JAK Inhibitors

Peter Lio, MD, FAAD, interviewed by Jacquelyn Dosal, MD, FAAD

JACQUELYN DOSAL, MD, FAAD: Welcome to *Dialogues in Dermatology*. My name is Dr. Jackie Dosal and I'm a practicing dermatologist from Skin Associates of South Florida in Coral Gables. Today's topic will be all about JAK inhibitors, with the esteemed Dr. Peter Lio. Welcome, Dr. Lio.

PETER LIO, MD, FAAD: Thank you so much for having me.

JACQUELYN DOSAL, MD, FAAD: Peter is a Clinical Assistant Professor of Dermatology and Pediatrics at Northwestern University. He received his medical degree from Harvard Medical School and his dermatology training at Harvard. And while at Harvard, he received formal training in acupuncture. Dr. Lio is the founding director of the Chicago Integrative Eczema Center and a founding faculty member for the integrative dermatology certificate program. He is a board member of the National Eczema Association and has written over 200 publications and 3 textbooks. So we're so happy to have you here, thank you again.—

--And this is a great topic. I was laughing to myself, thinking this is going to be JAK inhibitors for dummies, because I feel like we're going to review it all and try to get up to speed. Because so much has changed and advanced within the last few years. I know that we haven't had the in-person meetings and many of us feel behind the curve with these new therapeutics. So let's start with the basics, what is a JAK inhibitor? And can you sort of describe how it works and why we should know about it?

PETER LIO, MD, FAAD: First of all, I think in a way we're all kind of at that first stage of learning, because there really is a very big change for us. This is a totally new class of medications in dermatology. Of course, we've had these in other areas of medicine in the past, but this is a big deal. So I think it's worth spending a moment in understanding them. The JAK

inhibitor class has been around for quite some time in other uses. And it really is a targeted immunosuppressant/antiinflammatory class. It's a very small molecule, so it's actually able to penetrate through the skin very well and actually into the cell.—

--So it actually goes through the cell membrane, unlike other larger drugs, in particular biologic agents which can't penetrate into a cell, and therefore actually work on either the cytokines themselves or the receptor. And without a diagram, it's a little tricky but I still like to go through the cascade of thinking about how we have messages sent through our body from cell to cell. So one cell releases a cytokine, these are soluble factors that go through and they go to another cell. They bind then to a specific cytokine receptor.—

--So, for example, let's say we're talking about IL-13. That IL-13 cytokine binds to a cell receptor on the surface of the cell. When it binds, the proteins in that receptor actually undergo conformational change and quote, unquote, transmit that message through the cell membrane inside the cell. When that happens, the JAK enzymes are sitting down there nearby the base of that. They actually dimerize and they can activate STAT. STAT actually then goes into the nucleus and alters transcription. So that's kind of the whole relay race or cascade that goes through.—

--And we know that, of course, there are ways to block cytokines with some of our biologics, block the receptors with some of the biologics. And then if we go into the cell, we can actually affect JAK directly and that's what these JAK inhibitors do. It turns out you can even interact with STAT, there are other drugs that can do that. But this is at that point of the pathway.

JACQUELYN DOSAL, MD, FAAD: What I'm gathering is that the JAK-STAT pathway is involved in a lot when it comes to dermatology, more than we even knew?

PETER LIO, MD, FAAD: Yes, it is really, really broadly important in biology. And lots of different cytokines use this pathway. There are four members of the JAK-STAT pathway of the JAK pathway: JAK1, JAK2, JAK3, and then one called Tyk2 for tyrosine kinase 2. And there are different combinations. We said they dimerize, they pair up. But depending on what the cytokine is and receptor setup is, it may be JAK1 and JAK3, or JAK1 and JAK2.—

--It turns out that for allergy and allergic and atopic diseases, like in particular atopic dermatitis where we have our approval so far, JAK1 seems to be the commonality, that's the common thread. So you'll hear different JAK inhibitors talk about either being a pan-JAK inhibitor, they kind of block them all or interfere with them all, or they're selective. And in particular, you'll hear about this JAK1 selectivity. JAK1 seems to be a little bit more appropriate and concentrated in the area of the allergy things.—

--If you go to other members of the JAK family, you have a higher risk or a higher chance of interfering with different processes that may be for certain disease states you'd want to deal with. But in others, you might not want to because we know this affects, for example, granulocyte-monocyte factors and it can also affect platelet growth and all sorts of hematologic indices. So we have a number of different aspects that can be altered and we ideally would not want to mess with those for atopic dermatitis. We'd want to focus more on our JAK1 system if we can, or minimizing that.

