait and see if this holds up in the phase 3 trial, but the phase 2 study showed very favorable safety. You can see there's really not a lot to talk about as far as side effects. One patient with headache, Sorry, that was in the placebo. One patient with, with dizziness, a patient with transient, liver enzyme increases, so, so far it looks very favorable in terms of the side effect profile. And this is long-term, safety data. Again, small numbers. You can see started with, 30 patients and is now down to, this is sort of as they go along, but there's, almost 10 patients now that have been out for about 19 months, point being that there, continue to be very strong efficacy, very strong preventative effects, and really not much to talk about in terms of, adverse events. So we'll see. The phase 3 data, will come out hopefully in the coming year, and we'll see if this is a viable option for preventative treatment.

This is navenibart. This is a YTE modified monoclonal antibody. And remember the YTE modification allows, recycling of the, the antibodies so that the half-life is much longer, so the goal here is to have a kallikrein inhibitor that could be dosed every three months or maybe even every six months and still effectively prevent attacks. Three different dosing cohorts here, either 450 once, 600 followed by 300 or 600, which is repeated 28 days later. And you can see in all three of these cohorts, small numbers of patients, but very strong efficacy, so over 90% reduction compared to their baseline attack rate with this, monoclonal antibody, and so this looks very encouraging. Again, the safety, really not much to talk about, the most common being these injection site reactions in small numbers of patients. So phase 3 study also going on with navenibart, and we look forward to seeing a larger data set to see if this is safe and effective.

The last thing I'll mention is, gene editing, and this is just a, a quick diagram, a reminder of how gene editing works, in this case, CRISPR-Cas9 technology. Lipid nanoparticles that are loaded with this CRISPR technology, targets the hepatocytes and once in there is very specific at targeting a gene, in this case the KLKB1 gene. You insert an indel, you stop the transcription or translation of prekallikrein, and so you reduce the amount of prekallikrein that makes it out into the circulation, thereby preventing or reducing the ability to make excessive, bradykinin.

And so this is the data that was published this past year, in *The New England Journal*. Again, a phase 2 study, so relatively small numbers of patients, 10 in this, 25 mg dose, 11 in this 50 mg dose, but a one-time IV treatment that you can see very effectively reduces plasma, kallikrein levels. So at the higher dose, you get these fairly dramatic reductions, 80% or greater; at the lower dose, not as robust, but you get below this 60% line, you expect to see clinical preventative effects. And that was borne out in the clinical data where there was a, a 75% reduction in attack rate, compared to placebo, the mean number of attacks per month, and a 77% attack rate, in the higher dose compared to placebo.

They now have data that they've continued to report. These patients, some of them have been out to close to three years and continue

to see this significant reduction in attack rate from this single dose. So can't say it's a cure, don't know how long it will last for certain, but it does seem to accomplish a very durable preventative effect in this small, phase 2 study. The phase 3 is ongoing, and of course, we'll look at that closely. The, the side effects here were mostly related to the actual infusion, and you can see a number of sort of side effects that were reported in, in less than, half of the patients: headache, fatigue, nasopharyngitis. I think with gene editing, of course, we're going to look at the long-term what does that safety and efficacy look like, but so far, looks encouraging. And, and again, we'll have to see what this larger phase 3 study data looks like, over the coming year or two.

So, I'm not going to have time to go into these other, early developments, in clinical therapeutics, but be aware there's siRNA therapy that has now moved into, in fact, a phase 3 study. It's revving up, RNA interference treatment that might be dosed subcutaneously every three months, every six months, maybe even less, often than that; oral therapies, including a Factor XIIa inhibitor that's very early on; and, and there continue to be interest in some other types of gene therapy or gene editing, though none of those have made it, into human studies at this point.

All right, so all that being said, I'm going to re-reask you this question. How confident are you in your ability to appraise the safety and efficacy data for emerging long-term prophylactic treatments for HAE patients? Not at all confident, slightly confident, neutral, somewhat confident, or now very confident.

