CMEology

HAE – Hereditary Angioedema

Interview with “15”

March 20, 2024

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CMEology

Interview with 15 – Hereditary Angioedema

[START 15 3.20.24.M4A]

[IRRELEVANT MATERIAL OMITTED]

QUESTION: First question is, these are all about HAE, what is your personal experience evaluating the HAE literature in terms of its implications for clinical practice?

15: Wow, that's quite a question.

QUESTION: Yes, so let me ask you a couple, I realize that, too: so how do you approach looking, evaluating the literature? What are you looking for in the HAE literature, and what kinds of questions are you typically trying to ask or answer when you're approaching the literature on that topic?

15: Okay. Well, first I have to say that I have extensive experience in dealing with HAE. I was at the [redacted] described the actual mechanism of the disease and through the years have been very interested in that subject. As the Clinical Director of Allergy & Immunology at a [redacted], obviously, it's my job to make sure that we use evidence-based medicine in all of our treatments.

So as [redacted], which means my group is responsible for obviously treating a number of conditions, we have, I think, [redacted] physicians, MDs in the group, and we take care of allergy, immunology as the hay fever or hives; we treat immunological deficiencies, not HIV, that's infectious disease, but other immunodeficiencies, very sensitive [phonetic] autoimmune diseases which have long names and aren't real common, and a variety of other things like eosinophil-based diseases, mast cell activation diseases, and within the context of today, HAE.

I have, I believe, at the present time, 36 patients with HAE that we're pretty confident have the diagnosis. We have a number of other patients who have clinical disease which looks like it but we're not quite sure they have normal C1 esterases, the so-called type III, and we're not [phonetic] quite sure what to do with those patients.

But as I say, I have an extensive experience, so I know the current paradigms, I know the historical development of the different treatments and so on, and what I am looking for is making sure that I am using state-of-the-art treatments and state-of-the-art diagnoses with regard to the HAE. We are always looking for the latest treatment and evaluating it in terms of efficacy and safety. So what I do is I peruse the literature, and I'm also [redacted] [phonetic] in Clinical Epidemiology, so I'm used to evaluating prospective controlled double-blind studies which are the *sine qua non* of what we need before we accept a new treatment.

So what do I do? I try to be current by reading the literature. I also go to at least two national meetings a year. Lately, it's been virtual more than live for economic reasons and so on, but I try to do that. I keep up with my peers. We have at least two or three conferences a year at our meetings that involve HAE, and we'll have a Fellow review the recent literature in that context. I don't get a lot of direct contact with other, say, with the companies which are developing these agents at the present time. I am on the [redacted] Committee for our [redacted] but I'm not involved in any specific phase 1 or phase 2 trials with HAE.

So basically, what do I do? I peruse the literature; I try to read it critically. I converse with my colleagues at the local and the international level, and I think that I'm pretty current in terms of what the current treatments are. I know in terms of what's approved by the FDA, certainly I am well aware of what's happening there. I'm aware of the other medications which are in phase 2/phase 3 trials, some of them which may be coming onboard soon. And the other thing that I look at is a number of companies will have press releases, and the press releases sometimes are before they present the actual data at a meeting, and so, those are also useful.

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Credibility of research

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Literature review
Credibility of research

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Literature review

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Press releases

QUESTION: Okay. Just curious: what are your go-to journals that you look at regularly where you might come across something on HAE?

15: Well, JACI, Journal of Allergy and Clinical Immunology, is one of them. I tend to look at the basic journals like AAI, American Association of Immunology. I look at the published information from the ACAAI and the [inaudible] AI, the European Journal of Immunology. It's a broad group, and for basic science and so on, things like, well, the other one that I look at a lot is The New England Journal of Medicine because what's been happening lately is that proof-of-concept publications of new agents such as [unintelligible] -mycin and so on, I can never pronounce that name, are published in The New England Journal, which is probably the leading journal to see what's on the market, what's coming next.

(Overlapping Voices)

15: Pretty much, I don't read anything that's published in the book form or anything like that because by the time those things come out, they're out of date.

QUESTION: Right, okay. So it sounds like your go-to sources when you're thinking about research, translating that into clinical care, you are thinking about the major academic journals; you're relying on national conferences; I would imagine you might be going to poster presentations, symposia, other things you have. When you're at a meeting, do you have kind of a favorite way to update yourself on HAE if you can find stuff on it?

