Prurigo Nodularis: Recognizing, Diagnosing and Treating a Rare but Debilitating Disease

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OVERVIEW OF PRURIGO NODULARIS

Definition

Jonathan Silverberg, MD: The term prurigo is actually something that was introduced a long time ago by Robert William as a term to describe itchy papules and it's often used differently in different settings or broadly. Prurigo is often used without clear criteria and often can be used to reference multiple conditions. Historically, other terms have been added to further differentiate the specific subtype, such as prurigo mitis or prurigo pigmentosa and, of course, prurigo nodularis.

We'll focus on that specific subset of prurigo nodularis (PN) as a very distinct entity. It's thought to be a relatively uncommon disorder. It's a chronic inflammatory skin disease. I think this is something that, even in the past few years, our entire understanding of the pathophysiology has changed and now we recognize that this is an inflammatory skin disease which is characterized by the presence of chronic itch and multiple, firm, generally symmetrically distributed, itchy, pruritic nodules. And these can have a profound impact on patients' quality of life.

Classification

Jonathan Silverberg, MD: When thinking about classification of prurigo nodularis, it really depends on where in the world you are. And there is a little bit of a divergent perspective between the US and the European key opinion leaders in this field. In the United States, prurigo nodularis includes other variants, such as papular, plaque or umbilicated lesions due to similar clinical picture, whereas in Europe, PN is a subtype of chronic prurigo. We think of PN as a distinct entity and there can be mixed morphologies. In Europe, there is this broader lumping of chronic prurigo and PN is 1 subset of that, but they've tried to take everything that's chronic and itchy, and lump it into this broader chronic prurigo category. And there is always this philosophical debate of lumper or splitter, and whether these distinctions are that important is unclear.

But I think it's important for us to understand this background so that, when we are using terminology, we are as precise as possible, and we are referring to what we want to be referring to. We should also be careful when we are coding this in patient encounters because the International Classification of Disease 10 (ICD-10) classification lists prurigo nodularis as a distinct disease of L28.1, whereas previously, PN was grouped together with other pruritic conditions. So, there is an acknowledgment that this is a distinct disorder. I would be very cautious also in documentation and in interacting with patients to avoid using the prurigo term outside of prurigo nodularis or these very specific, chronic, itchy disorders. And what I mean by that is we can see prurigo nodules as a morphology as part of atopic dermatitis or even lichen planus or other inflammatory skin diseases. That's not prurigo nodularis. That just happens to be the morphology of prurigo nodules occurring in other inflammatory diseases. So, when we use this term, we should mean that this is specifically the entity of prurigo nodularis.

Epidemiology/Demographics

Najat Watch, PA: The International Classification of Diseases does estimate that, on average, 72 per 100,000 people in the United States have prurigo nodularis, although I think most people feel that this is an underestimation. There is a lack of disease awareness. There are stigmas associated with this disease and so the estimation is low. We know that this is more common in older adults over age 65 years, but we see this in all age groups, with the average being between about 50 and 65 years. What we do know is African Americans are 3.4 times more likely to develop this disease compared to Caucasians and we see, on average, about 5% of those with HIV suffering from this disease.

Disease Manifestations

Jonathan Silverberg, MD: The terminology prurigo nodularis implies nodules and that's what we expect to see, but it's not only those firm, rock-hard, dome-shaped nodules. First, they can be papules that technically fall short of the measurement specifications for a nodule. They can be in different stages of progression or healing. But the patients don't only just pick, they may also scratch, and we'll see erosions, ulceration of the skin. We'll often see erythema which, in darker skin tones, will show up more with shades of browns and purples, rather than shades of light pink or red. The lesions are going to be symmetric in terms of their appearance on the extremities, and they generally will spare certain key areas, like the butterfly area on the back, just because it's hard to reach and scratch there, although I've had patients get very creative and scratch in those areas with even toilet scrubbing brushes, causing those areas to be infected. And they won't scratch or pick at the face as much, and, even then, we see sometimes that patients will be itchy and have lesions around the head and neck area. It's quite heterogenous in terms of the distribution and the localization of the lesions.

Those are the visual aspects, but of course symptomatically, it's all about the itch. And the itch in prurigo nodularis tends to be far more severe than what we tend to see with other itchy disorders, more so

than in atopic dermatitis. It can be 24 hours a day. It can be one of those things that is there always, but they do not really get bothered by it until it is nighttime and then they are not distracted as much and then, boom, it just takes off. And it is often worsened by heat, sweat, contact with clothing, textures, stress, there are many different triggers that can come up. A lot of times, patients will say, "I don't know what happened. I was minding my own business and the itch got bad."

There are other symptoms beyond itch that are related. Certainly, we see skin pain come up, we see sleep disturbances, we see mood impact, etc. But, at the very least, the heart of this, that universal symptom is the itch.

Associated Conditions

Jonathan Silverberg, MD: We are just going to discuss a little bit about the associated conditions because we must recognize that, as we often see in dermatology, skin disease is often that window that reveals other systemic issues. What are some of the things that we need to think about? About half of the people with prurigo nodularis (PN) have a history of atopic dermatitis. That does not mean that PN is atopic dermatitis. They often have a remote history, in childhood, that burnt out decades earlier, but it is a notable association. Some patients may even have a mild winter itch or mild atopic dermatitis affecting the disease intermittently, but then they have an independent process of prurigo nodules affecting them all the time. There are other medical conditions found to be associated with prurigo nodularis in various case reports, case series, or smaller studies. Five percent of people with HIV are found to suffer from PN. Now, be careful how you interpret this. PN is itch in general and PN is something that can manifest in HIV patients, but it's not that 5% of PN patients all have HIV. It's relatively rare that a PN patient will actually be diagnosed with HIV, but we don't want to miss that either. We must think about that possibility.

Patients with PN have been reported to have a higher incidence of diabetes, chronic kidney disease, cardiovascular disease, hepatitis C, etc. The absolute risk of these disorders is quite low, but the relative risk is increased, and we want to make sure that we don't miss them in patients who have PN. More commonly would be the mental health issues that come up where patients with prurigo nodularis also suffer from anxiety, depression, emotional stress, etc. I think our thought on this has really evolved appropriately. We used to inappropriately think all these patients are crazy, they are all anxious and that is why they are getting PN. What we have learned is, no, it is the exact opposite. It is because they have bad PN that they are anxious, depressed and emotionally distressed, and that is really from the burden of untreated disease. This is certainly something that we need to address if we are going to manage the whole patient.

DIAGNOIS OF PRURIGO NODULARIS

Case #1- Initial Evaluation

Najat Watch, PA: For case number 1, we have a 54-year-old male. He has a history of human immunodeficiency virus. He's been seen by his PCP for follow-up. He is complaining of a multiple-month history of itching on the legs. In workup for this patient with possible prurigo nodularis, I think it is important to consider other conditions that might be associated with this pruritus. We may need a lab workup, we need a history with a timeline of the itching, what has been used for symptom relief, and then, more specifically, thinking about associated conditions, like hepatitis C, renal failure, diabetes, and cardiovascular disease.

Diagnosis

Leigh Ann Pansch, DCNP: Let's talk about what the initial diagnosis might look like once you've made your referral to a dermatology specialist. Certainly, we are going to take a thorough history. We are going to take time to understand the patient's unique symptomatology. And then we are going to get them in a gown, and we are going to look at every bit of their skin surface. We are going to talk about some of their symptoms and what types of therapies we might use to alleviate some of those symptoms, like itch, and further, we are going to have access to medications that are FDA approved to treat very specific things. And so, while in your office, you might have a bag of tricks for things that you see often. Prurigo is certainly something that we are very familiar with and have confidence in treating.

I think when you talk about the importance of a patient with a skin condition that is recalcitrant to treatments, that is very debilitating, and affecting a patient's life in such a negative way, a referral to a dermatology specialist then becomes the most optimal treatment so that we can get them access to very specific treatment options geared toward their issue.

In terms of the initial diagnosis of prurigo nodularis there are 3 core findings. The first is the presence of firm and nodular lesions. We often use words like "hyperkeratotic" and "lichenified." Hyperkeratotic meaning scaly and lichenified, like leathery or reptilian skin. The patients will often complain of intense pruritus and these lesions are often going to be grouped in areas, such as all over the forearm, for instance, but they may have other more diffuse lesions as well.