All right, and we'll see if anything changed here. Okay, good. Yeah, it was a lot to cover. It's a lot to digest in a short time, but, I'm glad to see more confidence, than when you started, and, and, and that's the whole point, that, we're getting some familiarity with this data and can communicate that to our patients.

So, we're near the end. Just a few closing thoughts. I hope that I've communicated that, you know, long-term prophylaxis really is an important part of how we manage patients. We have seen advances. We have many more options than we did a decade ago, to offer our patients, but we still see, patients having attacks; we still see a reduction in quality of life; and along those lines, there is also a treatment burden that we have to be cognizant of; and so that's the whole point of talking about this and, and looking at what's new and what's emerging, that we, we still may be able to improve the lives of our patients by, by looking at their treatment plan and making adjustments. There are a lot of factors to consider. Of course, as clinicians, we always hold safety and efficacy as, as the gold standard. If a drug's not safe or it's not effective, it's not going to be, a favored, by us or our patients, but there are other factors that are becoming important, the, the administration route, the schedule, and how does a given therapy fit into our individual patient's lifestyle and preferences.

And, and I know we're all aware of this, but increasingly, we really have to engage patients. Education is important, listening to their preferences. We know they come in with all kinds of notions, from outside factors, some of which are accurate and some of which are not, and so having these discussions, making sure they have good quality information and evidence to make their choices, that's really an important role that we play, but recognizing we also have to, bend a little bit sometimes, or at least recognize our patients', values. And again, I probably mentioned this. I tell my patients, "Listen, I'm, I'm an expert in HAE. It's part of my specialty. But you are the expert in how this condition affects you, and what you're willing to do to manage your condition," and so we have to meet in the middle, to make sure that patients get benefit from all these advances that we're discussing.

All right, so I, I appreciate your attention. I hope, I hope this was interesting. We do have a few minutes for question and answer, which I'm always happy about because that's perhaps the, the most valuable part of any of this. If you have questions, please put them in the, in the question and answer section, and I'm happy to take those as they come in. And there will also be a few polling questions as I go through that you can give some feedback, as we wrap up here.

So, let me look at what we've got. Here's a really interesting question. I get this often. What level of dental procedures would you recommend using short-term prophylaxis or not? Really, a, a good question and one we don't have a lot of study data on. I can tell you that most of the data that shows a increased risk of, of, HAE attacks is for, what I would call oral surgery, so really kind of invasive tissue trauma, things like root canals, wisdom teeth extraction, or tooth extraction in general. Routine dental cleanings tend to not be an issue. I also have not anecdotally seen problems with orthodontics for the most part. Invisalign, of course, is very popular these days. Generally haven't run into issues with dental cleaning, Invisalign, orthodontics, but I think anytime that there's, a lot of anesthesia used, injections, trauma to the gums, certainly extractions, that's where we tend to get into trouble, with oropharyngeal or throat swelling, and so, I recommend short-term prophylaxis for oral surgery, those things that are more invasive.

All right. Let me see what else we have here. Can you comment on any considerations in selecting between plasma kallikrein inhibitors versus other LTP options in patients with comorbidities or unique risk profiles? So, I think this is kind of getting at mechanism of action, which I also get a lot of questions about. You know, is there a mechanism of action that's right for a specific patient or a specific type of HAE or a specific age? And I would say generally no. If—when we're talking about C1 inhibitor deficiency, we haven't really seen any

