Improving Health Equity in Hereditary Angioedema (HAE): A Panel Discussion

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Introduction

Aleena Banerji, MD: Welcome. Our program today is on Hereditary Angioedema, and we will be focusing specifically on inequities of care that exist for patients with hereditary angioedema; this can include disparities in access to care, making the diagnosis, access to treatments, including enrollments in clinical trials for treatments in hereditary angioedema.

My name is Aleena Banerji, I'm a Professor of Medicine at Harvard Medical School in Boston, Massachusetts, and I'm honored today to be joined by Dr. Timothy Craig and Dr. Marc Riedl.

Dr. Timothy Craig is a tenured Professor of Medicine, Pediatrics, Biomedical Sciences, and OB/GYN at Penn State University, Hershey, as well as a Senior Medical Advisor for Vinmec International Hospital, Time City, Hanoi, Vietnam. Dr. Marc Riedl is a Professor of Medicine at the University of California, San Diego School of Medicine in San Diego, California.

These are our disclosures. To briefly introduce you, hereditary angioedema is a rare autosomal dominant medical condition that leads to recurrent and unpredictable episodes of swelling. When these episodes are untreated, the episodes of swelling can last anywhere from 2 to 5 days and are often categorized into peripheral episodes of swelling, which can involve the hands and the feet, abdominal episodes of swelling, and laryngeal swelling.

Almost all patients with hereditary angioedema will be impacted by peripheral attacks and abdominal attacks, while approximately 50% of patients with hereditary angioedema will have a laryngeal attack at

some point in their lifetime. A laryngeal attack or airway swelling is the most concerning as it can be life-threatening.

In terms of treatment, we know that over the past 10–15 years, we have made remarkable progress in the development and approval of treatments for hereditary angioedema in the United States. This includes four FDA-approved treatments for long-term prophylaxis, as well as four approved treatments for on-demand treatment.

However, as we will discuss and as the data show, there is still a significant impact on the quality of life for patients with hereditary angioedema, and there are significant inequalities which we will focus on today.

When looking at the pathophysiology of hereditary angioedema, we know that this is due to a deficiency of the C1-esterase inhibitor protein. This is a key inhibitory protein in the kallikrein-kininogen pathway. When there are low levels or a dysfunction of the C1-esterase inhibitor protein, the kallikrein-kininogen pathway does not have the normal inhibition from the C1 esterase inhibitor protein, which can lead to unregulated or increased levels of bradykinin.

We know that bradykinin itself is what plays a key role in increasing vascular permeability, and when there are elevated levels, we see an increase in vascular permeability, causing the symptoms of swelling that we see in patients with hereditary angioedema.

Timothy Craig, DO: Aleena, can you remind us how long the swelling lasts in these individuals and some of the other aspects in the sense of triggers since we didn't have that on a slide?

Aleena Banerji, MD: Thanks, Dr. Craig, for asking. We know that typical episodes of swelling for hereditary angioedema can last for 2–5 days, especially when they're not treated. In terms of triggers and what you hear from your patients, maybe I can ask both Tim and Marc to comment on that.

Timothy Craig, DO: I'll let you go first, Marc. Go ahead.

Marc Riedl, MD: I think there are certain triggers that are recognized. They include certain medications. We recommend people with HAE avoid ACE inhibitors for certain, which can lead to catastrophic swelling due to the bradykinin increases. Estrogens are a problem, and as we may discuss later, women tend to have a more difficult course with HAE phenotypically than men, although there are severe phenotypes in both genders. There are also other triggers like trauma, so accidental or iatrogenic

trauma, medical procedures like surgery, and dental procedures can really be difficult as they'll trigger severe oropharyngeal or airway swelling.

Certain infections may trigger HAE attacks. But one of the difficult things I hear from patients, of course, is that many times there are no clear triggers for their attacks. I think the unpredictability of this condition is one of the really difficult aspects. These attacks can happen anywhere, anytime without warning, and that's a difficult way for people to live.

Timothy Craig, DO: So the majority of people actually say they can't remember a trigger when you look at the data prospectively, which confuses the issue as you said.

Aleena Banerji, MD: I think it was really important for us to highlight those specific triggers, and also the fact that in over two-thirds of attacks, patients actually can't identify a trigger.

Let's move on to talk a little bit about the treatment options. As I mentioned earlier, there are eight different treatments that are currently FDA-approved in the United States for the treatment of patients with hereditary angioedema. There are four that are approved for long-term prophylaxis and four that are approved for on-demand treatment.

In terms of long-term prophylaxis, the first therapy that was approved initially was Cinryze or a replacement product with C1-esterase inhibitor protein that was given twice weekly. Then more recently, in the last several years, we have Haegarda, which is a C1 inhibitor replacement product given subcutaneously twice a week, as well as Lanadelumab, which we know is a monoclonal antibody to plasma kallikrein, and Berotralstat, which was the most recently approved in 2020, which is a once a day oral tablet.

Tim and Marc, how has your experience been with your patients for these long-term prophylactic agents that are approved in the United States?