15: Yes. Well, usually, you can find stuff on it. This is an important thing that I have to share with you, and that is that there are practically as many treatments for HAE as there are patients with HAE. The estimates are that between one-in-10,000 and one-in-50,000 [phonetic] people have HAE in the United States, which translates to about 8,000 cases. The treatments for HAE are very expensive, especially if you've got a combination of prophylactic and acute treatment. The only reasonably-priced drugs on the market are the non-androgenic androgens: danazol, stanazolol; they cost a few hundred dollars. But the other ones are $100,000 or so a year, or more. So even that with those numbers, even though it's not common, there's a big economic impact. They're talking about, what is it, $4-5 billion by year 2026.

So there are a huge number of studies out there, and the problem with them is that they don't necessarily use the same criteria in terms of efficacy and safety. As I said, I'm a [redacted] so I am well aware of what is necessary to establish a statistically significant and believable study. But if you look carefully at these various studies, they don't necessarily use the same criteria for efficacy. Some of them will, and obviously, the acute treatments are going to have a whole different set of criteria than the chronic treatments are. They don't have the same placebo groupings: for example, when Orladeyo first came out, it was the publications which got it approved used a group of people with HAE who had relatively mild HAE. And so, if you have a milder disease, it's easier to suppress it and it's easier to get a good response.

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Efficacy and safety data

Subsequently, when the drug came out on the market, it became obvious that it was not the drug of choice for the more severe cases of HAE, although I must confess that there is a recent study now with 56-week follow-up which showed that with time, the efficacy of that drug did get better and at the present time, is beginning to sort of challenge Takhzyro, which is the most effective of the agents for efficacy, and the GI side effects are becoming less as well.

So I'm kind of rambling here, but I want you to understand that the literature is very difficult to evaluate because there are no head-to-head studies. There's only one head-to-head study which is I think the PHA against, it'll come to me in a second, it's an acute treatment, and that was the only head-to-head study; and there's nothing on prophylactics. We are trying to get the federal government to fund a big

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Lack of head-tophead studies

study which would have several of the leading agents all participating, so it'd be a multi-arm massive study, but it's hard to say. Right now, based on the literature, you have to be a little bit circumspect in reading what's coming out.

And then, of course, there's a couple of new agents, especially in the area of genetics, which are very, very exciting which may revolutionize in talking about the anti-La 2002 study by Allerganchia [phonetic] which lead to the decrease of the kallikrein beta-1 receptor by a genetic substitution, and not on the market yet but even in animal studies, there are some other gene rearrangements, for example, [unintelligible], which are actually going to take the C1 esterase gene which is abnormal and replace it with a normal, which will then cure the disease.

So that's in the offing, and as I say, the Intelligentia [phonetic] one has been approved now, and yes, it's expensive but if it costs $350,000 but it lasts three or four years or more, and the competitors are $100,000 but they're per year, all of a sudden, it becomes promising.

So the field is interesting, and it's fun. This is an exciting time to look at this disease. And of course, then there are other now forms of HAE which may clinically look like HAE but which don't satisfy the criteria, say, with a demonstrable decrease in the quantity or quality of the C1 esterase per se, and approaches [phonetic] to inhibit the pathway consequences regardless of the upstream cause seem to be useful. So for example, there's a type of HAE, type III, type I is the classic HAE with no or reduced amounts of C1 esterase; type II has C1 esterase, is about 15% of the cases but the C1 esterase is functionally deficient; and type III has a clinical disease which looks like C1 esterase deficiency but has a normal C1 esterase, even a normal functional one. So that's an issue.

Now, do you know about the genetics of HAE because it's really important to understand what we're dealing with?

QUESTION: I am not familiar with the genetics.

15: Let me give you just a second here because it's critical if you're trying to understand the spectrum of disease and the approaches which are available. The C1 esterase deficiency is due to some kind of mutation in the serpin family of molecules which are esterases and which can lead to the degradation of a number of different proteins. Now, in this case, it's complement proteins, it's also the C1 esterase compounds and so on, IL12 and some other things.

What it is, this gene, the abnormal gene has the ability to turn off the normal gene. Every gene has two alleles because there is one on each of the helix, the double helix, so every gene has two alleles. Now, if you have two abnormal alleles in the C1 esterase gene, it's lethal, so you die. But the people that have the disease have one normal gene and one C1 esterase deficiency abnormal gene.