predictors of response based on levels, based on genetics, based on phenotype, if you will, and so I think it really does come down to efficacy, safety, and, and patient preference in terms of how a drug is given, and, and the dosing schedule. So I can't really say, you know, this is a plasma kallikrein inhibitor patient; this is a C1 inhibitor replacement patient; this is a Factor XII patient; this is a RNA interference patient. I would say one thing to be aware of is that with the oral medicines, there are a few drug interactions to be aware of. We've been maybe a little spoiled with protein therapeutics, monoclonal antibodies and C1 inhibitor, and even the RNA-targeted therapies that don't really have drug interactions. Now as we're getting more oral options, there are a few, drug interactions you have to look at based on CIP, inhibitors and so forth, so that's something to look at if you're prescribing oral medicines, is make sure you look at the patient's medication list, because now that's a factor that, that you may have to navigate not—They aren't common drug interactions, but they're there. But outside of that, I would say it's really mostly about the study data. How does the—well does a drug work? What are the side effects? And that's probably more critical for most of our decision-making than any known, MOA, if you will.

All right, we have time maybe for one or two more. Yeah, here's here's another good one worth pointing out. So have you had difficulties getting hospital systems to stock C1 inhibitors for unexpected acute management needs? Absolutely. This is still, this is still a little bit of a bane of our existence, particularly with the—you know, we take care of a pretty large population. It's still quite unusual for hospitals to have access to C1 inhibitors. And, you know, we're, we're fortunate in, in our hospital system where some of our patients go, we, we can sort of facilitate that, but most hospitals that we deal with for our patients that travel to see us don't have that, and so, if there's a need for rescue treatment using a C1 inhibitor, if there's a need for short-term prophylaxis prior to an unplanned surgery or even a planned surgery, we often struggle to get that in a timely fashion. So, we do often have better success, maybe not for rescue treatment because that needs to be there immediately, but if we have a little bit of lead time, we have some success getting, C1 inhibitor to our patients. We have to expedite it and through the payers, and as we all know, that's not—doesn't happen quickly sometimes, but getting it to our patients for them to take it to the hospital and then getting the hospital to understand they need to bring that medicine in if their pharmacy won't provide it. So that's why I say, especially for short-term prophylaxis, making sure our patients know, "Hey, we need a little lead time." If it's a trauma or unexpected, there's nothing we can do about that, but if there's a planned procedure, we need some lead time to get this medicine set up, ideally in your hands as the patient, and talk to the anesthesia or surgeon so they know to give this ahead of time, because to this, person's point, it's, it's unusual that they're going to have that sitting in the hospital pharmacy, and so we have to sort of, overcome that barrier.

And I would just add to that. We have very little data to know if short-term prophylaxis is still absolutely necessary for patients that are on effective long-term prophylactic therapy. Almost no study data to show if the LTP therapies we just talked about will prevent attacks during these sorts of surgical procedures and so forth. We need that data. And so, in the absence of it, we still err on the side of caution of, of trying to get, you know, short-term prophylaxis with C1 inhibitors. So, hopefully, we'll—There's been some efforts to collect that data. Hopefully, we'll know the answer to whether we need to keep doing this short-term prophylactic measures. But in the absence of that, ideally, we err on the side of safety, which is giving C1 inhibitor before procedures.

All right, we're, we're nearly out of time. Let me take one more, and then I know some people have to move on with their evening. The last question I wanted to address was LTP for younger children and adolescents. And, and again, be aware that if you have children or adolescents you're taking care of, have a look at the PI, have a look at the FDA-approved indications, because there are some age differences. We don't have as many—We have a couple of options but not as many options in children under the age of 12, and adolescence in particular is a, a time when, you know, being a teenager is hard enough. Many patients, in that age group, they don't want to have the condition, and they don't want to do the treatment because there's a stigma attached to that, so that's a time when they're exerting their independence where I think we need to be particularly careful, have discussions, not only with the parents, but ideally trying to talk with the adolescent as well. What are they willing to do so that we can keep them safe, keep them in sports, keep them in hobbies, keep them off to college or that first job without HAE being a burden or, or a disruption? And so, I think that's a really unique time. We need more, more data on adolescents to sort of figure out how best to navigate that. But, but those are unique populations where hopefully we'll learn more in the coming years and be able to better apply, and use long-term prophylaxis.

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