The second core finding is pruritus or itch lasting at least 6 weeks. Patients might say that this is a constant itch, that it's episodic, or that it's worse at night. The key is that this is a very severe itch. And finally, repetition. The patients are constantly scratching and picking. I often ask them about itching, first. Like, "How itchy are these spots?" I think then it gives them liberty to tell you, "Oh, these are keeping me up at night." And these types of things tend to be very helpful.

Additional findings might be specific areas of the body that we can touch if we are trying to scratch. We might see upper back or back of the neck or we might see the front of the arms. There might be areas of the arms that we can't quite get to easily, but then are not affected. Think about where can my hand reach to meet that need? Additionally, patients are going to typically lack lesions on the face, the palms, and the soles. Other lesions that we are going to find are maybe some excoriations, and some patients even complain of intense burning, stinging, or pain, in addition to pruritus. I think this is interesting when we look at the mental component of this situation. I say that not in a way that implies that someone has a mental illness, but I often like to ask my patients how good it feels to have your back scratched. And then I give them time to answer. When they have said, "Ah, that feels really good," well, we learn how to relax, calm, or soothe ourselves—or the opposite of that—to heighten and alert and awaken ourselves with these self-stimulating behaviors, like chronic scratching.

Diagnostic Evaluation

Lindsay C. Strowd, MD: When I approach patients that I think have a diagnosis of prurigo nodularis, or patients that are referred to me for suspected prurigo nodularis, I like to do what I call confirm and exclude. Confirm the diagnosis, but at the same time exclude other mimickers that can look a lot like prurigo nodularis. There are classic findings that you can see in patients with prurigo nodularis, both in terms of the distribution of the skin lesions, but also with how the individual lesions look, with firm, excoriated papules and nodules that oftentimes can be lichenified and distributed in areas where patients can reach with their own hands.

You want to look and make sure, as well, that there are no other underlying causes of itch that could be contributing to what you are seeing in front of you. And these can include other systemic illnesses, such as having chronic kidney disease or an underlying malignancy. Some patients with diabetes can have an associated itch. You want to do a thorough history and a past medical history to make sure that you are not missing another cause that could be contributing to the itch that the patient is describing.

At the same time, you want to exclude other diseases that can mimic prurigo nodularis. There are other things that we see in dermatology that can also cause these types of skin lesions to occur, as well as cause significant degrees of itch and burning in the skin. These can be conditions such as atopic dermatitis, cutaneous lymphoma, scabies, lichen planus and some other papulosquamous disorders. You want to screen with a family history by asking specific questions and potentially doing some additional blood work or other diagnostic studies to make sure that you are, in fact, making the correct diagnosis.

And lastly, it's important to qualify and quantify disease burden for the patient. Most patients that present with prurigo nodularis have a significantly decreased quality of life associated with this condition and I think it is important for your overall relationship with the patient to ask about that, as well as to document it in your clinic note for that day. This can help with obtaining approval of certain medications to treat this disease and can help when you see a patient in follow-up so you can compare how their quality of life is in response to the treatment that you've given them, vs how their quality of life was at baseline when they first came to see you.

US 2021 Expert Panel Consensus – Patient History

Lindsay C. Strowd, MD: A critical part of evaluating patients for potential prurigo nodularis is to get a great history from the patient, and this history has a couple of different purposes. One is it helps to elucidate some of those classic historical features that you can see associated with prurigo nodularis. The history also serves to look for other mimickers, other potential related or contributing illnesses to make sure that we are making the correct diagnosis and we are not missing anything that we need to treat in a different way, to make sure we are taking the best care of the patient.

When we are going through a dermatologic history, we want to get those classic history of present illness (HPI) features, such as the onset of the disease, the location, how intense, and what the pruritus feels like. I find it's oftentimes helpful just to ask an open-ended question of "What does your skin feel like?" instead of asking more closed-ended questions. Because then you really get a lot of rich data from the patient about exactly what they are experiencing. You can ask the patient about how these lesions have evolved over time. That can also be helpful. And, in terms of just screening for other mimicking diseases in the dermatologic history, you can ask about other family members that have a similar thing, which would steer you away from a diagnosis of prurigo nodularis. Other specific historical questions such as do they have pets at home or recent travel, can be helpful.

It is interesting to ask the patient what they are doing to relieve the itch or how they are self-medicating before they come to see you. And that can give you a lot of additional data about how patients are coping with their disease at present.

Getting a more in-depth medical history can also be helpful for these patients. Asking about their family medical history, what medications they are currently on, if there are any nonprescribed medications that they tend to use, even on an intermittent basis, can also be helpful for excluding other potentially medication-induced causes of itch or burning. A history of atopic dermatitis is important because there can be some overlap, and a lot of patients can have both atopic dermatitis and prurigo nodularis.

Another fascinating question is asking the patient why they think they have this, or do they have a theory about why this developed for them. This can give you a lot of valuable insight into where the patient is coming from and their level of medical education in terms of what they have going on with them. This can really be helpful as you build rapport with the patient and have that discussion later in the visit about treatment options and what we need to do moving forward.

Finally, with history, you want to screen for specific comorbidities that involve other organ systems that can lead to a chronic itch. Diabetes, kidney disease, metabolic deficiencies such as iron deficiency, HIV,

certain types of malignancy, especially blood cancers, can all cause pruritus.

US 2021 Expert Panel Consensus – Physical Exam

Lindsay C. Strowd, MD: You really want to do a full skin exam for these patients. It's ideal to have them change into a gown so that you can get a good idea of everything that's going on with their skin and all the areas that are involved. This will also help you in terms of determining what disease severity they have, if they do, in fact, have prurigo nodularis. It is hard to do that on a limited exam.

The full exam also allows you to look for signs of other skin diseases as well. Atopic dermatitis can be present in these patients, so you can see if there is evidence of that. There are sometimes patients that have bullous pemphigoid, which is an autoimmune blistering disorder, and they sometimes can present initially with prurigo-like lesions. It is important to look for any urticarial type lesions or any intact blisters on the skin during your exam to make sure that you are not missing that disease process. Also, cutaneous T-cell lymphoma can mimic prurigo and can cause severe itch in some patients, so being sure to check some of the double-covered areas is important to screen for cutaneous T-cell lymphoma.

US 2021 Expert Panel Consensus – Laboratory Assessments

Lindsay C. Strowd, MD: In terms of other additional things that you can do to help with the diagnosis, some people do a skin biopsy. This is really a clinical decision, but if there is concern about potentially other underlying dermatologic illnesses that could be muddying the waters, a skin biopsy can be helpful for confirming the diagnosis. Also, if there is a lot of patient uncertainty about the diagnosis, doing a skin biopsy just to make sure we are all on the same page so we can move forward with treatment can oftentimes be really helpful.

Intraepidermal nerve fiber density testing is something that you can do on a skin biopsy to look for small fiber neuropathy. It is a very specific test that you need to work with a dermatopathologist that has experience looking at nerve fiber density under the microscope in order to have a successful screening test. There are some blood tests that sometimes we will do, especially if patients haven't had some routine blood work performed previously. Again, this is going back to just making sure we are not missing something else that's going on. Some easy blood tests that we may do to screen a patient for other causes would be a CBC, a metabolic panel including liver function testing, a hemoglobin A1c to screen for diabetes, or thyroid function tests. Screening for HIV or viral hepatitis, especially if there are any risk factors present for those viral illnesses, could also be prudent.

Leigh Ann, in your practice, do you typically do a skin biopsy for these patients when you're thinking it's prurigo nodularis or are you mostly diagnosing it clinically?

Leigh Ann Pansch, DCNP: I usually diagnose prurigo nodularis clinically, but it is nice to have other diagnostic tools in your pocket. Sometimes patients absolutely know, and once you explain to them the itch-scratch-rash cycle, they are very much self-aware enough to say, "Yeah, I scratch these a lot," and there is no question. Other times, it's a little bit tricky because maybe this is a patient who has some underlying atopic dermatitis going on or there is something else at the base that makes this a unique presentation, or they didn't quite respond to a therapy that you would expect. And those are the times when I typically like to biopsy for confirmation.

Differential Diagnosis

Leigh Ann Pansch, DCNP: When it comes to ruling out other mimickers, I think one of the things that can be done at the bedside is to do a little skin scraping and rule out a component that is potentially fungal or a mite infestation. Certainly, if I biopsy a rash, especially given that in certain circumstances this patient has picked and picked and picked and I'm not exactly sure what the primary lesion was, throwing in a direct immunofluorescence to look at those autoimmune bullous conditions can be very helpful at the pathology level.