Now, the critical thing is that that abnormal gene turns off the normal gene. So if you have a way of getting rid of the abnormal gene, then you can have a person who's normal because the normal gene will take over. And so, that's what the promise of the genetics are, that if they can in some way remove the abnormal gene, then the normal gene, because everybody is heterozygous, will take over and the treatment will work. And then, the other thing is that if you can't affect the gene itself, then go downstream because it works by activating a pathway through the kallikrein-bradykinin system, and those activated molecules are what are responsible for causing the illness.

A lot of the recent studies and many of the newer agents coming out on the market are designed, in one way or another, to either interfere with the receptor or the actual molecule of various agents in the pathway of activation; and the genetic one right now didn't go after the C1 esterase gene per se but it

went after one of the rate-limiting inflammatory mediators that cause the disease. And so, the idea is, okay, the gene is deficient but we knock out the consequence of it. We can't stop the gun from firing but we can put on the Kevlar vest.

QUESTION: Yes, exactly.

15: So it's kind of complicated. I'm rambling here, and so, I don't know what you want to accomplish [unintelligible] answer your questions, I think.

QUESTION: Sure. I mean, in the interest of respecting your time, [redacted] I'd like to just turn our attention to some of the clinical factors that you, and obviously, I know you're probably very involved in teaching and training as well, some of the clinical factors that physicians encounter in the clinic with patients. The next question for you would be: can you describe any barriers to incorporating research findings into clinical practice that you've experienced with HAE? So patient-related barriers, institutional barriers, practice-related issues, economic things you did mention: anything else that you see as being some of the challenges of taking, really translating what's in the literature into practice in the clinic?

15: Sure. What we're looking for obviously is trying to minimize the impact of the HAE on the lifestyle of the patient. And so, we're looking for those agents which are the most clinically effective, but we also have to take into consideration that they have to be relatively free of side effects, certainly free of any dangerous side effects.

And so, what one does first of all is, well, let me just tell you quickly what I do to evaluate the patient and then the context of the other issues. The patient will come to see you. In the past, HAE was not diagnosed very efficiently up until not too long ago, but in fact, initially, the studies out of the [redacted] and so on, showed that the average person who had HAE had it for 17 years before it was diagnosed. Now, the first diagnoses of HAE were done by [redacted] in in-bred [phonetic] families, I think [redacted] in the 1880s or so; he described six generations of this recurrent swelling. That's just historical for you.

But what we do is we want to establish a diagnosis. Right now, about half the patients that I see with HAE have been referred to me by other physicians who have suspected the diagnosis, and the other half have come because they've had these idiopathic slow-swelling episodes which have been quite debilitating. So we'll see the patient, we'll evaluate the patient, take care of the history and so on, and if it looks like the patient has criteria which are compatible with HAE, we'll do appropriate laboratory studies which basically now, the most important things are: looking at the C1 esterase level, and as I said before, 15% of them will have the enzyme but it doesn't work, so we do a functional assay; we don't do an immunological assay.

We also then will check the complement levels because the C4 level will give you an idea of how relatively severe the biochemical impact of this disease is on a given patient. And we'll also look at a C1q level because that will help decide whether it's a primary or a secondary defect. And more recently in our patients, we have done some genetic sequencing to see what type of mutation they have, and I can't say in all honesty that has much therapeutic implications, but I think it's important to know and we can feed some of that information into larger databases, and so on.

So we'd get the diagnosis, and if we then have a patient who has a low C1 esterase functionally who does not have significant amounts of C1 esterase in their blood which is tested, have evidence of the complement are now not, measuring complement is a surrogate marker, we used to think it had something to do with the swelling. It doesn't; that's a different pathway. But it, along with the IL12, are surrogate

markers because they're also controlled by the same gene so that they also will give you some information.

Okay, so then we come to the patient and then we, basically based on the clinical history, ask a couple of questions. The first question we try to get is: how severe is this? Is it really impacting on your life so often that you don't want to just intermittently treat? I have some patients that have attacks less than once a month, and so, what they may say, well, yes, it's terrible, I don't want it, but I don't want to take a medicine every day if I can take something like Firazyr. By the way, Firazyr was the drug that went head-to-head with the PHA that I couldn't remember before.

QUESTION: Okay.

15: So some of the patients with relatively mild disease will do that. Not so much now but in the past, some of them also had a lot of economic constraints and so on, and they would have economic limitations. That's less of a problem now because the drug companies make such a huge profit on the medication that if we prescribe the drug to the patient, the drug companies by and large in most instances eat the copays because it's cheaper for them to eat the copay and distribute the drug because of the profit margin.