Timothy Craig, DO: One of the problems that you mentioned, it's the intravenous C1 inhibitor and SubQC1 inhibitor work. One requires IV, which is quite a burden. The other Sub-Q, is not too much of a burden, but both of them are every 3–4 days. The frequency of dosing is what makes them somewhat burdensome.

The Lanadelumab has the best efficacy when used every couple of weeks. You can go out once a month, but then you miss some of the efficacy. Berotralstat is a tablet which makes it convenient, but it's only

about 50% effective, whereas the others are approximately 85%. The one thing with that is an intravenous C1 inhibitor. If you're just giving it at the 1,000 units, you're probably only talking also about a 50% effectiveness or a reduction of a tax per month. If you use it at higher doses, the expense increases, but you can get better efficacy. But Lanadelumab and Haegarda, or I should say SubQC1 inhibitors, are about 85% effective.

Aleena Banerji, MD: I think it's important to highlight the significant efficacy of these treatments, but also that there still remains a treatment burden with using these treatments. In terms of on-demand treatment options, Marc, you know that we have four currently available on-demand treatment options. This goes back to 2009 when we had initial approval of Ecallantide, which is a plasma kallikrein inhibitor, as well as Berinert, which is a C1-esterase on-demand intravenous treatment.

Then in 2011, Icatibant, which is a Bradykinin B2 receptor antagonist. Then Ruconest, which again was about 10 years ago, is a recombinant C1 inhibitor. Tell me a little bit from your perspective about these on-demand treatments and how it has been for your patients with hereditary angioedema.

Marc Riedl, MD: Well, the on-demand treatments are critical. One of the things we continue to remind our patients is that everyone with a diagnosis of HAE needs on-demand therapy. As you mentioned earlier, this is a life-threatening condition, so not only really debilitating when these attacks hit, but there is a real risk of mortality if the airway is involved. So on-demand treatment continues to be really important to put into our treatment plans. The good news is we have options, just like the prophylactic medicines, we have a few different options. We discuss these with patients, and every patient selects a medicine that's going to be easy for them to use and effective to treat their attacks.

I think that one of the themes here is not only do we have options, but there's variability from patient to patient. Not every patient responds exactly the same to each medicine and side effects might be different in each patient. As you mentioned, I think on-demand therapy is another area where there still is a burden of treatment. These are all intravenous or subcutaneous medicines. As some recent studies have shown, that is a barrier to treatment in some cases that patients are either unprepared to treat their attacks or unwilling to treat their attacks because of some of the side effects and discomfort concerns. As you're going to show us, we have some exciting things in development that may further improve on-demand treatment as well.

Timothy Craig, DO: The one thing I'd add to that, we talked about long-term therapy, and we talked about rescue. We didn't mention anything about short-term prophylaxis, which is important. A drug of choice for that is an intravenous C1 inhibitor. You can use androgens if you have the time period to start

five days before, but that is not as effective as an intravenous C1 inhibitor. I think that is the drug of choice, usually given before a surgical procedure, especially if someone is going to be intubated.

As Marc talked about, that's such an important concept. If you have a medical procedure passing the airway, again, that would be a time you would want to have a person receiving short-term prophylaxis. Then also for dental work. Maybe not for cleaning, that's questionable, but definitely for extractions of teeth, you should really, again, use short-term prophylaxis.

Aleena Banerji, MD: Yes. We often forget to talk about short-term prophylaxis, but it's a very important part of managing our patients with hereditary angioedema and really giving them treatment prior to a known trigger, such as a dental procedure or surgery, where we know that an attack could be triggered by that procedure. In terms of using these therapies, I think one of the things that we often talk about is shared decision-making. Is that something that Tim and Marc that you often will use or think about when you're talking about these treatment options with your patients?

Timothy Craig, DO: I actually go through, as Marc mentioned earlier too, go through the process of explaining the drugs, how they're given, what their risks are. All these drugs have pretty minimal risks, how often they have to be given, and then allow patients to make up their minds. It's still in this day and age surprises me that some people will do intravenous C1 inhibitor as their primary long-term prophylaxis, but I have quite a few young ladies who are very athletic with very low BMIs, and they just prefer, it easier for them, to give an intravenous injection than it is a Sub-Q.

I usually talk about all the drugs. I also talk about all the drugs and research in case people want to come into a research study and let them make the decision. Obviously, there are some times when I try to sway that decision, depending on the patient, and that's why it's called a shared decision instead of a patient decision.

Aleena Banerji, MD: Marc, is that a similar approach to you?

Marc Riedl, MD: Yeah, it's a really important process, and I agree. We use it all the time with every patient. As we know, some patients are more engaged in that process than others. But I do think, as Tim alluded to, I view we're the experts in the condition, but the patients are the experts in themselves and what their preferences are and what's going to work best for them. We know from other fields that a shared decision-making process leads to better adherence, and better outcomes, hasn't been studied extensively in HAE, but in my experience, that's absolutely true. If that patient is active in making their

treatment decision, and setting up their management plan, they do better, and they are more satisfied with the outcome. I think you can't overemphasize the importance of that.