I love dermoscopy. I use it a lot. It's certainly helpful to get a close-up look at what's happening on the skin and, from a histopathologic perspective, things like hypertrophic lichen planus or lichen amyloidosis can really, really be tricky. And so, if the history isn't quite right, if there is something else about the patient's history that really makes me curious or question, that's when I might think about a confirmation diagnosis with a little skin biopsy. We can do these skin biopsies with hematoxylin-eosin staining and we can look at other allergic inflammatory conditions, but that's a conversation that you are going to want to have with the pathologist before you send it. And psychiatric evaluations. I word this a little bit differently. Believe it or not, I think that patients with any chronic disease can benefit from seeing a mental health provider to talk about a bag of tricks for things like relaxation, and other stress coping behaviors. If I'm dealing with a patient who's really struggling and not coping, I want to make sure that there are no other underlying conditions from a psychologic perspective as well. And again, maximizing those other health conditions, be it diabetes or mood, can really help me get the skin in check sooner.

Patient Evaluation Summary

Leigh Ann Pansch, DCNP: If we are talking about a summary of our workup here, we are going to recognize that patients with prurigo nodularis are going to have complaints of pruritus or itch for at least 6 weeks. I think this is one of those times when counting lesions becomes very helpful because I want to be able to, in a simple way, quantify their improvement and progress with a specific therapy or therapies. I will count those lesions. and expect them to have at least 10. All patients are going to get a little bit of a blood workup. We are going to do complete blood count with differential. We are going to do a comprehensive metabolic panel. We are going to order a hemoglobin A1c, consider some kidney and liver function tests. If my patient is really itching and there are reasons for me to suspect thyroid as a component, throwing in some thyroid function tests, maybe

considering an HIV antibody test as well as hepatitis serology, is helpful as well, just ruling those out. We are ruling out anemia. We are ruling out infection. We are ruling out other hematologic or other systemic conditions that are factoring in here.

And then, depending on my patient's history, depending on how I combine that history with a physical exam and the morphology, I might do a skin biopsy. I might also add a direct immunofluorescence or some special stains, looking to rule out autoimmune diseases, such as the bullous diseases or small fiber neuropathy. And then, in certain circumstances, I might also throw in some urine and protein electrophoresis tests, maybe a stool for ova and parasites or some iron studies, maybe some imaging studies such as CT, MRI or other imaging tests. I might do a depression/anxiety screen. This really is important when you look at the number of patients that are really struggling from a mood perspective who also have comorbid PN. And then, again, maybe some intraepidermal nerve fiber density exams. This workup is just a comprehensive way to evaluate and look at our patients that come in with these symptoms.

Validated Measures – Itch Assessment

Jonathan Silverberg, MD: There are several different validated measures that I like to use when assessing patients with prurigo nodularis (PN) and not all of these are even specific to prurigo nodularis. I use a lot of these for my atopic dermatitis patients, my psoriasis patients, lichen planus, etc, but these are certainly highly relevant in PN patients. I think, first and foremost, there is a need for a structured assessment around the intensity of itch. Now, there are several different ways to go about this. There is something called the visual analog scale (VAS). In the olden days, we used to have these paper forms and the patient would mark on this scale where there is no itch on one end and worst imaginable itch on another and they check off where on that scale they are. There is the numeric rating scale (NRS) which takes that same approach but divides it up into discrete numbers from 0 to 10. And then there is a verbal rating scale (VRS) which is just asking them, "How do you rate your itch? No itch, mild, moderate, or severe?" In truth, all 3 of these are slightly different, but they are all really similar to each other and they are all valid and perform very well against each other and in terms of assessing the disease.

I personally like to use the NRS Itch. The VAS gets a little tricky in terms of methodology, the measurements and stuff, so it's a little harder to pull off. But the numeric rating scale is super easy to do, but I also do a verbal rating scale. So, I actually do 2 different approaches. And then the question is do you do worst itch or average itch? I like to do both because I find that they give different results. These things take 10 seconds to complete. I mean, they are so easy to build in. You don't even have to ask this yourself. You could have a medical assistant who's rooming the patient ask this when they are being roomed, almost like a vital sign. It's simple to do, but it provides such rich information to guide you on how patients are doing.

Validated Measures – Quality of Life

Jonathan Silverberg, MD: There are a number of different quality-of-life tools that have been used in dermatology in general, but certainly apply to prurigo nodularis. There are some that are more specific to itch, like the ItchyQoL or the PROMIS (Patient-Reported Outcome Measure) Itch Questionnaire. And then there are those that are a little bit broader and can be used across a variety of different dermatologic diseases and are not unique to PN. The most familiar to all of us in dermatology would be the Dermatology Life Quality Index (DLQI). It's a validated tool that has 10 questions, scale of 0 to 30, where 0 is no quality-of-life impact and 30 is the absolute worst. You really get an idea on how it is affecting them in terms of itch and activities of daily living. It is weighted towards functional impacts such as school/work performance, etc. This is an important tool and it's one that you don't have to only use for PN patients. You really can use it for any of your chronic inflammatory skin diseases and other dermatology patients. It's something easy enough to build into your practice.

PATHOPHYSIOLOGY / TREATMENT TARGETS

Itch-Scratch Cycle

Jonathan Silverberg, MD: The pathophysiology of prurigo nodularis is complex. It's multifactorial and it's one that—you'll pardon the pun—but we barely scratch the surface of in terms of our understanding, and it's really evolving quickly. There are certain key features though that we've known about for a very long time. We understand that there is a cycle here in terms of itch and scratch. When patients itch, it's wired, as part of us, to react to that itch, and we scratch to induce a pain response and suppress that itch. Scratching or that pain suppressing of the itch happens at the interneuron level, and that's something that's wired at multiple levels. But the problem is when patients scratch, the more they scratch, the more damage they are going to do to the barrier, the more damage they are going to do to the peripheral nerves and the more inflammation there is going to be and so we get into this trap or vicious cycle.

Regardless of what that initial trigger of itch is, once the patient is scratching and may not be able to control that scratch, it's just going to perpetuate things more. The one thing that's important to recognize is we may be fooled into judging the extent of a patient's itch by looking for those visual nodules because those visual nodules are where patients are scratching and picking. But recognize patients could be itching everywhere and they may just not be able to reach certain areas, or they are embarrassed to scratch or pick certain areas during daytime because of the location or the visibility of it. There is a complex interplay, not just of inflammation happening within the superficial dermis and affecting the epidermis, but you've got the nerve involved which is transducing those itch signals. And that's going through the spinal cord and up to the brain and even at that interneuron level, we've got that interplay of itch and pain signals that are happening and, of course, the central processing and amplification of itch within our brains.

But really, where the state of the art is and what we've learned so much over the past couple of years—it's really been very rapidly evolving—is that in the superficial dermis, we see up-regulation of a variety of different cytokines. Interleukin-31 (IL-31) is thought to be the itch cytokine, but even recognizing now potentially up-regulation of interleukin-4 (IL-4) and interleukin-13 (I-13). Some of the cytokines, like interleukin-22 (IL-22) which is thought to play a role in epidermal hyperplasia, interleukin-17 potentially, as well, which is what we think about more for psoriasis and why patients may have more psoriasiform-like lesions or well-demarcated lesions. We believe that the primary effector cells here are the T-cells, although we still need more translational research to definitively demonstrate that.

And there are a few different growth factors that are involved in terms of nodule formation and recruitment of other cell types and a few other factors that are contributing to itch signaling at the neuronal level or amplifying the itch signals as well. So, it's a little complicated.

Immune Factors

Jonathan Silverberg, MD: Within the immune factors, there are multiple cell types that have been implicated, including eosinophils and mast cells, but we do believe that it's the T-cells that are the primary effector cell type, although that needs to be definitively shown. There are several different cytokines that are produced. There is certainly an interaction of neuronal pathways with other cell types, like eosinophils, that have been shown not necessarily in prurigo nodularis, but in general in the skin, and so there may be other factors like substance P, nerve growth factor. These can be released by mast cells as preform mediators and dumped in large quantities, even by a few of those immune cells. And we see that, in general, it's not a histaminergic process. We generally classify itch as histaminergic vs nonhistaminergic. And the itch in prurigo nodularis and in atopic dermatitis and other inflammatory skin diseases, is not histaminergic, contrasting that with urticaria, which would be histaminergic.

Why does that matter? Because if it's not a histamine-mediated process, we really need to be practical about it and not be going after histamine as a treatment target if that's not actually what's driving the disease.