So because of that, the drug companies have been extremely cooperative with us in terms of getting things approved. So if the third party payer is dragging their feet, for example, and so on, well, we let the big pharma do some of the fighting for us, although that's not really much of a problem. The drugs which are available on the market are all, once we make the diagnosis, we may have to be able to show the chemical data, but getting it approved is usually not a problem.

So the next question we have is: how severe is this? As I said, if the C1 esterase deficiency is relatively mild, we can get by with just the acute treatment because these drugs, these treatment drugs are available in preloaded syringes or Epipen-like devices, and they're stable, so the patients can treat themselves quickly. And that's important because the data shows that the faster you treat in terms of the onset of the illness, the better the benefit, which is why there is this push, for example, for oral meds and so on.

QUESTION: Sure.

15: Now, if the patient has more frequent attacks, or if the attacks are severe, by that I mean that because, for example, angioedema or other types of respiratory effects, because you have to deal with a number of criteria in judging the severity of the HAE attack: now, how often do they occur, how severe are they, do they require a visit to the emergency room, do they respond easily to a single dose of a rescue medication, and so on; and also, what organ systems are involved in the illness. So as I say, if somebody has relatively few attacks but those attacks are respiratory and wind up with, ut-oh, we may have to intubate because of laryngeal edema, then even though the frequency is low, the severity is high, so you have to take that into consideration.

Then after that, then the next question which I ask because it's critical is: how important is it to you in terms of what the mode of administration is, because we can give it three different ways. We can give it by an IV injection, we can give it by a subcutaneous injection, and we can give it by oral therapy. And a lot of patients now, there was a study which was done by the people that make Orladeyo which says that almost 90% of patients given their choice would prefer to have an oral agent rather than an injectable agent; and since Orladeyo is the only orally-available agent, of course, that's kind of a self-serving conclusion, but it is a conclusion. And it is true.

QUESTION: Okay. That's been your experience in practice.

15: Yes. And so, if I have a patient that comes in and if they have very severe HAE, life-threatening HAE, frequent HAE, and so on, I will try to steer the patient away from the Orladeyo because it's not quite as effective as Takhzyro or other forms of C1 esterase replacement therapy. But for at least half the patients, the severity is such that it's very reasonable to start with the oral medication, and as I say, the patients very often prefer it. So we'll start with the Orladeyo.

Now, the drug which is the most effective right now is Takhzyro, which is a monoclonal antibody against the receptor, and that agent is the agent that from my standpoint is the drug of choice in terms of the ability to really control the patients. It is initially given by once subcutaneous injection every couple of weeks, but what I have found is that in several of my patients, I can increase the interval so that I have some patients who are getting an injection once every six weeks. And there are drugs now in clinical trial phase 3 which claim that a single injection may be effective for up to six months, so with a six-month efficacy, that becomes very, very enticing.

QUESTION: Sure, absolutely.

15: And so, the KalVista agent, which is imminently coming on the market, may have the disadvantage of being an injectable, not IV, of course, but the long-term efficacy. Dauricin [phonetic] also has a longer half-life. So there are a couple of other agents which may be coming out soon, but right now, the two, the three major treatments are either giving somebody a C1 esterase replacement, that used to be what we had with the exception of the non-androgenic androgens; everything else was an injectable replacement, in one way or another, of giving C1 esterase.

Now, the first one that people used was fresh frozen plasma. Fresh frozen plasma works but you can appreciate that every plasma is going to be different. So when you say, okay, I'm going to give you three units of fresh frozen plasma, some of it will work better than others; there's the question of transmitting other kinds of diseases like [unintelligible] and other kinds of stuff; plus it has to be given intravenously; and it has a relatively short half-life. So disadvantages to it, but that was what we had.

Then when the C1 esterase was shown to be the problem, then again, the pharma companies taking very large groups of pooled serum will make a C1 esterase cocktail, and those are injected usually twice a week. But I've had some patients, for example, who were pregnant, and pregnant women had increased metabolic rates and other things; they had worse C1 esterase clinical disease that gets worse because of the metabolic effects and the stresses of pregnancy, blood volume [phonetic] increases, and so on. So I've had some patients who had to get an IV injection every day or two for their pregnancy. Now, it works and the babies were fine, but you can understand it's hell-on-wheels to get an injection every other day for nine months.