Timothy Craig, DO: Yeah, I think just the fact that a discussion itself, too, is so, so important for people to feel reassured in what they're doing and realize that you have their concern in mind. So, yeah, I agree with you 100% Marc.

Aleena Banerji, MD: Yeah. It's not just a one point in time conversation. It's that this is a long-term relationship and ongoing communication and having these discussions at routine regular follow-up visits that we have with our patients.

To move on a little bit, we all know that there are multiple new therapies that are in development for our patients with hereditary angioedema. At a high level, just to briefly mention a few of them for long-term prophylaxis, we know that Garadacimab, which is a monoclonal antibody to factor XIIa, so early in the pathway, is in development.

We also know that Donidalorsen, which is an antisense oligonucleotide, which is actually designed to target the production of prekallikrein, leading to decreased levels of bradykinin. We also know that Deucrictibant is being studied for long-term prophylaxis as well as on-demand.

There's a gene therapy which may move the needle forward using CRISPR-Cas9 technology, which inactivates or targets the KLKB1 gene responsible for producing prekallikrein, also mentioned in the pathway.

Then Subertralstat, which we know is an oral therapy that would inhibit plasma kallikrein. Again, this inhibits multiple places in the pathway, but leading to decreased activity of bradykinin or decreased generation of bradykinin. Marc and Tim, any thoughts on these products that are in development and how that might move the needle forward or really impact the care of our patients?

Marc Riedl, MD: Well, it's an exciting time with the continued development of these multiple therapies. I think that the trend that you're seeing, which isn't surprising, is this recognition that while we do have effective medicines, there's still a considerable burden of treatment. At the moment, HAE remains a lifelong condition. It's genetic, and we don't have a cure at this point. People using medicine month after month, year after year, we do hear that there's a burden. A lot of the things that you just mentioned, Aleena, are targeted at, can we find ways to be as effective and as safe, but make it a lot easier for patients to stick with that treatment plan, whether that's less frequent dosing or easier dosing with oral

medicines, or in the case of the gene therapy, a one-time dose that would last for, we don't know how long, years, maybe.

I think that these are, again, exciting times. Of course, as you said, these are all investigational drugs, so we have to see where the studies go and what the regulatory bodies think about the data that's produced. But I do think we continue to take steps forward and have more and more impressive options to offer patients.

Timothy Craig, DO: Yeah, I think the excitement of oral rescue medications is so cool when you think about two of the rescue medications are IV, one can't be self-administered because of the risk of anaphylaxis, and the other one has a 97% injection site reaction, the ones that are approved for rescue right now. To have an oral medication where you don't have to inject is going to be so good for the patients.

I think it might even change some people away from prophylaxis and instead go for just on-demand medication, but we'll see how good the results are when everything's finalized. But also, so many injections are looking at once every six months, and that'll make a big change to the field of two injections a year. If the studies turn out to be as we expect, it would make the burden minimal. Like you said, the Intellia drug, it'd be so cool if it is just one injection for maybe your entire life. Who knows? We'll see what happens with that.

Aleena Banerji, MD: It's clear that even though we all have seen so much progress in treatment options and even what we have available, that there is so much in development that is going to really move the needle so much for our patients. It's really an exciting time, to say the least.

But to really bring us back to one of the main things that we wanted to address today, let's think a little bit about the disparities that we're seeing in the diagnosis and management of patients with hereditary angioedema. This includes the years that it can take to reach a correct diagnosis across the spectrum of patients with hereditary angioedema, access to specialized care, access to therapies, all the things that we talked about.

Tim and Marc, maybe I can ask you to talk a little bit or comment a little bit before we go into the data about what you're seeing from your perspective about some of these things and why it's so important for us to talk about the disparities in patients with HAE and how it's impacting their care.

Timothy Craig, DO: Yeah, I think Marc and I have both written on research studies, and that's really what led me to believe that there's such inequality in minorities because in almost all our research studies, it's 90% Caucasian. There are very few Blacks, few Asians, and very few Spanish-speaking people.

Along with that, when we looked at a group of Black Americans, what they showed was that it took about 8.5 years or 8.3 years, which is longer than Whites usually say. That is usually about 6.3 years or 6.5. They also found that they needed, say, five, sometimes even 7–8 doctors as compared to three doctors to make the diagnosis. There is a big disparity there. I guess Marc will spend some time talking about that now.

Marc Riedl, MD: We'll look at the data that's out there, and I think there's not a lot. This is an understudied area. But certainly in our practice, and I know you both run large centers as well, we see people from many areas, many regions, all walks of life. You do recognize that where you live, how much money you make, what your insurance is, these things all, unfortunately, affect access to care and affect the ability to get this specialized care and sometimes the treatment that people need.

Anecdotally, I absolutely think this happens, and I think we have some data we'll walk through, but we need more focus on this, really, as we move ahead. Especially as advances are made, we've got to make these things more equitably accessible to our patients, and that includes the global community. I think, Tim, you'll talk a little bit about outside of the US, but this is an area we've I've got to work on.