Interleukins

Jonathan Silverberg, MD: The role of interleukin is something that we are learning at just a ferocious pace. Interleukin-31 has been referred to as the itch cytokine. There is increased interleukin-31 expression in the skin of a variety of different pruritic disorders, but particularly in the skin and the blood of prurigo nodularis patients. Interleukin-31 is a neuroimmune cytokine, so it's a cytokine floating around outside the cells in the milieu, but it can bind directly to receptors on peripheral nerves and trigger that sensation of itch. The receptors are heterodimers and, in this case for interleukin-31, we've got a subunit for the interleukin-31 receptor alpha subunit as well as the oncostatin M receptor beta (OSMR beta) subunit. And so, both potentially are playing a role in that signaling of interleukin-31.

There has also been work shown more definitively in atopic dermatitis, but we believe generalizes to prurigo nodularis as well, that shows that there are receptors for interleukin-4 and interleukin-13 on peripheral nerves. Those cytokines can amplify or potentiate the signal of itch. We believe that that is what's happening as well in prurigo nodularis, and those T helper 2 (Th2) cells also are producers of interleukin-31. And so it's important for us to acknowledge both possibly more direct or semi-indirect with the potentiation of itch and then even more downstream effects in terms of the Th2 cytokines driving IL-31 production as well.

Substance P

Lindsay C. Strowd, MD: When I'm talking to patients about prurigo nodularis, I like to tell them that there is a whole chicken soup going on underneath their skin and there's a lot of different ingredients in this soup that are all interplaying with each other to create what we see on the outside of the skin. Substance P and calcitonin-related gene peptide are just 2 other ingredients that are involved in this inflammatory milieu or soup under the skin. Substance P is not an interleukin, but it functions like a proinflammatory player in the pathophysiology of prurigo nodularis. It is causing degranulation of mast cells as well as promoting local growth of endothelial cells and, along with the calcitonin-related gene peptide, both of these are creating abnormal mast cell activation and, particularly the calcitonin-related gene peptide, can promote Th2 type signaling. And all of these combine with cytokines to create this intense pruritus and other symptomatology, as well as the clinical appearance of the lesions.

Vanilloid Receptor Subtype 1

Lindsay C. Strowd, MD: Vanilloid receptor type 1 has several different names, but functions as a receptor on both nerves and certain inflammatory cells that, again, when activated, induces the release of substance P and calcitonin-related gene peptide. This is really creating a feed-forward mechanism for the itch. The nerves that carry these receptors also have receptors for interleukin-31, which highlights the ongoing role of interleukin-31 in the pruritus pathway.

GUIDELINE-BASED TREATMENT

Treatment Considerations

Lindsay C. Strowd, MD: For treatment, we want to find medications that work on these specific immune factors and receptors, and these medications would not only work on those factors and receptors, but also would address symptom management for the patient.

If the medications work on these factors, but they are not actually decreasing the itch or improving the quality of life in patients, then they are not going to be effective. This underscores the importance of—when we are considering treatments—to be able to have clinical trials where we can really see objective symptom improvement in our patients. We also want to make sure that our treatments are restoring

normal skin function and physiology which is going to allow for skin healing to occur.

Our treatment, in terms of FDA-approved options for prurigo nodularis, is currently limited. Dupilumab is the only FDA-approved therapy right now for prurigo nodularis. It is a medication that we often reach to, especially for our more severe patients. But treatment needs to be patient-centered and I think you need to consider a lot of different factors of an individual patient, such as their age, other medical illnesses that they have, the severity of their disease and potential adverse effects of treatment on that individual patient to come up with what's going to work best for them.

Case #1 Continued; Interprofessional Approach to Symptomatic Treatment

Jamie L. McConaha, PharmD: It is very important that we have an interdisciplinary team caring for these patients with prurigo nodularis. There is a specialist role in treatment for these patients. They should be referred to a dermatology specialist, but we also have numerous other professions that are going to be involved in the care of these patients as well, particularly primary care, nursing, and pharmacy. These specialties are oftentimes the place where the patient first presents. We have an obligation to assess the patient and refer on as necessary, but also to play a supportive role in their care as well. For example, we can develop a trusting relationship or partnership with the patient using tools like motivational interviewing. These can be used to identify any special barriers or psychosocial barriers that the patient may be experiencing because we all know the psychological impact that this disease state can have on patients. We need to make sure that we are expressing empathy and compassion towards the patient and ensuring also that their treatments are meeting their needs and expectations.

We also can talk with the patient about appropriate goals and what to expect regarding drug treatment. Whether it is over the counter or self-care type of treatment, we can recommend and counsel the patient about and helping them with setting realistic expectations of what they can achieve with those types of therapies. Then, providing appropriate counseling and even helping with medication access, as needed, with some of the prescription medications. This disease state involves treatment by all healthcare providers, whether it's the person that the patient is first presenting to or that referral when it occurs, we all play an important role in the treatment of patients with prurigo nodularis.

Najat Watch, PA: I believe that it is paramount to have coordination of care for these patients. There are social, psychological, physical issues in patients with this disease. It is multifactorial. Upon getting a referral from a primary care provider, at the minimum, communicating back to that PCP regarding our recommendations for care for these patients is needed. It's also important, especially if you have a team that is caring for these patients, to talk to attendings, talk to residents, anyone who might be associated with this patient to make sure their care is optimized. That might include psychology or psychiatric referrals and some hospitals have coordinated appointments for the physical aspects and the mental health aspects of this disease. Coordination of care, making sure patients are monitored regularly is paramount, and that might be coordinating between a PCP, a dermatologist, and it might also involve a psychologist as well.

Jonathan Silverberg, MD: Unfortunately, in the US, multidisciplinary care settings are not money-makers, so we don't see them used as often. I ran a multidisciplinary clinic at Northwestern, when I was still there, for atopic dermatitis and other itchy disorders, including PN, and having the various providers there on-site was just invaluable in terms of getting at the underlying comorbidities and addressing the mental health issues, making sure we could reduce polypharmacy, etc. I think it's such an important issue. In the absence of that, though, I think it really behooves all of us to try to do the best we can to coordinate that care in a little bit more of a disjointed healthcare setting.

Najat Watch, PA: We are very lucky at Henry Ford Hospital. We have a lot of multidisciplinary appointments. We have a whole psych-derm group, and I can't tell you how wonderful it is to be able to coordinate care. We also have a rheumatology-dermatology coordinated clinic as well. Instead of these patients going to 5 different providers, we sit down together, get everything coordinated, and patients are not only satisfied, but really, going forward, they do better. They do better, mentally and physically, because they feel they have a team of people that are rooting for them.

US 2021 Expert Panel Consensus – Tier 1/2 Medications

Lindsay C. Strowd, MD: We do have some treatment guidelines that have been offered by experts in prurigo nodularis, particularly addressing the many off-label uses of certain medications. The first tier of this consensus panel was looking at topical medications. We have both topical immunologic medications, such as topical steroids and calcineurin inhibitors, as well as intralesional corticosteroids that we can use. We also have topical medications that work more on the nerves in the skin. This is topical capsaicin and there are also some specific compounded medications that you can get, such as topical ketamine, that can be combined with lidocaine plus amitriptyline, or either one of those alone. These preparations can sometimes lead to some mild improvement in the symptomatology of patients.

As we move up the therapeutic ladder, we get to this tier 2 from the consensus guidelines, and these are really directed at more systemic therapy. We have these broad categories of immunomodulatory medications, such as methotrexate and cyclosporine. We also have medications that are going to work more on the nerves in the skin, such as gabapentin or pregabalin, as well as selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants. All of these medications have been used off-label in patients with prurigo nodularis.

Typically, as a rule, especially with these neuromodulating medications, we start with a lower dose of these medicines and titrate up to effect, as opposed to starting with a high dose. For the immunologic medicines, like methotrexate and cyclosporine, there is some data that suggests in certain patients that it may be helpful, but

there is not extensive data on the efficacy of these medications, so they are not used as commonly for prurigo nodularis.

We also have phototherapy or light therapy. This can include both narrowband UVB and PUVA therapy. And phototherapy has been shown to be helpful in diffuse pruritus, both in prurigo nodularis patients and in patients without prurigo nodularis. I find that phototherapy is most helpful when used as an ancillary treatment in combination with either topical or systemic agents, but there is limited efficacy when it's used as monotherapy.

