Updates on Chronic Spontaneous Urticaria

Adam Friedman, MD, FAAD, interviewed by Charles Dunn, MD

CHARLES DUNN, MD: Hello and welcome to another exciting episode of *Dialogues in Dermatology*. It is my honor and privilege to welcome one of my favorite guests that I've ever spoken with. My name is Charlie Dunn. I'm a chief dermatology resident down in KCU/ADCS in Orlando. I'm with Dr. Adam Friedman. Dr. Friedman is the Professor and Chair of the department of dermatology at the George Washington School of Medicine and Health Sciences. Dr. Friedman, thank you so much for joining us.

ADAM FRIEDMAN, MD, FAAD: The pleasure is all on this side of the table.

CHARLES DUNN, MD: This is going to be a very fun interview. I know that there are many things that you can talk about. The main emphasis that we're going to talk about today is actually chronic spontaneous urticaria, with an emphasis on immunomodulators. So I want you to treat me as if I am a Neanderthal because I am, in fact, a Neanderthal in this case. Let's start off with something basic. Could you talk me through what is chronic spontaneous urticaria?

ADAM FRIEDMAN, MD, FAAD: It's funny, that was how this was prefaced, talk very slow, don't make any sudden movements to set you off. So chronic spontaneous urticaria is one flavor of the urticarias. The way we start to divide it up is acute versus chronic. For some reason, we have this line in the sand of six weeks. Why, how, who? Probably a bunch of people in a hotel room during a conference like this that said, "Six weeks sounds good, let's go with that."—

--It probably wasn't like that, I'm sure I'm going to get some hate mail. But with acute urticaria, I just want a moment on that, I would argue most people experience one bout of it. I certainly have, my son has. And we can narrow it down typically to food, drug, or bug, bug being infection and I think infection play a very big role. Typically this will manifest and last maybe about four to six weeks, usually less than that. Not like we're going to wait for it to burn out. But being very

common, 80 percent of individuals in the United States alone get this, that's not the burden we're talking about.—

--What we're really focusing on is chronic disease. I think it's really important to mention that it's not that you have this for six weeks continuously and now magically you're in the chronic category. But it can wax and wane. I think that adds to the burden and it's a unique burden in that as opposed to all the horrible diseases we manage that impact so many facets of daily life that we certainly take for granted, urticaria comes on like the DeLorean in "Back To the Future," zero to 60, 66, 60-something, I clearly have to watch that again, it comes on in nanoseconds.—

--The fact that you never know when that shoe is going to drop. And it's not that you get the boiling up of atopic dermatitis, rather that you could be sitting there, hanging on, just throwing some rizz, and all of a sudden you are covered head to toe in urticarial plaques. Threw that in there for my son. Also, all you lovers of the word "rizz," as it was the word of the year, 2023 was such a fortunate year for humankind based on that alone. So I think it's really important to take this seriously, even the acute phase.—

--But when you start to get chronic, something to note, the longer you have it, the less likely it will go into remission. The more resistant it is to first line therapies like antihistamines, the less likely it will go into remission. There's a good subset of patients who will have this ongoing. Now, given this sounds like something very much in our wheelhouse, this sounds like so many diseases we take care of, you would think that we're the go-to people, that when you think of urticaria you think dermatology. That's not the case and that's a real problem.—

--I think there's a big set and collection of misinformation on this, first and foremost, that this is an allergy. Chronic spontaneous urticaria was once called chronic idiopathic urticaria, idiopathic being the fancy word for we have no freaking idea why this is happening.

CHARLES DUNN, MD: We're idiots.

ADAM FRIEDMAN, MD, FAAD: I wasn't going to go there. This is television, my friend. Like FCC is going to shut us down. So I think that it's important to emphasize that this is a chronic inflammatory disease, with most likely no real cause that we can identify. There are subsets, we know there's maybe 30 percent population of this group that has some underlying autoimmune disease. If in your wonderful review of systems, which I know everyone does, there's something that stands out, like "Oh, yeah, I'm gaining weight. I feel very puffy. My hair is thinning," like maybe hypothyroidism, autoimmune thyroiditis, sure.—

--But in general, you're not going to find something so please, do not waste time, dime, and blood to work these patients up to the ends of the earth, because you're probably not going to find something related to this, but you might find something else that causes more issues. So we really need to maintain that idiopathic piece of the former name, even though it's chronic spontaneous urticaria. In chronic urticaria, we also have inducible hives which are so much fun as a dermatologist. We get to do a lot of stuff at the bedside. I love doing a good KOH, which has nothing to do with this, but I'm going to make a plug for KOH. Conflict of interest: I love KOH's.—