So the treatments now that are available are the C1 esterases which have become increasingly less popular because obviously, if we have, I'm talking about Berinert and Cinryze, those were the state-of-the-art for a while, Ruconest has come out which is a recombinant which also can work, and so, those agents; and then there is Haegarda, which is a subcutaneous injection that has an advantage obviously because it's subcutaneous, not IV. So those are available, but what we have been doing is we have been increasingly converting them to either the Orladeyo, which is the orally-active inhibitor of kallikrein, or the Takhzyro, which is the monoclonal antibody which lasts longer and is slightly less effective, but again, it's by injection.

So those are the two agents which are dominating the marketplace now, and all of the other agents are, as I see my patients and discuss them, we tend to convert them. And in the line, there are

other agents which are going to be here imminently, so it's hard to predict where the market is going to be going. And then, of course, the light at the end of the tunnel hopefully would be one of these genetic approaches.

QUESTION: Mm-hmm. So quick question: when you are talking with your patients about impact on their lives and quality of life, school, ability to work, things of that sort, and also just, of course, as you've talked about, the treatments that we choose impact people's quality of life as well, and clearly, that's a personal decision, are you using—

15: It's a personal decision but I emphasize that words like compliance are really bad words because—

QUESTION: —yes, I understand.

15: —the patient-doctor relationship is a bidirectional communication and the patient has to make the ultimate decisions, and my job is to minimize the impact of the disease on that patient in a way which is safe.

QUESTION: Of course, yes. Are you using any of the validated tools or questionnaires to look at quality of life? You're probably familiar that these have been the topic of research papers, presentations at conferences and the like. Are you guys using anything like that in your practice in a formal way?

15: Not in a formal way. These kinds of criteria are obviously necessary for the epidemiologic studies—

QUESTION: Mm-hmm, of course.

15: —[unintelligible] get the FDA to approve them, you have to show that they work. And there are the objective measurements, for example, how long it takes for the attack to occur, how frequently is there an attack, how fast will the attack respond to therapy, and so on. So those are a bunch of different objective treatments which, as I already mentioned to you, aren't always the same for each study but they kind of overlap, and those are important. But the most important thing, obviously, is the subjective because there are drugs, for example, like the original, I think the original treatment for HAE was turned down because of efficacy issues, but the patients liked it so much that using those criteria got approved.

So those objective types of questionnaires and so on, are very useful and are critical for the objective approval of agents, and for hopefully the evaluation of agents in terms of their efficacy and their safety. It's very important. However, there is a bunch of problems with them. One is that my patients aren't always the same: that is, I have some patients that for mysterious reasons, their C1 esterase manifested disease gets worse for no apparent reason and the darn treatment becomes inadequate. I've got others that all of a sudden, they got better, and I don't know why. Some of them stop menstruating and that may become an issue because there is a relationship with those issues. But each patient is different in terms of the stability.

Second, each patient is different in terms of the patient, the severity of disease, the frequency of disease, their perception of it, and that's important because some people are perfectly happy having one or two attacks a month, and other patients are miserable if they have one attack every three months. So there's that issue. So in other words, to apply these criteria to a given patient becomes very, very difficult. They're useful if you're looking at large numbers of patients.

The other thing which is really important is time because the way medicine works is that I only have a certain amount of time to evaluate my patients. I am there a long time so I can find, so I get as long as an hour for a complicated new patient and half-an-hour for follow-up, but most doctors don't have

that much time, and even with that much time, these questionnaires take time. And sometimes, it's not as simple as just giving them the questionnaire and having an MA look at it, so the patients themselves often are confused; it takes a long time for some. Some of them have 30-40 questions in them, and yes, it's great for a study but for an individual patient, it's not practical.

So my answer is I will do this occasionally if I have patient who we're kind of wrestling with optimal therapy and such, and to try to see where on the spectrum this patient is presenting because that will give me a little bit more information in terms of how aggressive I should be. But the patient is going to override whatever the questionnaire says [unintelligible] and it happens all the time.

And then, there are different, you know, some questionnaires are good for long-term control; others are better for acute control; some are better for severities. And I'm not denigrating them and they have been validated as measurements, but in the past, I've been in a couple of clinical trials and there, of course, the third party who is doing it, they're paying to have all of this additional information gathered. And it's not not useful, but on a clinical daily basis, no, I don't usually use it.

