Autoinflammatory Diseases

George Han, MD, interviewed by M. Laurin Council, MD

M. LAURIN COUNCIL, MD: Hello and welcome to *Dialogues in Dermatology*. I am Laurin Council at Washington University, in St. Louis, Missouri. And I have the distinct honor today of speaking with Dr. George Han. Dr. Han is Chairman of the Department of Dermatology at Mount Sinai Beth Israel, where he is also the Director of Teledermatology. Today, we're going to be speaking on the topic of autoinflammatory diseases for the dermatologist. Welcome.

GEORGE HAN, MD: Thank you very much.

M. LAURIN COUNCIL, MD: Dr. Han, can you first take a moment to define autoinflammation for our listeners?

GEORGE HAN, MD: Sure. So autoinflammation was a concept that's just introduced within the past few decades. It was originally thought to be a mechanism whereby some of these neutrophil-rich inflammatory diseases expressed themselves. And we've gotten a lot of understanding about the basic science behind autoinflammation. I would say in general, autoinflammation is characterized by neutrophil-rich inflammation, so activation of the IL-1 interleukin pathway, and by triggering of something called an inflammasome, which we'll talk about, I'm sure, as well. And it's really gotten a lot of traction recently, both because it really classically drives a lot of these autoinflammatory diseases that we see in dermatology, although rarely. But also has a big component to play in some of the more common things that we deal with on a day-to-day basis, as well.

M. LAURIN COUNCIL, MD: And autoinflammation is different from autoimmunity, correct?

GEORGE HAN, MD: Yes. So they're pretty different concepts. There is some degree of overlap, of course. But in general, they kind of have differing, and in many ways opposite, driving factors. So I would say in autoinflammation, it's really neutrophil-characterized. Whereas in autoimmunity, we tend to think about more T and B cells and lymphocytes as the active mediators. There's really no activation of the adaptive immunity response system in autoinflammation, which is what drives autoimmunity. In autoimmunity, you often have soluble autoantibodies. Whereas in autoinflammation, you don't see any of that. And I would say in general, the way to think about this is that autoinflammation is characterized by really host versus danger signals. So when your own body senses either a foreign invader, bacteria, or cancer cells that aren't supposed to be there, that's when we think of activation of the autoinflammatory pathway. Whereas autoimmunity, it's more self versus non-self. So you're looking at autoantibodies in that sense.

M. LAURIN COUNCIL, MD: And there are some key molecules that are central to autoinflammation. What are these?

GEORGE HAN, MD: In autoinflammation, the most critical regulator is IL-1-beta. There to a lesser degree, IL-18 is also involved in autoinflammation. But really much of the research has centered around IL-1-beta, how it's activated and what the pathway is. And certainly, IL-1-beta is the effector molecule. It has a lot of downstream effects, such as activating TNF-alpha, IL-6, leading to pyrogens such as Cox-2 being released. So it's really a pretty powerful inflammatory mediator. In terms of looking at how it all ties together, there's the concept of the inflammasome, which is a molecular platform for really driving the autoinflammation. And IL-1-beta is activated by the inflammasome. There actually is some crosstalk between this pathway and the toll-like receptor pathway, because when you have a foreign pathogen-associated molecular profile, for example, it can activate the toll-like receptor pathway, which then leads to up regulation of pro-IL-1-beta production.

And then that kind of ties in over to the whole inflammasome cascade, where you have the same pathogen-associated molecular profiles, which then activate the inflammasome and convert the pro-IL-1-beta to its active form. And then that leads to the inflammation that you see in autoinflammation.

M. LAURIN COUNCIL, MD: Autoinflammation is a critical component of several diseases. And you mentioned that interleukins are important in these diseases, as well. Do we have any commercially available inhibitors of interleukins?