--It's not like I'm wearing a Swartz-Lamkins t-shirt right now, I wish I were, that's my favorite stain. But I think that there's things we can do bedside that really make a big difference. Doing inducible testing, whether it be dermatographia, using an ice cube, having them do jumping jacks for cholinergic urticaria, even if you think something is chronic spontaneous urticaria, you still want to do those because they overlap. So you're allowed to have more than one flavor of disease and also allowed to have more conditions.—

--So with all that said, your passed the acute mark, your chronic spontaneous urticaria, what do we do about it? I think you have a good conversation with the patient, tell them what it is, what it

isn't. But then you turn to our whopping, not so whopping armament. I think that's one of the reasons why this isn't considered necessarily in the derm space or our patients don't necessarily know that, because we don't have a lot of things to do. And I think we really get behind a disease when there are a lot of great options. Antihistamines, second generation, nonsedating are going to be our first line.—

--The key thing is you want to ramp up. I definitely had some fun this morning in my talk saying you want to push it, not just real good but real great. I think I highlight that because when you say push, it means you're going to do it quickly, like you're pushing towards something. You're not going to wait weeks, you're going to push, and it varies from patient to patient, but usually I'll start them on double the standard dose. And in a week if they're not clear, they're going to three times. In a week if they're not clear, they're going to four times.—

--A week after that, they're going to reach out to me in MyChart, because we have Epic, and they're going to tell me how they're doing. If they're not better at that point, that's the beauty of these antihistamines, if they work, they work; if they don't, they don't, you know. You know what you're getting, face value, then you're going to the next thing. There may be some adjunctive things I'll do in the meantime, but in general I'm going to then go to the next level, which will be omalizumab. If the patient is willing, if I can get it covered, which usually there is no issue with that, it's become a lot easier but I think that there's a lot of baggage historically why I think derms don't necessarily jump at the occasion to use it.—

--You just have to stir it up, it's really viscous, draw it up, keep patients in the office for the 0.2 percent risk of anaphylaxis. Yeah, 0.2 percent.

CHARLES DUNN, MD: That is 0.2 percent, just to clarify.

ADAM FRIEDMAN, MD, FAAD: 0.20000 percent. Listen, any risk of anaphylaxis, we're going to be worried. But I think that black box is really overstated. And because of the real lack of concern, it's gotten easier. Certainly not having to keep them every time. So now you're supposed to keep them in the office the first two or three times and then with a prefilled syringe, you can do it from home. Standard dosing is 300 mg a month. I do off-label sometimes 450. If someone is breaking through towards the end of that four week period, I'll do the 150 every two weeks.—

--There's a lot of ways you can do it, so long as you can get access to it. That's about it for on-label, which I think is one of the reasons why we're not jumping to really manage these patients. But there's a lot of off-label and I think that that's the most fun thing about being a dermatologist. Because of the way our training is structured, there's such a focus on bench to bedside. We can think of a mechanism how a drug works, think about the underpinnings of disease, and bring the two together for some sweet love and make some magic. And that's what we have to do for a lot of these patients.

CHARLES DUNN, MD: And we have a lot of uncomfortable listeners right now in their cars but that's totally okay, I think.

ADAM FRIEDMAN, MD, FAAD: They're hot and bothered. Really, what's happening here?

CHARLES DUNN, MD: I have a couple maybe like finetune points that I'm just personally interested in.

ADAM FRIEDMAN, MD, FAAD: It's not all about you, okay?

CHARLES DUNN, MD: I'm sorry, that our listeners are interested in. Is there any difference between the nonsedating antihistamines in terms of efficacy from what you see?

ADAM FRIEDMAN, MD, FAAD: That's a great question that I don't have a great answer for. Maybe a better way to start is which of the nonsedating antihistamines are truly nonsedating, because I think that terminology is misleading, Many of them are for patients. Fexofenadine by far is the least. So if you were coming in, we make the diagnosis of CSU or even acute urticaria, most likely you've tried something over-the-counter. And so that's a good starting point. "Oh, you took loratadine. You took cetirizine. Did it make you drowsy?" "No, not at all." "Okay, I want to keep it simple. We're going to ramp that up."—

--If they're like, "Yeah, I'm really struggling. I don't really know what to do. I take it, I need it, but then I feel badly," then I'll go with two. I'll do fexofenadine in the morning and in terms of what has the most efficacy would be levocetirizine." Which when over-the-counter, actually this is an interesting pearl, if you were to buy it over-the-counter, the trade of it, it's pretty expensive. You can write the generic form, that's still covered by insurance, it's actually cheaper. The problem is you only can get the standard daily dosing, whereas we go higher. So you have to kind of mix and match.—

--I think it's the same, depending on insurance, is cetirizine as well. But I think levocetirizine is the most impactful, it's also the most sedating. So it's going to be a personalized approach. The other thing I always like to throw in there is vitamin D. We talk about high dose vitamin D, meaning like 4,000 IU, which is not the high dose we think of with internal medicine, like a 50,000. I'm not talking about that, this is you can buy this over-the-counter. There's some evidence that low vitamin D is a biomarker for disease severity and that patients with CSU tend to be vitamin D deficient or insufficient.—

--At the end of the day, we all need vitamin D and patients love the fact that we acknowledge, "You should probably take some vitamin D," kind of a no-brainer. Maybe it boosts the effect of your fourfold dosing of antihistamines. How much? I don't know, there have been a couple

published studies but it's low hanging fruit. And it's also a way to say, "I'm not just doing what you expect. I'm throwing you a curveball with some vitamin D. You didn't think I was going to say that or throwing it your way." So I think that's a way of getting them also more engaged and more adherent with your approach.