QUESTION: Yes, okay. I think you bring up some good points. Just to kind of let you know, I have an asthma research background; I was actually trained at [redacted] as a [redacted]. So like you, I probably did have the luxury of a lot more time than some of our colleagues in private practice have with our patients. But questionnaires take time and they take the time of our staff as well, and I think we all appreciate how busy our staff are. It's not just us running from room to room, right?

15: Yes.

QUESTION: I mean, they are trying to go through asthma action plans and teach people how to use an Epipen and it just gets, it's very time-consuming. And it sounds like—

(Overlapping Voices)

15: Yes, I'm just saying it's a respiratory experience you have, then obviously, you're aware of the ACQ scores and all those sort of things?

QUESTION: Mm-hmm.

15: And mostly they get you frustrated more than help you because the next time you do it, you get a totally different answer. So I'm all for science, believe me.

QUESTION: Oh, me too, yes. Absolutely.

(Overlapping Voices)

QUESTION: You're right, and ACQ is what, five questions?

15: Yes.

QUESTION: Right? And I have looked at—

15: And it's good for the last couple of weeks.

QUESTION: —exactly.

15: But if you see them [phonetic] for more than six months, it doesn't tell you anything about the other ones.

QUESTION: Exactly. So I think that's, you know, I have looked at the HAE instruments and I've looked carefully at the literature on those as well, and of course, FDA wants to incorporate patient experience and patient perceptions into outcomes, right?

15: Yes. [Unintelligible].

QUESTION: And those are very useful instruments. If you've got a research coordinator who is sitting down with someone to do a 30-question—

15: Yes, and somebody to pay that coordinator—

(Overlapping Voices)

QUESTION: Then that's fine. But yes, it can be very complicated even with the best intentions to look at things in that formal fashion. And you also mentioned that once you have laid out the options for patients, then you're having a pretty complex and nuanced discussion with them about what steps they want to take next.

15: Exactly, exactly. As I say, the decision is not mine to make. Now, I can obviously, based on my experience and my preconceived notions and whatever, whatever, can guide the patient and I'm sure nine times out of ten, the patient winds up doing what I kind of infer they should be doing, but you always have to keep looking at that and each patient may not give you the same answer to your own notions.

QUESTION: Sure, yes. Even on multiple occasions, people, patients like the rest of us, they change their minds over time.

15: Well, that's what I said earlier that I'm never quite sure what patient I'm going to see until I see that patient.

QUESTION: [laughter] Yes.

15: "But Mr. Jones, last, a few months ago, you were doing fine." "Yes, but I've had three attacks in the last week." So you understand that there is no stability here.

QUESTION: Yes.

15: HAE is especially variable.

QUESTION: Yes, yes. And of course, that makes it very challenging for our patients who have HAE to live with it, right? It's that uncertainty: will I have an attack, how bad will it be, what am I going to need to do, who's going to be around me when this happens? And asthma to a certain extent is like that as well, of course, when people have severe disease but it does make it, I think, a very, very challenging condition to live with. Do you use clinical guidelines? I mean, you may have actually even contributed to the writing of the clinical guidelines. I know these papers, obviously, they have dozens of authors. But are you using those in practice or in your teaching?

15: Certainly I'm using them in my teaching and sometimes in my practice. They're not as well-defined and they're not as believable and there aren't as many options as the clinical guidelines, for example, in asthma. In Europe, they have gotten some, they have done an even better job of giving us these steps and so on, and there are so many more options and there are so many more patients that there is a better clinical experience. So I wish that HAE had the same degree of guideline confidence that asthma does; it doesn't and there is a lot more variation there.

So I must confess that yes, I know the guidelines, I discuss them with our residents and our Fellows and so on in training, and I think it's useful, it's also useful in reading the literature critically to know what guideline, if any, they have been following, but on a daily basis with clinical patients, it's not so useful.

QUESTION: Do you see any issues, you know, clearly, you're someone who has kept up with this field, you're extraordinarily well read in it, you have literally dozens of patients with this condition, you've had the opportunity to have clinical experience over decades now—

15: Yes.

QUESTION: —and that's going to change the way that you see things and make your decisions. When you think about the solo practitioner who is out in private practice where these patients, they may only have one or two in their entire panel, what do you think are the barriers? What kinds of problems do you think they have? Maybe you've seen some of these come through in some of the referrals.