US 2021 Expert Panel Consensus – Tier 3 Medications

Lindsay C. Strowd, MD: Tier 3 in these guidelines talks about more experimental type therapies and, interestingly to note, these guidelines came out in 2021 and they included dupilumab in this experimental category, so these guidelines are dated. As we know now, dupilumab is approved for prurigo nodularis, so I think that has moved that up a little bit in terms of the treatment algorithm for patients with prurigo nodularis. In this experimental category, we have medications such as thalidomide which has been around for a long time but used off-label for prurigo nodularis. There are medications such as naltrexone or butorphanol that have also been shown in case reports or small case series to be helpful with prurigo nodularis. And then medications such as nemolizumab which is currently in phase 3 clinical trials. So, there is a whole host of different medications that potentially can be used. Although I think with the approval of dupilumab, that one has really leapt to the forefront of the systemic therapies that we are using for this disease.

I think one of the key points to remember is that these guidelines are very helpful for the treatment of prurigo nodularis because we do have limited options, but now that dupilumab is FDA-approved, I think we have more widely adopted that medication into our treatment algorithm for these patients.

Leigh Ann Pansch, DCNP: In general, the guidelines that were developed by the [International Forum for the] Study of Itch agree with the US 2021 Expert Panel Consensus, though these recommendations stress basic skin care, and supportive emollients across the board. There is a recommendation for antihistamines for no longer than 4 weeks as a monotherapy and a strong consensus recommendation for the use of nemolizumab. So, we really look forward to having that medication readily available as well.

International Forum on the Study of Itch Guidelines

Leigh Ann Pansch, DCNP: When we talk about prurigo nodularis, there is the International Forum on the Study of Itch Guidelines. I think it's important when we look at this ladder to really get an understanding for what is baseline, for what types of conversations we are having with every single patient we see with this condition. First, we need to stress the importance of skin care. We want to make sure that they are moisturizing, that they are using some gentle cleansers, and this is the basis of everything else that we do.

I often tell patients this is your portion and the rest we are going to weigh in on other therapies for. Oftentimes, we do incorporate other disciplines based upon a patient's unique history. For instance, if there are some concerns about underlying disease states that may be factoring into a patient's problems with the rash, we might pull in primary care for some help with ruling out and getting other disease states in check, such as diabetes or renal disease. In addition, if a patient is having very specific neuropathic complaints with stinging and burning or hot poker sensations, we might pull in a neurology specialist to help.

And so, when we talk about individual therapies, we are going to talk about step 1 which are often our topical corticosteroids. I think it's important here to think about what formulation of topical steroid we would typically use. Here it's more of an ointment form because we want it to penetrate those large, thickened nodules. To avoid the use of topical corticosteroids for this chronic illness constantly, to avoid side effects, we might also incorporate some topical calcineurin inhibitors as well as our antihistamines.

Other things that can be helpful to use as additive therapy is something like topical capsaicin. Capsaicin is available over the counter. It's certainly easy to access for a lot of our patients and, for some of our patients who love the idea of a rhythmic schedule, having them apply it 3 to 4 to 5 times a day on a schedule and then, once the symptom goes away of itch or pain or irritation, pulling off 1 of those times a day, and getting into a rhythm, has been found to be beneficial in some patients. Additionally, we love intralesional corticosteroids. Once we've identified that we are dealing with a prurigo nodule, to inject a steroid directly into that nodule tends to be a very fast way to address that itch.

Ultraviolet phototherapy can be helpful as well. Neuropathically, we might consider some gabapentin or pregabalin as well as some antidepressants, in certain cases, can be very helpful. And, if there is an inflammatory component that we feel just needs something from a systemic standpoint, we also might consider cyclosporine for a short period of time, or methotrexate.

We might consider a therapy specific for itch reduction or some of our other systemic agents, such as dupilumab. In cases where we are just using all our therapies and everything else has been used and abused and we really don't know what to do, sometimes we scratch our heads and we do have a couple of patients in our office who are on thalidomide, with very specific guidance, much like our REMS program for oral isotretinoin. There are some other therapies that are currently in clinical trial, including nemolizumab, and we have seen some early preliminary data and are very excited about those options when they become available after the FDA approval process.

Monitoring Using Validated Measures

Jonathan Silverberg, MD: I use several validated measures to monitor treatment response and I love using structured assessments around monitoring the intensity of itch. There is the visual analog scale (VAS), verbal rating scale (VRS) and the numeric rating scale (NRS). I personally, in practice, like to use the verbal rating scale and the

numeric rating scale. So, the numeric rating scale is a scale of 0 to 10, for the 0 being no itch, 10 being the worst imaginable itch. Verbal rating scale is just how do you rate your itch—no itch, mild, moderate, severe—in terms of the intensity of the itch. These are quick, simple questions that can be assessed. You can assess both the worst itch, you can assess the average itch, both provide very rich, meaningful information.

I also like to use the Dermatology Life Quality Index in practice. Whatever tools you are going to use at baseline, you certainly would like to use on follow-up and make sure to go back to those original scores and make sure that there are improvements. I started doing this almost a decade ago because, from anecdotes where I had patients where I thought—I assumed—that they were getting better on the therapy and I said, "Oh, you look much better!" and the patient said, "Really? Because I didn't get better at all!" And I realized I just assumed they were getting better, but I needed to do a better job of assessing that in a formal way. And once I introduced these structured assessments into practice, I realized I was missing a lot of stuff beforehand.

You could also think about numeric rating scales for skin pain and numeric rating scales for sleep intensity. Those 2 domains are extremely important for patients and can be assessed with single questions that take about 10 seconds to assess.

When looking at the lesional severity, there are a couple of different ways of going about this and there we never really had structured assessments for clinical practice. There are some that have been developed more recently as part of a clinical trial; however, there I s no clear consensus on what's the best way to do it. One would be to count the number of nodules. Certainly, if they have more than 100 nodules, everyone would agree they are severe. Moderate in clinical trials has been defined as 20 to 100 nodules, mild would be 6 to 19 nodules. But, as we know, some patients may not have 100 nodules. They may have only 20, but those 20 are so debilitating and so nasty, oozing, weeping, getting super-infected, dyspigmenting, super thick, fibrotic lesions, and so we also need to think about the quality of the lesions. How red, raised they are, how rock hard they are, hypertrophic, etc. So, you can use some of those investigator's global assessment (IGA) scales in clinical practice, but some of that may be fuzzier and more of a qualitative judgment call. Most importantly, I would say, both at baseline and on follow-up, is gown your patient up, making sure you are able to do a full count of the lesions. Because if you are only looking at certain representative areas, like the forearms or the shins, which are areas that tend to be effected quite badly, you may miss the fact that they are covered on the back or the chest, etc, and under-appreciate the severity of the disease or how well they are doing or how poorly they are doing in terms of treatment response.

FDA APPROVED THERAPY

Case #2 – Adjusting Therapy

Jonathan Silverberg, MD: For case number 2, we have a 71-year-old female with type 2 diabetes, hypertension, and chronic kidney disease who's being seen in the dermatology clinic following referral by her primary care clinician. She was diagnosed with prurigo nodularis 5 months ago by her primary care provider and she has received little benefit from skin care, emollients, and topical corticosteroids.

The first thing to consider would be how to proceed in modifying this patient's therapy. There are several important considerations in terms of thinking about optimizing the existing therapies, but also making sure there is good adherence, making sure you have appropriate potencies for topical steroids, and appropriate quantities. You should also be thinking about the importance of stepping-up therapy and really thinking about what the ideal next step would be, because there is clearly an inadequate response from the current options. Additionally, we should consider the importance of assessing how the disease is impacting patients and how should we really be thinking about these and incorporating them into our treatment decision making.

Sometimes you'll have patients who don't even look so severe, but the patient is telling you it's really destroying their life. How is it impacting them at work, at home, in terms of activities of daily living, sleep, just daytime functioning, mood, etc? All of these are things that if the disease is really impacting any of those domains in a way that is not adequately controlled by therapy, I would certainly think about stepping-up therapy. Try to take that more holistic approach and not just focus on just 1 score, like the severity of itch, but really think about the broader impacts on patients, and then stepping-up appropriately.

Case #2 – Emerging Treatments and Monitoring

Najat Watch, PA: When patients have failed these more symptomatic approaches and are not getting clearance, it is time to think about dupilumab. What else is emerging or what is in clinical trials. We have 2 new monoclonal antibodies that are in phase 2 and 3 trials, 1 being vixarelimab and the other nemolizumab. And the way that these work is they are man-made proteins that are acting like the human antibodies in our immune system and they can be very effective, hopefully, for giving more long-term relief of this pruritus. Another medication that is being looked at is the opioid analgesic nalbuphine, formulated as an oral extended-release tablet.