CHARLES DUNN, MD: I also feel that there is maybe certain patient populations where they're appreciative of the fact that you're considering complementary and alternative medicine approaches, which I think is really valuable I think for patients. So what about things like H2, like H2 blockers? Or we can even go down kind of other things that maybe you've seen that are false, that aren't true, or are true, could you speak to that?

ADAM FRIEDMAN, MD, FAAD: Let's take a walk down memory lane, where we used to have what I like to call the triple threat, which was your H1, H2, and leukotriene antagonist. So things like montelukast, ranitidine, famotidine, studies supporting their use. It's so hard to keep track of which one is in favor and which one isn't. It's a whole lot of flipflopping in the guidelines. First, leukotriene antagonists were kicked out, now they're back. Then it's H2 were out. It's a bit confusing. I used to put patients on all three and I loved it. I'm like, "Yeah, it's like Chuck Norris, triple threat. Chuck Norris walks on water."—

--Go roundhouse kick your urticaria with the triple threat. So it keeps going back and forth. So at this point, I've just said forget it. It's a lot of pills to give someone. Is it really adding that much? So I've kind of gone away with it. Vitamin D, I think that's one of those things they need anyway. It's hard, the recent European guidance was to say no to H2 blockers. I think one thing to comment on, granted this is not over-the-counter, prednisone. Let's address the elephant in the room. Your Medrol Dosepak, you get them better real fast, and then they are back with a vengeance and they will hate you for it.—

--There is evidence that adding prednisone is no better than levocetirizine. I will say it works fast and I would say that if you want something fast, cyclosporin works fast too and has more evidence and still in the guidelines. The problem with cyclosporin is your really not supposed to be on it longer than six months to a year. This is a chronic, longstanding disease. It's a good way to get them clear and keep them clear while you're figuring out what on earth are you going to do next. But there's some nice, small level data outside of cyclosporin, methotrexate, mycophenolate mofetil.—

--Even some immunomodulators like dapsone and colchicine, which I think you can work through. Those guidelines I just mentioned said not to do that. They also talk about don't waste your time with things like doxepin or SSRIs. It's easy to say that but what are you going to do? You have so little options. Like, "Oh, don't do that," but "hey, don't do anything?" So I still do employ them and I think there are definitely a subset of patients on omalizumab that do not respond even at up dosing. So at the end of the day, we need industry to really push and bring some new things to the table.

CHARLES DUNN, MD: That was actually going to be my next question. What sorts of new things have you seen or heard of that are on the horizon that are maybe promising or not so promising?

ADAM FRIEDMAN, MD, FAAD: There finally is a horizon. And that's not such a surprise. If you look at history, let's think about some other diseases for which there was nothing and now there's so much. Atopic derm would be a great example. Everything is like psoriasis, psoriasis, psoriasis, everyone loves psoriasis. Yet AD affects god knows how many more people? But now we have that. We're at a point where we're getting lots of things for atopic derm. Hidradenitis suppurativa, CSU is following the suit. We are seeing a pipeline. We are seeing

lateralization of certain medications we already have, like dupilumab. We're seeing novel molecules that are targeting things that as derms we've never gone after, like BTK.—

--So remibrutinib, for example. And there are other biologics coming down the road. But the first two, dupilumab and remibrutinib, we're probably going to see I'm hoping at least in the next year plus. And there are many more coming down the road. So hope is on the way. I think we've seen this pattern before. As soon as you get some new drugs and industry is like, "Look at me, look at the shiny new thing. We're going to throw a ton of money at it." One, everyone gets really interested, and we really need that. But two, there's all this funding for education.—

--There's funding to understand the disease better. So often, we learn more about a disease when we have a new drug for it. It's not the other way around. You don't have this massive, multibillion dollar lab being like, "We're going to cure CSU in the next three months." But as a drug comes out and how it behaves tells you a lot about the underpinnings of disease and I think there's a lot we don't know about CSU.

CHARLES DUNN, MD: That's I think a pretty hopeful view and approach on it, that's really encouraging. I think there's so much more that we can say. What are some resources that you might point dermatologists to, as well as maybe patient-focused resources that you know has been really helpful in your practice?