To add to that, it is amazing the difficulty for our patients that have Medicaid or Medicare and getting the copay assistance because all these drugs are $500 plus minus a little bit, but close to that, whereas with private insurance, at least the pharmaceutical companies pay their copay. Usually, we are very successful in getting the copay for Medicaid and Medicare patients, but I'm always worried about that amount of money drying up and not being available to subsidize those people who are in state or federal insurance.

Aleena Banerji, MD: Marc, can I ask you now to talk a little bit about hereditary angioedema and rural settings and some of the data that we have on that topic?

HAE in Rural Settings

Marc Riedl, MD: Yeah, thanks, Aleena. Happy to launch into that topic, which I think is important. Let me share a little bit of some broad concepts first, and then we'll dive into what we know, which isn't enough, about HAE in rural areas. This won't come as a surprise to anyone, but there's a fair amount of data to show that globally, if you look at all of medicine, residents in rural areas in the US have greater health inequality than people that live in urban or suburban locations.

If you look at a map of the United States, there are large swaths of areas that are underserved medically, and there simply aren't sufficient medical professionals or medical specialists to take care of the people who live in those areas. There are a number of reasons for this, and of course, it's complicated, but we know geography is a factor. We know there are economic barriers, and there can be higher rates of uninsured patients or lower-income patients in rural areas.

It would be difficult to recruit and keep physicians or other healthcare providers in rural areas. That's particularly true for specialists who may not have a sufficient population to support a specialty practice. I would say it certainly appears to be true for allergens immunologists, which I'll share some data on that in a moment.

As we talk about HAE, you recognize this is not unique to hereditary angioedema. It's been shown by the CDC data to be true for heart disease, stroke, cancer, and respiratory disease. If you live in a rural area, unfortunately, you're at risk for getting a lower level of care or at least specialist care compared to people who live in cities.

Now, when we talk about rare medical conditions, which HAE is a rare medical condition, that problem is likely to be compounded. We don't have a lot of data on HAE in rural areas, but let me share a little bit of data which suggests we may have some problems here. There are a couple of patient surveys, going back to 2013 and 2015, that show about 22% of people with HAE live in areas with a population of less than 20,000, so quite sparse and diversely populated, and another 25% or so that live in towns that have between 20 and 100,000 people.

If you put those numbers together, that means almost half of people with HAE, at least based on these surveys, live in what might be considered a rural area. Now, these are surveys. You have all the limitations of surveys, selection bias, and so forth. Nevertheless, there's probably a large proportion of patients with HAE who do not live in cities or suburban areas.

The other thing I'll share with you is a 2013 survey of physicians, and this was physicians who take care of HAE. That showed that less than 20% of the population is in these population areas of less than 100,000. So you start to put these numbers together. There's a huge mismatch between where the patients live, almost 50% in these sparsely populated areas, and less than 20% of the specialists that take care of them in those same areas.

That leads to the concern that these people either don't have access to specialists or are having to travel away from their homes. Sometimes considerable distances to get the care that they need. Certainly travel to get medical care can be done, but it means time away from work, time away from school, and sometimes economic hardship for patients that need that special care.

The last piece of data I'll share with you and then interested in your thoughts. Aleena, you did a study, a patient survey a few years ago that showed over a quarter of patients, 27 of patients had their general practitioner, family physician, or primary care physician, heavily involved in the management of their HAE. Now, that's not a bad thing. We need people locally, and sometimes the more, the better to help patients.

But it does suggest that there's a large number, at least a quarter of patients, where they're not probably close to a specialist, which means that their primary care doctor has to take a large role in managing their condition. So these are just some numbers that suggest, yes, there is an inequality. There is a problem with HAE care in rural areas. We can tease that out a little bit as to what exactly, where are those pressure points, and what can be done about it? But let me pause there and just ask for feedback, comments from you guys on what I just mentioned or any anecdotes you may have from your own practice.

Aleena Banerji, MD: Marc, I think it's important to highlight that patients are living in these rural areas. While we can't assume that rural areas are necessarily underserved, that certainly is the case in a majority of areas. In my experience, one of the things that I have certainly tried to do living in the New England area is if I identify a patient because they were referred to me, and they live hours away, I try to collaborate or develop a partnership with their local doctor who can be their go-to for the more regular routine aspects, but provide care, offer telemedicine if that's possible.

But think about ways to continue to support both the patient and the physician, so the patient can live their life in that area that may be more rural and not necessarily have to drive multiple hours or have to think about getting an ambulance and going multiple hours in the midst of an attack, but really trying to provide that care locally.

Timothy Craig, DO: Yeah, we do have people, too, who travel many hours. Where I'm located, people in Western New York, Maryland, West Virginia, Delaware, and New Jersey, all come to us. It's many hours, but also long distance. Unlike Marc, we're going around the block and take many hours. With us, it's usually easy driving but takes people who are traveling hundreds of miles. We really do similar to Aleena in that we see them once a year and then count on most of their health care being provided by a PCP and do communication back and forth.