Jonathan Silverberg, MD: Monitoring is tricky, and I think it varies by practice, based on both pragmatic and theoretical considerations.

Certainly, whenever you are assessing at baseline, to make that decision about stepping up therapy, whatever domains were being impacted, you want to assess after treatment how well the patients are doing. I would advocate for at least doing a structured assessment

like the NRS Itch. For a disease like prurigo nodularis, that single question can tell you so much information.

But there are other things to assess as well, like impacts on sleep and mood and, again, activities of daily living, etc. So, some of these can be open-ended questions, but I think a structured question around the severity of itch can be very helpful here. I think the trickier part is at what interval because, in an ideal world, we might see these patients back every 1 to 2 months. I don't know about you; I just don't have the bandwidth in my practice to accommodate that. And so, especially when a patient is put on something like a biologic, that follow-up often gets extended, maybe even more to 4 to 6 months. And yes, I accept I could be missing some things that happen in that initial period, but I'm just being practical in that respect, knowing that some of the therapies can take a little longer to hit that peak efficacy. And, knowing that they overall have very clean safety profiles, I'm often willing to take that chance. But, of course, that's going to vary by drug.

Dupilumab- Mechanism of Action

Jamie L. McConaha, PharmD: Dupilumab is currently our only FDA-approved medication for prurigo nodularis. Its mechanism of action is that it is our only dual inhibitor of both interleukin-4 and interleukin-13 signaling. Interleukin-4 and interleukin-13 are 2 of the key drivers of type 2 inflammation. Increases in interleukin-4 and -13 signaling enhance the stimulation of sensory neurons and leads to dysregulation of the immune system and the skin, which results in the itch/scratch cycle. Through inhibiting interleukin-4 and interleukin-13 signaling, dupilumab has substantial impact on this disease state. Specifically, it's going to help reduce type 2 inflammation, it's going to decrease itch to break the itch/scratch cycle, it's going to decrease nerve sensitization, and it also helps clear nodules.

Dupilumab- Efficacy and Safety

Jamie L. McConaha, PharmD: Dupilumab was approved in September of 2022 based on the results of 2 pivotal trials, PRIME and PRIME2. If we look at the PRIME trial, it had a population of 151 patients, and these were adults with prurigo nodularis that were inadequately controlled on topical therapies or for whom topical therapies were not advisable. In this study, the intervention group received dupilumab subcutaneously every 2 weeks and that could be with or without topical treatments, depending on if the patient was previously using them at time of randomization. This was compared to a placebo group. The length of the study period was 24 weeks or 6 months of treatment, which is a longer time compared to other dermatologic trials. The trial was specifically designed this way to give the nodules time to heal so that we could see that as 1 of the outcomes. Generally, with this medication, we see that the itch improves first but we need to give the nodules more time to clear.

The results of the PRIME trial were that the dupilumab group was associated with significantly greater improvement in measures of overall health-related quality of life, skin symptoms, skin pain, as well as even secondary measures, such as anxiety and depression.

We also have the PRIME2 trial which had 160 patients enrolled. The intervention group received a 600 mg loading dose of dupilumab, then 300 mg every 2 weeks subcutaneously for 24 weeks. This was compared to placebo. The results of PRIME2, showed statistically significant improvement in the numerical rating scale (NRS) as well as investigator's global assessment (IGA) in our dupilumab group. These improvements were seen as early as 12 weeks, but more significantly at that longer time point of 24 weeks.

Looking at the safety of both trials, PRIME and PRIME2, dupilumab was well-tolerated and really the side effects or the treatment-emergent adverse effects (TEAE), were really like what we know about the drug when being used for disease states such as atopic dermatitis. One of the most common adverse effects that resulted from these trials was headache, but really none of the adverse effects that were seen led to discontinuation of the medication in the intervention group.

Dupilumab – Place in Therapy

Najat Watch, PA: The US Expert Panel Consensus and the International Forum on the Study of Itch guidelines were published before FDA approval of dupilumab in September of 2022. I think that we need to incorporate dupilumab for patients due to the efficacy in the controlled trials, the FDA approval, and the lack of other treatment options for patients who had no success with symptomatic relief. I think we need to move towards a disease-modifying medication and dupilumab.

Dr. Silverberg, I'm interested to know how dupilumab has affected your practice and how you feel it will be going forward.

Jonathan Silverberg, MD: Dupilumab has been a real game-changer for PN, not just from the clinical practice perspective, but it has completely changed our perspective on how we think about the disease. Until dupilumab was studied and worked, we didn't even understand that there was an immune component and that this was a chronic inflammatory skin disease. So, this has completely changed our thought process around pathophysiology, mechanisms, and what's driving the disease. Now, specifically for clinical practice, it's the first approved option we have as a systemic therapy. It's the first approved option we have, period. We don't even have approved topicals. It's something that with the track record it's had in atopic dermatitis in terms of both safety and efficacy, and approvals down to the youngest age groups and being tested in some of the oldest patients as well, we've got a lot of comfort, even for some of our perhaps more fragile patients with comorbidities. I have very little concern about using dupilumab in almost any patient with PN who would be eligible. From my perspective, if I can get it covered by insurance, then if the patient's having an inadequate response to topicals, which in my practice would probably be everyone, I'm going to already have that conversation early on. But I think dupilumab has also opened the entire field of investigation because it has taught us that there is a very specific and targeted immune mechanism at play here. And now it's just changed the entire landscape of development for this disease.

Dupilumab – Dosing and Administration

Jamie L. McConaha, PharmD: Dupilumab is given subcutaneously, and, after proper training, this is something that patients can self-administer at home or have a caregiver administer for them. The dose is an initial loading dose of 600 mg subcutaneously followed by 300 mg subcutaneously every other week. That 600 mg loading dose is given as 2 separate injections of 300 mg. Dupilumab is available in 2 ways. It comes as a prefilled syringe or as a prefilled pen. They both have 300 mg in either instance and both can be self-administered by the patient. With the syringe, it's a subcutaneous injection with a needle shield and, with the pen, the needle is hidden, so that might be a nice option for patients that have a needle phobia. For storage, dupilumab should be kept refrigerated until it's time to give the injection. We oftentimes tell patients with any injection that's kept in the fridge to remove it and allow it to warm to room temperature prior to injection. With this medication specifically, the recommendation is to warm to room temperature at least 45 minutes prior to injection. So, make sure that the patient is aware of that and that they give themselves enough time to allow that medication to warm up prior to administering. Once it is taken out of the refrigerator, it is stable at room temperature for 14 days.

Dupilumab can be administered in the thigh or the abdomen. If it's given in the abdomen, we want to stay 2 inches away from the navel or if this is administered by a caregiver, you can also use the upper arm. For that initial loading dose of the 600 mg, those 2 injections should be given at separate sites.

Dupilumab – Monitoring and Side Effects

Jamie L. McConaha, PharmD: In terms of monitoring and side effects, as we saw again in our trials, there were not too many severe side effects. We do have very limited case reports, as well, in terms of the use of the medication in pregnancy or nursing. These case reports have not shown any adverse maternal or fetal outcomes, but we do know that IgG antibodies have been shown to cross the placenta. The fetal exposure of this crossing is dependent on many factors such as what type of IgG subclass it is, the maternal serum concentration, the birth weight of the baby, the stage of pregnancy, etc.

Some of the adverse effects seen in studies included things like arthralgias, conjunctivitis or eye problems, as well as infection. Because of the risk of infection, it is recommended that all patients complete any age-appropriate vaccinations prior to beginning therapy with dupilumab and, while they are using dupilumab, they should avoid the use of live vaccines.

EMERGING TREATMENTS

Nemolizumab- Mechanism of Action

Jamie L. McConaha, PharmD: The next medication that we are going to discuss is nemolizumab. And this medication is not currently FDA-approved for any indication, but it is a medication that we are going to be hearing a lot more about, especially with prurigo nodularis. Just like dupilumab, nemolizumab is a human monoclonal antibody. Nemolizumab inhibits the binding of interleukin-31 to its receptor and the subsequent sequence and signaling. It was granted FDA breakthrough therapy status in 2019, so even though it is not technically FDA-approved, therapies that are granted this breakthrough therapy designation are those that target serious or life-threatening diseases or conditions and provide preliminary clinical evidence showing substantial improvement over existing therapies.