15: Yes, and the reasons why a lot of referrals come through, they come for two reasons. One is this patient has recurrent episodes of swelling and I read in this journal of this drug, of this condition, HAE, it's beyond the scope of my confidence, please evaluate. And then, there are a few patients who I made the diagnosis, and this is even allergy immunologists, but reading between the lines, it's not worth my time and effort to take care of that patient.

QUESTION: Oh, really?

Commented [7]: Codes (34616-34713)
Cases too complex for diagnosing MD

15: Yes. I mean, I don't have the experience; I don't have the time for these complicated patients. It's like patients with autoimmune disease: they may make the diagnosis of lupus but they surely don't want to take care of the patient with lupus once they've made the diagnosis. We're talking about doctors in general practice. Now, an allergist who is more familiar with this may not refer that often, but I can't say that that patient doesn't get as good care. There is really no, there has never been a head-to-head study saying how does the patient with HAE at a medical center, say, at [redacted] or [redacted] or [redacted] or something, do compared to an HAE patient in [unintelligible] [redacted]? We don't know that.

QUESTION: Yes, yes. That's interesting.

15: The internet, of course, closes that gap a lot.

QUESTION: Yes, of course, because I'm sure you have patients who are finding you via the internet and kind of self-referring them, right, if they're not, for whatever reasons, happy with their personal [phonetic].

15: Right. Or they go online to our medical center and they see the doctors and they see that [redacted] is here and he specializes in bah bah bah bah bah, and HAE, and they say, ah, oh, and there aren't a lot of doctors that have 30 years [unintelligible] patients.

QUESTION: Yes. The people who are referred to you with HAE, are you seeing any missteps, and I'm not laying blame on anybody, I really do believe that all providers no matter where they're practicing are trying to do their best, but are you seeing any missteps in terms of treatment or diagnosis that kind of pop up to you when you evaluate these folks in your practice?

15: Well, sometimes, I will get a patient who has been referred by another doctor who has been treated for HAE for a period of time and has not been doing well clinically, and it turns out that they have not been monitored properly; or they have not been educated in terms of what's going on with their illnesses and so on; or they stayed on, say, androgens longer than maybe they should have or something like that. Generally, the more patients you see, the more experienced you are and the more you can pick up on some nuances of modifications of treatments in the patient, and having them balance the acute and the chronic therapies is important. And so, those kinds of things are important. But I can't say, yes, this particular issue has been, yes, the diagnosis has been missed, but I have probably missed a diagnosis, too.

QUESTION: Oh, I think we all have. You practice long enough, that's the way that medicine is. And I have often said to my colleagues because I have also a critical care background, is that in critical care, you find out within hour, hours or days if you did something that wasn't quite right. And sometimes in clinical practice, things move so much more slowly that it takes a lot longer, right—

15: Yes, right [phonetic].

QUESTION: —for us to understand how we could have done things better. And so, anyway, I am just curious to hear your thoughts because I did see in my practice a lot of people who were referred with severe asthma or what was thought to be severe asthma, and again, no one was doing anything that intentionally was wrong; it's just that we often at a tertiary care, quaternary care setting, we have the advantage of seeing multiple complicated—

15: That's right [phonetic].

QUESTION: —bulk.

15: And you know then that asthma is a description of a clinical syndrome, and it can be primary or it can be secondary to a whole lot of other conditions, and with your greater knowledge, you can feed into those. C1 esterase is the same way, deficiency, because there are all kinds of idiopathic anaphylaxis that patients have: they have different kinds of acute allergic reactions, they have a lot of things which kind of look like but aren't HAE, and in those kinds of patients who have, I have more facilities, I have more experience and so on, and I can be more accurate in terms of making sure that, in fact, this clinical syndrome is due to a deficiency in the C1 esterase.

And the other point, too, is being in a major medical center, we can treat acutely with some of the IV medications, we can send nurses to the home so that patients can get treated at home, be treated more rapidly, for example, or prophylactically in situations where they themselves can't inject themselves but we can arrange for them to get that. So there are advantages that we have as a tertiary medical center that help the patients. Doesn't make me any better, but I can do a better job because I have more ancillary help.

QUESTION: Absolutely, yes, it's definitely a different situation. How did your participation in the CME activity influence the way that you think about HAE or translating evidence into clinical practice?