I do have, just because it's a rare disease, I do tend to have some of my patients have my cell phone so that I can deal with emergencies. Often, I get calls from the emergency rooms and hospitalists on how to manage patients. But I'm sure all three of us have that. It's interesting, though. You're talking about rural. When I think about some of the New York or Philadelphia or Baltimore, that the access to care if you live in a poverty-stricken area of Baltimore is very difficult, too. Maybe the hospitals may be closed, but if you don't have money to take a bus, and you just don't have to know how to seek good care, it can be just as bad as living in a rural area in some ways.

Marc Riedl, MD: Yeah, it's a great point, Tim, and we're going to touch on that a little bit, I think, with some of the data that's been presented. But you're right, it doesn't have to be rural. There are other factors that can really lead to inequality in terms of medical care. Let's unpack this a little bit. I presented some of the challenges but if we think about how we would like to optimally manage patients, and we talked about this a little bit at the outset when Aleena introduced the program, it can be a lack of access to this specialist.

Again, that doesn't have to be an allergist-immunologist. There are internists pediatricians or family medicine docs that can do a really good job of this if they're interested and learn about HAE. But having a specialist so to speak, someone who's very knowledgeable about HAE can be a real challenge if you live in an area where there just aren't many health care providers.

Lack of recognition, and we talked about the delay in diagnosis a little bit, that can be an issue simply because you have a limited number of health care professionals and if no one's ever heard of HAE and aren't aware of it, it's hard to get diagnosed because you get misdiagnosed and treated for other conditions, allergy, gynecologic issues, intra-abdominal issues, food allergy, you name it, all the misdiagnoses that our patients get over time.

Additionally, getting the lab testing done, which we don't think about a lot in the United States because we have excellent laboratories around the country. But again, some of the testing for HAE, particularly the functional C1 inhibitor testing, which is important to do, can be very susceptible to handling shipping, temperature, storage, and so forth. If you live far away from a hospital or a lab, that can affect the quality of the laboratory testing that needs to be done to make the diagnosis of HAE.

There are a number of things that can go wrong or can be barriers in rural areas. One of the ways that we talk about improving this, and I know we'll talk more about opportunities in a moment, but telemedicine, certainly since the COVID pandemic, telemedicine has become mainstream, and that can be a real benefit. But it does require access to technology. It does require some reimbursement structure.

We know that there can be some challenges with some plans for that. It's actually subject to a lot of regulatory rules right now across state lines. That can be an issue depending on what state you live in and what specialists are available. Telehealth is a real opportunity but doesn't always solve the problem.

Then we talked a little bit about that partnership and the importance of having a willing person locally to help. That's excellent when it works. Like you guys, we do the same thing, partnering with local physicians or healthcare providers who can help the patient. But that's not always available. Sometimes the local people, don't feel like they can handle this. Patients do struggle to find someone who will engage in this complex condition and help them out.

Lastly, I'll just mention the medications. We talked about some of the very effective medicines we have and those that are coming along in the pipeline. Unfortunately, those medicines can be difficult to obtain. There's often a complicated prescription and authorization process. Tim mentioned earlier the cost of these medicines and how even with insurance coverage, they can be unaffordable to some patients because of out-of-pocket costs.

Then that doesn't even speak to some of the logistical challenges. These medicines usually are handled by specialty pharmacies with a certain chain, and there can be difficulties in getting medicines to more remote areas safely and stably.

I think there are a lot of both practical and bigger-picture problems that we have to think about in trying to do our best for our patients in rural areas. Any comments from you all on any of these points that I just mentioned?

Timothy Craig, DO: The one thing I would mention is exactly what you said about the medications. Going back to short-term prophylaxis, people are getting care in smaller community hospitals. Often, they don't have any of the drugs we need, especially IVC-1 inhibitors. That's one of the things the education of my patients, especially when they travel a distance to us, is to make sure they call the emergency rooms in their area to see if they have the medication, and then if they don't, to make sure they have the medication at home to Brown bag.

Now, that's a problem. A lot of hospitals won't allow patients to bring in medication, but it is an alternative sometimes to get around to a hospital that doesn't want to carry it.

Aleena Banerji, MD: I'm glad that we're thinking about this and talking about this because as we've mentioned, there are no easy solutions, but this is a challenge that those of us who are taking care of HAE patients need to talk about more. I find that this relies on patients advocating for themselves and so those that aren't advocating for themselves are the ones that are really in a place where they're not getting the care that they need and those are the ones that we have to reach more.

I don't actually have any easy answers other than all the things that you've talked about and for us to continue to educate and continue to teach and continue to improve care in the way that we have been doing.

Marc Riedl, MD: It's a really good point, Aleena. It's We only know what we know. I think about that a lot, too. The patients who may be struggling the most are the ones we're not even aware of because they're not getting to a specialist or a center or someone who can help them optimize their plan. It's also a nice segue to talking about opportunities or strategies to improve. I'll be brief here because I don't think there are easy answers.

There's a lot to think about, but let me just say a few words, and then I'll invite you guys to add your thoughts. Barriers to diagnosis. You have to think of the diagnosis. This goes back to education. We need to do everything we can to educate our colleagues, particularly those who may be in underserved areas, to put this in their minds and remember it if they see patients with recurrent swelling or recurrent abdominal pain.