Nemolizumab – Phase 2 Trial

Jamie L. McConaha, PharmD: We will discuss a phase 2 trial of nemolizumab. This was a 12-week study that showed this medication had a very significant improvement in patient itch. It was a phase 2, randomized, placebo-controlled trial that compared nemolizumab to placebo with 70 patients. The patients in this study had moderate to severe prurigo nodularis, meaning that they had at least 20 or more nodules, and they also had severe pruritus, meaning that they had a mean score of at least 7 on the numerical rating scale.

In the intervention group, patients received nemolizumab, given subcutaneously, every 4 weeks. The dosing is different than what we saw with dupilumab, which was every other week. The primary endpoint was the change in the pruritus score at week 4. We saw a 53% improvement in the nemolizumab group. The onset was very fast and really we started seeing a reduction in itch within the first couple of days in these patients.

Other outcomes that were looked at were the continuation of the reduction in pruritus at 12 weeks, as well as patients achieving an investigator's global assessment (IGA) score of 0 or 1 or clear or almost clear. We saw very significant improvements in our intervention group.

Nemolizumab – Phase 3 Trials

Jamie L. McConaha, PharmD: There were 2 twin phase 3 trials for nemolizumab called OLYMPIA II. The trial had a significant number of patients. There were 274 patients in this study and what was interesting is that this was done in pure prurigo nodularis patients. These patients did not have concomitant atopic dermatitis, they were not on topical steroids or anything else. We were solely looking at the treatment of prurigo nodularis with nemolizumab. Fifty-six percent of patients treated with nemolizumab achieved a 4-point reduction at 16 weeks, which is a significant reduction in their pruritus score. We also had significant clearing of those nodules, as early as 16 weeks. And in other studies, we said that sometimes the clearing of those nodules can take up to 24 weeks. So, even at an earlier time point, we saw an improvement in the intervention group.

We had very similar safety events that were reported in the phase 2 trial, primarily they were GI or just musculoskeletal complaints, but nothing that caused the patient to end the trial early or discontinue therapy.

Vixarelimab

Lindsay C. Strowd, MD: Vixarelimab is another medication that is currently making its way through the clinical trial progression for prurigo nodularis. This is a medication that is a human monoclonal antibody, and it binds to the beta subunit of the oncostatin M receptor. This allows vixarelimab to inhibit signaling of both IL-31 and oncostatin M. In phase 2 studies, we did see a significant decrease in the disease burden in patients with moderate to severe prurigo nodularis at the primary endpoint which was at 8 weeks of therapy. And so this did justify progression to phase 3 clinical trials, which is currently where this medication is being studied.

Nalbuphine

Jamie L. McConaha, PharmD: Nalbuphine is an oral medication that has a different mechanism of action from what we've discussed so far. This is a mixed agonist/antagonist. It works as an agonist at the kappa-opioid receptor and an antagonist at the mu-opioid receptor. Nalbuphine has been shown to reduce both interleukin-31 as well as substance P. We have some early phase 2 trials with smaller numbers of patients, about 62 patients with moderate to severe prurigo nodularis who received this medication compared to placebo. The data with nalbuphine is much more modest than some of the data that we have with dupilumab or nemolizumab, and there were some reported issues in terms of side effects with things like nausea, dizziness, and headache.

INTERPROFESSIONAL CARE

Case #1 – Associated Conditions and Initial Evaluation

Najat Watch, PA: For case number 1, we have a 54-year-old male. He has a history of human immunodeficiency virus. He's been seen by his PCP for follow-up. He is complaining of a multiple-month history of itching on the legs. In workup for this patient with possible prurigo nodularis, I think it is important to consider other conditions that might be associated with this pruritus. We may need a lab workup, we need a history with a timeline of the itching, what has been used for symptom relief, and then, more specifically, thinking about associated conditions, like hepatitis C, renal failure, diabetes, and cardiovascular disease.

Leigh Ann Pansch, DCNP: Let's talk about what the initial diagnosis might look like once you've made your referral to a dermatology specialist. Certainly, we are going to take a thorough history. We are going to take time to understand the patient's unique symptomatology and then we are going to put them in a gown, and we are going to look at every bit of their skin surface. We are going to talk about some of their symptoms and what types of therapies we might use to alleviate some of those symptoms, like itch. And further, we are going to have access to medications that are FDA approved to treat very specific things. And so, while in your office, you might have a bag of tricks for things that you see often. Prurigo is certainly something that we are very familiar with and have confidence in treating.

I think when you talk about the importance of a patient with a skin condition that is recalcitrant to treatments, that is very debilitating, and affecting a patient's life in such a negative way, a referral to a dermatology specialist then becomes the most optimal treatment so that we can get them access to very specific treatment options geared toward their issue.

In terms of the initial diagnosis of prurigo nodularis there are 3 core findings. The first is the presence of firm and nodular lesions. We often use words like "hyperkeratotic" and "lichenified." Hyperkeratotic meaning really scaly and lichenified, like leathery or reptilian skin. The patients will often complain of intense pruritus and these lesions are often going to be grouped in areas such as all over the forearm, for instance, but they may have other more diffuse lesions as well.

The second core finding is pruritus or itch lasting at least 6 weeks. Patients might say that this is a constant itch, that it's episodic or that it's worse at night. The key is that this is a very severe itch. And finally, repetition. The patients are constantly scratching and picking. I often ask them about itching first. Like, "How itchy are these spots?" I think then it gives them liberty to tell you, "Oh, these are keeping me up at night." And these types of things tend to be very helpful.

Additional findings might be specific areas of the body that we can touch if we are trying to scratch. We might see upper back or back of the neck or we might see the front of the arms. There might be areas of the arms that we can't quite get to easily, but then are not affected. Think about where can my hand reach to meet that need. Additionally, patients are going to typically lack lesions on the face, the palms, and the soles. Other lesions that we are going to find are maybe some excoriations and some patients even complain of intense burning, stinging or pain in addition to pruritus. I think this is interesting when we look at the mental component of this situation. I say that not in a way that implies that someone has a mental illness, but I often like to ask my patients how good it feels to have your back scratched. And then I give them time to answer. When they have said, "Ah, that feels really good," well we learn how to relax, calm, or soothe ourselves or the opposite of that, to heighten and alert and awaken ourselves with these self-stimulating behaviors, like chronic scratching.

Case #1 – Referral and Diagnosis

Lindsay C. Strowd, MD: When I approach patients that I think have a diagnosis of prurigo nodularis or patients that are referred to me for suspected prurigo nodularis, I like to what I call confirm and exclude. Confirm the diagnosis, but at the same time exclude other mimickers that can look a lot like prurigo nodularis. There are classic findings that you can see in patients with prurigo nodularis, both in terms of the distribution of the skin lesions but also with how the individual lesions look with firm, excoriated papules and nodules that oftentimes can be lichenified and distributed in areas where patients can reach with their own hands.

You want to look and make sure as well that there are no other underlying causes of itch that could be contributing to what you are seeing in front of you and these can include other systemic illnesses, such as having chronic kidney disease or an underlying malignancy. Some patients with diabetes can have an associated itch. You want to do a thorough history and a past medical history to make sure that you are not missing another cause that could be contributing to the itch that the patient is describing.

At the same time, you want to exclude other diseases that can mimic prurigo nodularis. There are other things that we see in dermatology that can also cause these types of skin lesions to occur as well as cause significant degrees of itch and burning in the skin. These can be conditions such as atopic dermatitis, cutaneous lymphoma, scabies, lichen planus and some other papulosquamous disorders. You want to screen with a family history by asking specific questions and potentially doing some additional blood work or other diagnostic studies to make sure that you are, in fact, making the correct diagnosis.

And lastly, it's important to qualify and quantify disease burden for the patient. Most patients that present with prurigo nodularis have a significantly decreased quality of life associated with this condition and I think it is important for your overall relationship with the patient to ask about that, as well as to document it in your clinic note for that day. This can help with obtaining approval of certain medications to treat this disease and can help when you see a patient in follow-up so you can compare how their quality of life is in response to the treatment that you've given them vs how their quality of life was at baseline when they first came to see you.

Case #1 – Treatment Options and Interprofessional Care

Leigh Ann Pansch, DCNP: When we talk about prurigo nodularis, there is the International Forum on the Study of Itch Guidelines. I think it's important when we look at this ladder to really get an understanding for what is baseline, for what types of conversations we are having with every single patient we see with this condition. First, we need to stress the importance of skin care. We want to make sure that they are moisturizing, that they are using some gentle cleansers, and this is the basis of everything else that we do.