15: Well, I have to have a certain number of CME credits. It's pretty easy though because with the internal conferences that we have, we had it automatically [phonetic], and with a couple of meetings, you

can get 35 or 40 CME credits in one meeting, so it's not that bad. But if I see somebody who is a thought leader, every so often, I will take one of these CME courses, and even if you don't get too much out of it because it's watered down for a different population of people, but I think they are useful not so much for me because I'm a super-specialist but for the average physician; and it's an interesting disease, too, because of the manifestations because of what we know about the etiology and because of the multiple therapeutic approaches.

Commented [8]: Codes (39735-40055)
CME

QUESTION: Yes. I think it's fascinating to see targeted therapies coming onboard. I'm a medical writer in CME, so I cover a variety of different disease states, and I just finished a project on [redacted] where really for the first time, there are some targeted therapies that really target the disease mechanisms just like in HAE, not just kind of telling patients, well, you just have to be on tons of steroids, right?

15: Yes, when I was at the, I trained at the [redacted] in the [redacted] under [redacted] and at that time, IGA nephropathy was just coming out on the market and at that point, they were saying, ah, it doesn't cause any disease; it's just [unintelligible].

(Overlapping Voices)

15: —you've got a bad podocyte and you leak a little protein. Now, we're beginning to understand suddenly like you say, it is not a benign disease and there are specific treatments. And HAE is going in that direction as well, and asthma really has gone that way a lot in the [unintelligible] stuff.

QUESTION: Yes, yes. Asthma absolutely is in a different spot. Well, I do want to close because I know you have many important things that you need to get on to do today. I do appreciate your time. Is there anything else that you feel that I should know or that you'd like to share with us about HAE, or about education about HAE?

15: Well, I think the important thing is that HAE is a phenomenon which is being increasingly recognized, so we are picking up more cases. If you look at the frequency of the disease in, say, [redacted], it's really higher than it is in [unintelligible] [redacted]. So there is work to be done to popularize the importance of the disease. And also, it's a very exciting time because of all of these drugs now which many of them are on phase 2 or phase 3 trial, and they promise long-term benefits. Some of them, like I say, one injection every six months leads to a 95% decrease in the frequency of disease and a prolonged decrease in the mediators of the disease. So I think it is an exciting time, but I wish I was, I am predicting that within ten years, it won't exist anymore. It will be like sickle cell disease: you know, they have cured it a few times. So we will have the potential of curing it within the next few years.

QUESTION: Yes. That would be amazing. That would be so exciting especially for our patients who have to deal [phonetic] with these long-term conditions.

15: Well, I want to compliment you on the way you asked the right questions today in terms of—

QUESTION: Oh, thank you.

(Overlapping Voices)

15: —understanding.

QUESTION: Well, I very much appreciate your feedback, and I have talked to a variety of people. You are the first academic, academician in the area. You clearly have a longstanding interest in the area of

specialization around this, and I do appreciate the background and insight that you have been able to give me. I have to say one of my impressions in talking to many people in private practice is they struggle with how rare it is, and they just don't feel like they necessarily are able to stay up-to-date on a regular basis because again, they're just not seeing many people come in with this, versus your more typical allergic rhinitis, allergy, eczema, sort of allergy patients [inaudible].

(Overlapping Voices)

QUESTION: It makes it tough for them.

15: If my whole life was taking care of [unintelligible] allergies, I would go nuts. [laughter] It's good to be in a tertiary referral center like I'm at, and that gives me, that makes C1 esterase deficiency not so terribly uncommon, two or three new cases a year. That's not very common but it's pretty common compared to the average practitioner. And if you don't feel comfortable with it, you know, the first time I saw my first case of asthma, I panicked, and now, all we have [unintelligible]. All right, so thank you very much.

[IRRELEVANT MATERIAL OMITTED]

15: Are you going to be incorporating this into a publication or what?

QUESTION: We will, and of course, everything, you know, none of this is going to be, it's all de-identified data. We're going to use some software that basically extracts common and important themes from all of the conversations that I'm having with healthcare providers.

15: If I may make a request?

QUESTION: Sure.

15: When you publish this, if you could let me know because I think I'd find it very interesting to read.

QUESTION: Oh, absolutely. Yes, thank you. We would be delighted to try to pass that on to you. First steps first, we've got to write it and publish it, but yes, thank you.

15: Okay.

QUESTION: We appreciate your interest. Thank you.

[IRRELEVANT MATERIAL OMITTED]

[END 15 3.20.24.M4A]