GEORGE HAN, MD: That's a great question. So we really do have three current medications in our armamentarium specifically targeting IL-1. And it really begs the question, there were some others in the pipeline and maybe some others that are being worked on, too. You start to wonder whether this is going to be the next great frontier in dermatology really. Because not only are these medications now FDA approved for some of the classical autoinflammatory diseases that are genetically linked to autoinflammation, but there is some mounting evidence that use of these inhibitors targeting IL-1-beta can really help us in our recalcitrant cases of other inflammatory skin conditions that we've traditionally relied on other mechanisms to treat and we'll talk about that later, I'm sure. In terms of what's specifically available, there's anakinra, which is a competitive inhibitor of IL-1. That one has been out probably the longest and we have some good experience with it. However, it's a daily subcutaneous injection and there are some downsides, compared to the newer medicines which are canakinumab and rilonacept. Those have longer half-lives. They can be dosed anywhere from one week to two months, in some cases. The other two medicines in this realm are rilonacept and canakinumab. Rilonacept being a fusion protein and canakinumab being a monoclonal antibody. And both of these inhibit IL-1-beta. The dosing of these is much more favorable, with rilonacept being every week and canakinumab being up to two months, in some cases. So we do have several medicines that seem to work well for some of these diseases and we'll talk about the uses, I guess.

M. LAURIN COUNCIL, MD: Sure. What are some of the classic autoinflammatory diseases?

GEORGE HAN, MD: Our understanding of these diseases has evolved. So I think the nomenclature, as well as the categorization is still evolving in some ways. The most common autoinflammatory disease or classic autoinflammatory disease is familial Mediterranean fever. It's still quite rare in this country, although the incidence can be higher in other areas of the world. The other one that we hear most about are now known as the cryopyrin-associated periodic syndromes. And this encompasses the entities that we may have heard of more often in the past, which are familial cold urticaria, Muckle-Wells, and NOMID, or neonatal-onset multisystem inflammatory disease. So these are all examples of the kind of zebras that we might have remembered to learn in our residency. I actually remember one of my attendings, I asked him, "Have you ever seen these diseases?" And he replied, "Only in my dreams." So we might not see them so often, but in essence they are out there. And they are important to know, because when you treat them and catch them early, it really makes a difference in these patients' lives. For example, if you look at Muckle-Wells syndrome, part of the cryopyrin-associated periodic syndromes, the earlier you treat these patients, the better chance you have of saving their hearing and saving their kidneys, as well. Because one of the issues that people get with that is amyloid deposition in the kidneys, leading to kidney failure at a very young age and also the deafness, as well. There are some other more rare entities, hyper-IgD syndrome, TRAPS or the TNF-associated, TNF-receptor associated periodic syndrome. And these are interesting, as well, characterized by autoinflammation. It's difficult to really put it together in a clinically relevant way, because they are so rare. But I think at least having a knowledge of these entities and knowing what to look out for is important in our patient care, so when you do see somebody with episodes of joint pain associated with urticaria-like plaques, you might do a biopsy and the biopsy might return as neutrophilic urticaria. I would say it's important to think about these autoinflammatory syndromes.

M. LAURIN COUNCIL, MD: Thank you. I also cannot say that I've actually seen any of these patients in person. But certainly, there are many patients who have autoinflammatory diseases. What are some of the more common conditions that we see in dermatology where autoinflammation may play a role?

GEORGE HAN, MD: So it turns out autoinflammation has a big component in a lot of things that we treat day to day, that I'm sure the listeners are seeing today even, such as acne. So there's been mounting evidence that acne is really driven by autoinflammation. The P. acne is when it gets out of the pilosebaceous unit, does activate IL-1-beta and lead to activation of the inflammasome and then the neutrophils come in and create inflammation, so especially in your pustular acne.And by extension, you look at these juvenile syndromes that we're looking at, PASH, PAPA, all of those seem to be tied pretty strongly to inflammasome activation and autoinflammation. So that's one aspect of acne that we always think about treating things like acne and rosacea with our antiinflammatory antibiotics, right? We think about how to target inflammation here. And so we've really been thinking about these concepts for a long time but it's really coming together now, where the basic science is tying together nicely with what we're seeing in the clinics. So hopefully, this will lead to more and more evolution of how we treat these diseases. Other conditions that are pretty common include hidradenitis suppurativa. So it's been shown that there's increased levels of IL-1-beta in hidradenitis suppurativa. There are some case reports out there of IL-1-beta inhibitors, such as anakinra, working in recalcitrant cases of HS that failed on treatment with steroids, cyclosporin, and even infliximab. So that is one thing to look out for, if you have a particularly recalcitrant case of HS that not even the FDA-approved treatments are working, it might be worth thinking about reaching for an IL-1 inhibitor. Another condition that often flummoxes us is pyoderma gangrenosum. It's obviously very difficult to treat in severe cases, it takes a long time to get better. It's again been shown that IL-1-beta is increased in pyoderma gangrenosum. And the thought is here that this chronic, longer