I often tell patients this is your portion and the rest we are going to weigh in on other therapies for. Oftentimes, we do incorporate other disciplines based upon a patient's unique history. For instance, if there are some concerns about underlying disease states that may be factoring into a patient's problems with the rash, we might pull in primary care for some help with ruling out and getting other disease states in check, such as diabetes or renal disease. In addition, if a patient is having very specific neuropathic complaints with stinging and burning or hot poker sensations, we might pull in a neurology specialist to help.

And so, when we talk about individual therapies, we are going to talk about step 1 which are often our topical corticosteroids. I think it's important here to think about what formulation of topical steroid we would typically use here is more of an ointment form because we want it to penetrate those large, thickened nodules. To avoid the use of topical corticosteroids for this chronic illness constantly, to avoid side effects, we might also incorporate some topical calcineurin inhibitors as well as our antihistamines.

Other things that can be helpful to use as additive therapy is something like topical capsaicin. Capsaicin is available over the counter. It's certainly easy to access for a lot of our patients and, for some of our patients who love the idea of a rhythmic schedule, having them apply it 3 to 4 to 5 times a day on a schedule and then, once the symptom goes away of itch or pain or irritation, pulling off 1 of those times a day and getting into a rhythm has been found to be beneficial in some patients. Additionally, we love intralesional corticosteroids. Once we've identified that we are dealing with a prurigo nodule, to inject a steroid directly into that nodule tends to be a very fast way to address that itch.

Ultraviolet phototherapy can be helpful as well. Neuropathically, we might consider some gabapentin or pregabalin as well as some antidepressants in certain cases can be very helpful. And, if there is an inflammatory component that we feel just needs something from a systemic standpoint, we also might consider cyclosporine for a short period of time or methotrexate.

We might consider a therapy specific for itch reduction or some of our other systemic agents, such as dupilumab. In cases where we are just using all our therapies and everything else has been used and abused and we really don't know what to do, sometimes we scratch our heads and we do have a couple of patients in our office who are on thalidomide with very specific guidance, much like our REMS program for oral isotretinoin. There are some other therapies that are currently in clinical trial, including nemolizumab, and we have seen some early preliminary data and are very excited about those options when they become available after the FDA approval process.

Dr. McConaha, how can we help with the patient when it comes to self-management and coordinating care within the healthcare team?

Jamie L. McConaha, PharmD: It is very important that we have an interdisciplinary team caring for these patients with prurigo nodularis. There is a specialist role in treatment for these patients. They should be referred to a dermatology specialist, but we also have numerous other professions that are going to be involved in the care of these patients as well, particularly primary care, nursing, and pharmacy. These specialties are oftentimes the place where the patient first presents. We have an obligation to assess the patient and refer on as necessary, but also to play a supportive role in their care as well. For example, we can develop a trusting relationship or partnership with the patient using tools like motivational interviewing. These can be used to identify any special barriers or psychosocial barriers that the patient may be experiencing because we all know the psychological impact that this disease state can have on patients. We need to make sure that we are expressing empathy and compassion towards the patient and ensuring also that their treatments meet their needs and expectations.

We also can talk with the patient about appropriate goals and what to expect with regards to drug treatment. Whether it is over the counter or self-care type of treatment, we can recommend and counsel the patient about and helping them with setting realistic expectations of what they can achieve with those types of therapies. Then, providing appropriate counseling and even helping with medication access as needed with some of the prescription medications. This disease state involves treatment by all healthcare providers, whether it's the person that the patient is first presenting to or that referral when it occurs, we all play an important role in the treatment of patients with prurigo nodularis.

Najat Watch, PA: I believe that it is paramount to have coordination of care for these patients. There are social, psychological, physical issues in patients with this disease. It is multifactorial. Upon getting a referral from a primary care provider, at the minimum, communicating back to that PCP regarding our recommendations for care for these patients is needed. It's also important, especially if you have a team that is caring for these patients, to talk to attendings, talk to residents, anyone who might be associated with this patient to make sure their care is optimized. That might include psychology or psychiatric referrals and some hospitals have coordinated appointments for the physical aspects and the mental health aspects of this disease. Coordination of care, making sure patients are monitored regularly is paramount, and that might be coordinating between a PCP, a dermatologist and it might also involve a psychologist as well.

Jonathan Silverberg, MD: Unfortunately, in the US, multidisciplinary care settings are not money-makers, so we don't see them used as often. I ran a multidisciplinary clinic at Northwestern, when I was still there, for atopic dermatitis and other itchy disorders, including PN, and having the various providers there on-site was just absolutely invaluable in terms of getting at the underlying comorbidities and addressing the mental health issues, making sure we could reduce polypharmacy, etc. I think it's such an important issue. In the absence of that though, I think it really behooves all of us to try to do the best we can to coordinate that care in a little bit more disjointed healthcare setting.

Najat Watch, PA: We are very lucky at Henry Ford Hospital. We have a lot of multidisciplinary appointments. We have a whole psych-derm group, and I can't tell you how wonderful it is to be able to coordinate care. We also have a rheumatology-dermatology coordinated clinic as well. Instead of these patients going to 5 different providers, we sit down together, get everything coordinated and patients are not only satisfied, but really, going forward, they do better. They do better, mentally, and physically, because they feel they have a team of people that are rooting for them.

Case #2 – Adjusting Therapy

Jonathan Silverberg, MD: For case number 2, we have a 71-year-old female with type 2 diabetes, hypertension, and chronic kidney disease who's being seen in the dermatology clinic following referral by her primary care clinician. She was diagnosed with prurigo nodularis 5 months ago by her primary care provider and she has received little benefit from skin care, emollients, and topical corticosteroids.

The first thing to consider would be how to proceed in modifying this patient's therapy. There are several important considerations in terms of thinking about optimizing the existing therapies, but also making sure there is good adherence, making sure you have appropriate potencies for topical steroids, and appropriate quantities. You should also be thinking about the importance of stepping-up therapy and really thinking about what the ideal next step would be because there is clearly an inadequate response from the current options. Additionally, we should consider the importance of assessing how the disease is impacting patients and how we should really be thinking about these, and, incorporating them into our treatment decision making.

Sometimes you'll have patients who don't even look so severe, but the patient is telling you it's really destroying their life. How is it impacting them at work, at home, in terms of activities of daily living, sleep, just daytime functioning, mood, etc? All of these are things that if the disease is really impacting any of those domains in a way that is not adequately controlled by therapy, I would certainly think about stepping-up therapy. Try to take that more holistic approach and not just focus on just 1 score like the severity of itch, but really think about the broader impacts on patients and then stepping-up appropriately.

Case #2 – Emerging Treatments and Monitoring

Najat Watch, PA: When patients have failed these more symptomatic approaches and are not getting clearance, it is time to think about dupilumab. What else is emerging or what is in clinical trials. We have 2 new monoclonal antibodies that are in phase 2 and 3 trials, one being vixarelimab and the other nemolizumab. And the way that these work is they are man-made proteins that are acting like the human antibodies in our immune system and they can be very effective, hopefully for giving more long-term relief of this pruritus. Another medication that is being looked at is the opioid analgesic, nalbuphine formulated as an oral extended-release tablet.

Jonathan Silverberg, MD: Monitoring is tricky, and I think it varies by practice based on both pragmatic and theoretical considerations. Certainly, whenever you are assessing at baseline, to make that decision about stepping-up therapy, whatever domains were being impacted, you want to assess after treatment how well the patients are doing. I would advocate for at least doing a structured assessment like the NRS Itch. For a disease like prurigo nodularis, that single question can tell you so much information.

But there are other things to assess as well, like impacts on sleep and mood and, again, activities of daily living, etc. So, some of these can be open-ended questions, but I think a structured question around the severity of itch can be very helpful here. I think the trickier part is at what interval because, in an ideal world, we might see these patients back every 1 to 2 months. I don't know about you; I just don't have the bandwidth in my practice to accommodate that. And so, especially

when a patient is put on something like a biologic, that follow-up often gets extended, maybe even more to 4 to 6 months. And yes, I accept I could be missing some things that happened in that initial period, but I'm just being practical in that respect, knowing that some of the therapies can take a little longer to hit that peak efficacy. And, knowing that they overall have very clean safety profiles, I'm often willing to take that chance. But, of course, that's going to vary by drug.

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