There is work on diagnostic testing. There have been some publications now on dried blood spot testing, which may or may not take off in the United States, but certainly globally shows great promise as an easier way, a more stable way to transport a sample and test for both C1 inhibitor levels and function. I think access to specialist care is one of the biggest challenges, and just doing our best to network, and make our colleagues aware that we're here to help, that the community of HAE specialists is here to help.

Partnering with local physicians and local health care providers, as we've already talked about, is really critical to be successful in these areas. Patient education and I'll put in a plug again for the US Hereditary Angioedema Association, which is really centered on educating patients, giving them opportunities to learn and advocate for themselves. Lots of materials, and lots of programs for patients to be engaged in improve their own knowledge and care.

Also, health care providers. The HAE is very active in CME and reaches out to areas where they are hungry for this information. So education is really important. In terms of treatment strategies, there's a good

argument to be made that long-term prophylactic therapy makes a lot of sense in areas where you don't have immediate access to specialist care or even emergency care.

I think that's something I talk about with my patients who may live in more remote areas, if you're on the fence about prophylaxis, that may be a good move to try to prevent any catastrophic attacks where you can't get to the emergency department quickly, although hopefully, the on-demand medicine will take care of those attacks.

We talked a little bit about telemedicine, and I think this is really a huge opportunity, but we will require regulatory agencies or governments to make that a stable way to provide care, far-reaching care to people who need it, especially with rare conditions. We're all aware of economic disparities, and that's a real challenge, a societal challenge, that we need to think long and hard about, how are we providing medical care? Are we ensuring people and thinking about equality in that sense? I've rambled on enough about this. Do you guys have other strategies that you're thinking about or that you use currently to try to overcome some of these barriers?

Timothy Craig, DO: I see you're going to be talking about that in a second, but I do a trifle card, too, for everybody. It has information for the emergency department, it has the patient's information, God forbid they have a throat swell, and they can't really communicate well. It has what rescue medications to use for that patient. It has what prophylaxis they're on, and it has just a little discussion on general about treating hereditary angioedema patients in the emergency room. I find that really helpful, and I give it to 100% of our patients. Well, maybe I should say 99. I try to give it to 100% of our patients. But I think for remote emergency rooms, that's a really helpful thing for them, especially if they can't get hold of someone to communicate with.

Marc Riedl, MD: Really important Tim, and that was going to be one of my next points, but you said it well. Preparing the patient to navigate that healthcare system with this rare condition of HAE. A wallet card, a letter, an app, something that will outline what they have, the treatment they need, and ideally, how to get in contact with their specialist if there are questions. That's true for all patients with HAE, but especially true in rural areas where they may have to access care. They may not have a lot of choices of where they're getting their care, I should say.

Aleena Banerji, MD: I'll just put in another plug Marc, as you had mentioned for the US HAE Association, that they actually are able to guide care if you are in an area where you don't know where to go. They have a number, you can call them, and that tends to be another way to navigate some of these tricky situations for patients who are struggling with care.

Timothy Craig, DO: Yeah, and they can also assist and copay information. They do provide an excellent service, and everybody who's a patient should be part of the HAEA.

Marc Riedl, MD: In this section, let me share one last piece of data. There was, in fact, very timely. There was a poster presentation at a recent Allergy Congress at the college meeting. This was an effort to try to look at some of these questions. I'll talk a little bit now about the rural portion of it, but they also looked at other predictors or factors that might be involved in social determinants of health.

Some data was presented by Alan Baptist, who's in Michigan, this was a retrospective claims database review. It looked at an insurance claims database from 2017 to 2021, identified over 1,200 patients with a diagnosis of HAE and really tried to look at these social determinants of health, namely rurality, where they lived, race and ethnicity, and then income. This has all the limitations of claims databases, right? We don't have lab results to confirm their HAE diagnosis, but they were coded that way from their doctor. We don't know a lot about the individual patients, but you can look at what medicines were claimed, meaning, if they got prescriptions for certain HAE medicines.

You can also look at claims for things like FFP, which would be potentially used to treat HAE when modern, more proven medicines are not available.

Let me just show you quickly, specifically looking at whether patients lived in a rural area versus an urban or suburban area. If you look at a claim for a long-term prophylactic HAE treatment. This included all the modern therapies, but it also included androgens, which are effective but have been moved away from largely because of side effect concerns.

If you look at this figure, you'll see that in the rural versus non-rural patients, those who lived in a rural area were less likely to have a prescription for a long-term HAE prophylactic medicine. You can see 27% in the non-rural and 18% in the rural areas. So not statistically different, but numerically different. In that little box you see in the figure, that's actually a visit with an immunologist or an allergist-immunologist. Interestingly, that's pretty close to the same, 18 versus 17.8%. Interestingly, they had similar, at least, access to specialists, but this differential in who is getting long-term prophylactic therapy. There could be many explanations for that, but it's an interesting observation.