term activation of the inflammasome leads to all this unproductive inflammation that you see in pyoderma gangrenosum which just leads to a non-healing wound. So targeting this with IL-1-beta inhibitors has been really successful in some cases. There are many case reports of canakinumab working well in really, really refractory cases of pyoderma gangrenosum. The last topic we'll talk about here is psoriasis. We know certainly psoriasis, there's a lot of great medications out there for psoriasis. But I think there are certainly some cases of psoriasis that are tied to specific genetic defects. In the caspase, the CARD mutations that we've heard of, the CARD being caspase-associated recruitment domains. So caspases are actually part of the inflammasome. So when you look at certain familial forms of psoriasis, and these are clinically characterized more by pustular psoriasis, you really might think about these tying in more with autoinflammation and that might be an attractive target down the line. Now, I will preface this by saying that IL-1 inhibition hasn't been consistently successful in psoriasis, but I think part of it might also be selecting out the right patient with psoriasis. Certainly, I would not reach for these at all in patients with plaque psoriasis. But certain pustular forms, you really might think about or consider it in your treatment armamentarium. I think as we go forward, there will be more and more coming out with relating autoinflammation to how we understand a lot of the diseases that we treat. There certainly is a role in some of these cytokines that we're talking about in tumorigenesis, in metastasis of melanomas, for instance. So I think there's a lot in there, in the basic science, that will help us tease out better treatment strategies for a lot of things we deal with on a day-to-day basis.

M. LAURIN COUNCIL, MD: That's a very good point. Some of these classic conditions have led us to understand the role of autoinflammation in some of the things that we see more commonly. And as our understanding increases, we can certainly expand it to help us in other conditions, as well. Dr. Han, thank you very much for this interesting discussion. You've clarified the difference for our listeners between autoinflammation and autoimmunity. You defined the

key molecules and how this is important for therapeutics. And you've reviewed the common dermatologic conditions that evolve within this realm. Do you have any final thoughts with which you'd like to leave our listeners?

GEORGE HAN, MD: I think the traditional view of autoinflammation has been one that's somewhat confusing. I mean, whenever you pick up a journal article about autoinflammation and you start reading about all this alphabet soup of IL-1s and CARDS and caspases and ASCs, it gets a little confusing. But I think what's really important here is knowing that we've been thinking about autoinflammation and the role of these molecular patterns activating this very, very exuberant inflammatory response in a lot of dermatologic conditions. I mean, there has been an argument made recently that all neutrophilic dermatoses are actually manifestations of autoinflammation. So these are concepts that we've been maybe not literally thinking about, but actually knowing about for quite some time. And I think now we've entered an era in this space where the basic science finally is catching up with our clinical practice. And we already have three medications that can target this pathway. I would imagine there will be more coming down the line. And as we learn how to use these better, I think it really will improve our treatment for our patients. Not only with these rare zebras or these autoinflammatory diseases, which really by the way it changes these patients' quality of life drastically, but also for really common conditions that we deal with on a day-to-day basis. So hopefully, there's a lot more to come in this realm and I'm looking forward to see a lot more progress here.

M. LAURIN COUNCIL, MD: I'm looking forward to that, as well. Thank you.