ADAM FRIEDMAN, MD, FAAD: That's such a great question because there really isn't much. I will say there are these things called UCARE centers, which are the Center of Excellence for Urticaria. Probably most people don't know these exist and to actually have one, you need to have a collaboration with allergy immunology. There are several in the United States, which is great. They're more prevalent, they actually came out of Europe. So there are these resources, there is stuff that comes out of these centers. But you actually bring up a great point that I'm glad I can comment on.—

--We need a patient-facing organization for chronic spontaneous urticaria. We have it, National Eczema Association, HS Connect, NPF kind of plays both sides of it. There is nothing that I am aware of, and if I'm wrong I would love to be wrong, I'm not aware of anything for urticaria. And your question points to us needing that very badly. So that's a great question.

CHARLES DUNN, MD: For all you interested residents out there, this is a great quality improvement initiative opportunity. So thank you so much. Maybe just to finish this out, can you give us maybe three or four pearls that kind of you think of whenever you want to communicate with people about chronic spontaneous urticaria?

ADAM FRIEDMAN, MD, FAAD: It's all in the history. You have to ask the right questions. And the number one question is, will that spot I see right now on your skin be there tomorrow? If something lasts longer than 24, 48 hours, it cannot be urticaria. Number two is do not go crazy with the workup. They may be referred for a biopsy. Explain that you do not need to cut into them unless, once again, it's urticarial and not urticaria. From a treatment perspective, we are so used to using things off-label, we're also used to combining therapies.—

--We are the combination king, queens, whatever you define yourself as, we know how to do that. Do not lateralize. If something fails, you add on, you don't kick it to the curb.

CHARLES DUNN, MD: Those are great pearls. Thank you so much, Dr. Friedman, for joining us.

ADAM FRIEDMAN, MD, FAAD: My pleasure.

CHARLES DUNN, MD: Thank you so much to the audience for joining us. I hope you guys have a wonderful rest of your day. Thanks for joining *Dialogues in Dermatology*.

Commentary

Eryn Patin, BS; Kathyana Santiago, BA; Arianne Shadi Kourosh, MD, MPH with Benjamin Stoff, MD, FAAD (ed.)

Chronic spontaneous urticaria (CSU) is a chronic inflammatory disorder characterized by the spontaneous development of urticarial lesions, including wheals and angioedema, on various body sites. Individual wheals typically resolve without scarring within 24 hours of onset and recur. Symptoms persist for a minimum of six weeks with waxing and waning, and urticarial lesions can recur months or even years following what may appear to be complete remission.[1] Although CSU has been associated with autoimmunity due to the presence of mast-activating autoantibodies, most cases persist in the absence of an identifiable trigger. In this episode of Dialogues, Dr. Charlie Dunn interviews Dr. Adam Friedman of George Washington University about various updates to the management of chronic spontaneous urticaria.

First-line therapy for CSU involves second-generation antihistamines, such as cetirizine, fexofenadine, and loratadine or third generation antihistamines, such as levocetirizine. If symptoms are initially unresponsive to the standard dosage of these antihistamines, dose escalation up to four times the standard dose may be necessary and is considered standard practice.[1] For patients with antihistamine-refractory variants, biologics like dupilumab and remibrutinib have shown efficacy as off-label treatment options.[2] In some cases, a short course of systemic corticosteroids may be used in conjunction with antihistamines in order to control acute exacerbations. However, this approach is not suitable for long-term management .[3] Low vitamin D levels may serve as a biomarker for disease severity in patients with CSU, who frequently have vitamin D deficiency or insufficiency. Consequently, vitamin D supplementation may not only reduce disease severity but has also been shown in recent studies to enhance the efficacy of antihistamines.[4] It is important to note that nonsteroidal anti-inflammatory drugs (NSAIDs) and other medications that can cause non-allergic hypersensitivity reactions should be avoided in patients with a diagnosis of CSU, as they have been shown to trigger acute exacerbations.[1]

5 key takeaways on this topic from today's episode include:

1. CSU persists for 6 weeks or longer. It is characterized by the spontaneous development of urticarial lesions, including **wheals** and **angioedema**, which may arise on any body site.
2. Once chronic spontaneous urticaria develops, the longer it persists and the more resistant it becomes to first-line therapies such as antihistamines, the less likely it is to enter remission.
3. While chronic spontaneous urticaria may be associated with autoimmune conditions, a comprehensive workup is generally unnecessary unless the patient presents with specific concerns during the review of systems.
4. First-line therapy for chronic spontaneous urticaria involves the use of **second-generation antihistamines**, which may need to be titrated up to **four times** the standard dose to effectively manage the condition.
5. The use of biologics, such as dupilumab and remibrutinib, represents an emerging therapeutic strategy that has demonstrated promise in the management of antihistamine-refractory variants of chronic spontaneous urticaria.

Thanks for listening!

References

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