Another point that was made is that the claims for FFP were higher in the rural patient population versus those that lived in cities or suburban areas. Again, not statistically different, but 59% versus 50%. Perhaps

suggests that some of the older modalities are being used for on-demand or acute treatments in the rural areas, at least a bit more frequently than in cities or suburban areas.

If you look at visits to emergency departments or the odds of having an emergency department visit, this is interesting because it's actually somewhat higher in urban or suburban areas. We talked a little bit about how it might be difficult to get to an emergency department, or maybe you have to depend on the emergency department for your medical care. But at least this claims data showed that you're actually more likely to be in the ED in a city or suburban area than in rural areas. I don't know if that's good or bad, but it just shows that there are at least numerical differences that we're seeing depending on the geography of where you live.

We'll dig into some of the racial and ethnic data a little bit later in the program. But this is hot off the press. Hopefully, we'll have more studies, more refined, more rigorous studies looking at this issue in hereditary angioedema. Any thoughts about… Does that data surprise you guys or sort of as expected?

Aleena Banerji, MD: It's nice to see that we're collecting data because we can talk a lot about these things, and we presume a lot of these things, and we're guessing a lot of these things and making educated guesses. But I think really looking at these data, trying to understand the reasons behind the data, trying to make an impact, and measuring the data is really the best way for us to understand the situation and how best we're making an impact and then following that over time. It's nice to see that we're starting to look at some of these things.

Timothy Craig, DO: I think, if it's okay with the other two, I'll move on to some more of the information that's based on international disparity. When we look at different countries around the world, Marc mentioned it before, is that most countries throughout the world don't have the C1 inhibitor function assay. It's mainly Western Europe, Canada, the United States, and Japan that have the functional assay. Some other countries too. But the vast majority of people throughout the world don't have the functional assay.

Without the functional assay, you cannot easily diagnose those people who have hereditary angioedema type 2. You should be able to diagnose one with just the C4 and a C1 inhibitor, which is what Marc was talking about, that they're trying to develop spot tests for that. And that'll at least help in a diagnosis, but you'll still miss 15% of people who have type 2. Obviously, you would also miss those people who have hereditary angioedema and normal C1 inhibitors, but that's a story upon itself.

This series of slides right now, which I'm not going to go through too closely, but what it does, it shows you that really the economics of a country determine not only the medications but also access to genetic tests and also access to C1 inhibitor functional levels.

If you live in a low-income country, your ability to get anything but maybe FFP and androgens is minimal. Even in most middle-income countries, the ability to have access to these drugs is, again, very minimal. Almost all the countries that have access to all the drugs we've been talking about are mainly Western Europe, United States and Canada. Australia and also Japan have similar drugs, but their restriction is far greater for using prophylaxis than it is here in most of Western Europe. Do you have any comments? I know you both have international ties, and we all do much travel to different countries. Do you want to talk a little about your experience in foreign countries and access to care and hereditary angioedema?

Aleena Banerji, MD: I think most of my experience is similar to what you're describing, Tim. In speaking with colleagues and understanding what treatments are available. We know that many, many countries have very few, if any, of the treatments available, and that they are continuing to use treatments like the androgens, which, while effective, can have a lot of side effects. There's still a lot of work to do to really address these disparities that we're seeing worldwide.

Timothy Craig, DO: Yeah. Imagine being a person in a country that doesn't have any medications available, and you're looking to have a spouse, and you know that the 50% chance that your children will have it and be born into a country where you have no access at all to medications that are well tolerated and very effective. It really is a major problem. But also when we look at United States itself, there are some major disparities between minorities and the majority. We did a TriAx where we looked at the general population and then studied that to people who have been in studies in phases one, two, and three research studies.

You can see on the one chart here, it shows you that almost all the patients who are in clinical trials are Caucasian, and usually not Hispanic-speaking Caucasians. When I mentioned the figure before, it's close to 90% in most cases. If you look at the difference between the rate in the population of HAE and the rate of patients in clinical trials, actually that percentage is higher in Caucasians as compared to the in-clinical trials as compared to those in the general population.

But if you look at Blacks, you look at Spanish-speaking individuals, and if you look at Asians, very, very few are in any clinical trials, much less than the HAE in the general population.

That's a problem, somewhat, because all the data we're collecting is equal between the different races. We don't know. We assume that's the case, but almost everything's based on all the efficacy and side effects, which are basically based on Caucasians.

When you look at it a little differently, too, somewhat we can show we've looked at drug responses in different races. This was a study done with Takeda. We looked at the HELP study, which is the Lanadelumab study. If you look at the data carefully, you can see it looks like, at least in the first part of the Lanadelumab study, it looks like that actually, Hispanics responded much better than Blacks Asians or Caucasians. But if you look at these numbers, there were only two Asians. It was only a handful of Hispanics and only a handful of Black people, so how do you tell if that's the case? So, we looked actually into the HELP study in the long-term open-label part, and you could see similarly that there seem to be somewhat changes.

But I really do think that the open-label, made it likely that these drugs, at least Lanadelumab, are just as effective in minority groups as it is in the majority.

But still, it would be nice to have more Asians, more Black Americans, and more Spanish-speaking people in the trials to ensure that's the case. I guess either one of you has any comments in the same sense of disparity in clinical trials and also the disparity in responses to medications?

Marc Riedl, MD: Just to quickly review that claims database study that I mentioned earlier, but now look quickly at the ethnic and racial groups. Again, this was looking for disparities amongst these different races or ethnicities. Remember, if you look at the claims for long-term prophylactic HAE treatments, these would be prescriptions for long-term prophylactic therapies.

You'll note that across the board, the outlier here is in the African-American population. At least numerically, there were many fewer claims for long-term prophylactic therapy compared to the other ethnic groups, and certainly below the overall mean percentage. You'll also note that the small bar in the box, again, is a consultation with an allergist-immunologist, and so a much lower rate of seeing an allergist amongst the African-American population compared to other groups. Similarly, for FFP, that is older treatment for HAE attacks, much higher prevalence or percentage of prescriptions or claims for FFP in the African-American population compared to the other groups. Lastly, looking at the odds of having an emergency department visit.

This was statistically significant, the odds being much greater in the African-American population and greater also in the Hispanic population compared to the other ethnic groups.

Now, we don't know if those ED visits were for HAE specifically. There could be other factors leading to that odds ratio being much higher. Nevertheless, this is a statistically significant difference in where people are seeking their care amongst these different groups.

Well, I think as you said, Tim, it's hard to draw any firm conclusions from comparing such small numbers, especially for these underrepresented ethnic groups. There's no question that we need to better include those groups in clinical trials because as you said, almost all the studies are far predominantly in Whites. We need to continue to recognize this and make efforts to be more inclusive as we do clinical trials. The interesting thing is that, as you know, but it's important to state, as far as we know, there is no ethnic… HAE plays no favorites when it comes to race or ethnicity. It affects all different races around the world. Interestingly, in pretty similar prevalence, regardless of which country you look at, this is a systematic issue.

It has something to do with, who's interested in studies. How are we presenting it? Who's given the opportunities? It's something that we should hopefully be able to address in the future to get better data, more representative data.

Timothy Craig, DO: That's true. Like in Vietnam, there are supposed to be 2,000 people who have HAE, and we only know a few handfuls. Somewhat, just social, I talked about if you don't have medications, are you really going to go to the hospital? Nobody knows if they have the disease or not. It's really difficult, especially since you don't have the functional assay, it is a major problem. It's also hard to do research in a lot of countries. We've tried to do some research on HAE in Vietnam, but the national restrictions make so difficult to really perform studies there. It makes it almost impossible.

Aleena Banerji, MD: I think these are challenges in clinical trials, not only in hereditary angioedema, but we see this in a lot of data in many, many clinical trials in many different clinical conditions. I think that recognizing this and actually understanding how can we impact these communities or these ethnicities. And why are they not participating? Is it a lack of trust? Is it a cultural belief? What are the barriers? And then actually spending the energy and the time to address it is going to be important going forward.

Timothy Craig, DO: With the time element that we have right now, if it's okay, I'll summarize everything in just a few minutes, and then we'll open it up for final comments. I think we looked at the disparity. It occurs in race, it occurs in countries, it occurs in urban and rural areas, less than urban, but definitely rural as Marc talked about.

This has a problem in the sense that people get inadequate care. It has a problem in the sense of having emergency care in emergency rooms that don't have the medications. Maybe in those populations, at least in the rural, in high-income countries, there may be a greater reason to discuss prophylaxis. Well, you should discuss prophylaxis at every visit, but maybe have that person on prophylaxis and encourage it because of their inability to get good emergency care.

In addition, I think in response to that is the education of patients, making a shared decision, making sure people have some identity card on them that helps emergency room physicians have a center, maybe see the patient on a regular basis, maybe once a year or maybe every six months to ensure that the patient's up-to-date in medications. Again, going back to the HAE, having patients introduced to HAE, so they can reach out.

I think we have a lot to do about correcting disparities. I think as Aleena pointed out, just the fact of discussing it is very critical and collecting the data so that we can react to it and see how we can improve the care of patients who have HAE. In fact, as again, Aleena, you pointed out, it's true that almost all rare diseases have that same issue that hereditary angioedema patients do. So Marc, and Aleena, do you have any closing comments?

Aleena Banerji, MD: Just to highlight that this remains a very important issue, and I think that we need to continue to collect data, raise awareness, and actually put forth a lot of effort to understand the reasons behind these inequities and how best we can make an impact over time.

Marc Riedl, MD: I'll just add, I think these are complex issues, right? As you said, Aleena, it's going to take energy, it's going to take resources, but recognizing that this is a potentially occurring. The data we have is insufficient to really answer the question, but it sure looks like there are these disparities out there in rural areas in certain ethnic or racial groups. I think, as you said earlier, we're talking about it. That's important. This should be just the beginning to recognize these are challenges we've got to tackle and then put our heads together and find some solutions and opportunities. I look forward to more programs like this and more studies that we can report that will hopefully solve some of these problems or at least improve the status quo.

Timothy Craig, DO: Good. Thank you all so much.