JACQUELYN DOSAL, MD, FAAD: That's fascinating. And I think getting down to the nitty-gritty of each of these will be important as we start to refine our knowledge, because this is something that's important as we understand the side effects, is what I think you were alluding to before. Do you mind taking a step back and just sort of talking about what's happened in the last few years? I remember hearing about tofacitinib for rheumatoid arthritis a few years ago. And I don't know if it was serendipitously but hearing Brett King talking about some of the off-label uses that

we're finding in things like vitiligo or alopecia areata. Do you have any comments on that, on how things have sort of evolved or how they came to be?

PETER LIO, MD, FAAD: The history is so fascinating, to see how everything has played out. I've been focused on atopic dermatitis for more than a decade. And I really have to thank Dr. Amy Paller, who is my mentor, and she's the one who sort of said "this is what you should focus on." And she's a genius in many ways, but this was another one of her moments because I think she saw that we were on the cusp of something big, with really seeing far into the future. Because it took a number of years before anything happened. When I first got interested, we had almost nothing focused on atopic dermatitis.—

--And it was really difficult. We were using everything off-label. Meanwhile, we're watching psoriasis get all of these new and exciting treatments, more and more targeted, than ever before. And it's been fascinating. Well, you're right. Dr. Brett King at Yale has done some incredible work, looking at some of the JAK inhibitors, in particular one of the oldest ones, tofacitinib, which has been approved for rheumatoid arthritis for a number of years. And early on he thought, "Boy, this makes sense." This pathway is not so specific to rheumatoid arthritis, it could potentially help with other inflammatory conditions, especially ones for which we have unmet needs.—

--In particular, I think he's looked at atopic dermatitis and alopecia areata. Those are kind of the two major areas, although that's certainly not the end of where this might be able to help. And he's looked at it both in terms of oral preparations, that's actually the approved way that it's been on the market, not for atopic dermatitis or these other indications of course, but also people have compounded it. There have been other folks compounding it topically in using other agents, like topical ruxolitinib. Now we actually have that as an FDA-approved preparation.—

--But there were reports in the literature years ago of people just having it compounded, because you could get that again as a pill form or a powdered form and a specialized pharmacy could make that for you. So we've known for a number of years that these pathways are integral to a number of inflammatory problems that we deal with. And this is my opinion firmly right now, but I think that they are more targeted and in general have a better balance of risk and efficacy than corticosteroids. So at some point, you could start to say, "Well, gosh, these sound a lot like corticosteroids." And we've been using these since the 1950s, since the advent of Compound F and all of these things, absolutely.—

--And they are comparable in some ways. They kind of have a broad antiinflammatory effect, anti-itch effect. They work in a number of different conditions. But I do think they are slightly more targeted, is a helpful way to think about it. And although we don't really have direct comparative data, I think we can infer from, and I'm working on a paper right now, trying to be a little bit more rigorous than just general inference and getting a gestalt, but I think we're going to be able to say, "Okay, look. Yes, these are some serious risks that are associated with the JAK inhibitor class."—

--But if we look at some of the things we've used much more nonchalantly, prednisolone for kids all the time if they have an asthma flare or a bad urticaria case, and of course for atopic dermatitis, arguably somewhat inappropriately using it there, I think we'll see that these are actually a better bang for your buck, so to speak. So we've watched these get refined and refined. And then there was this long teasing period, where they were submitted, a number of companies, three to be exact, had submitted oral JAK inhibitors to the FDA for atopic dermatitis.—

--And then we expected them kind of in the summertime and nothing came. And finally it didn't happen until really the beginning of this year, January, that we had two of the three approved.

And the third one, baricitinib, remains approved only for rheumatoid arthritis and not for atopic dermatitis in the United States. Now, in other countries across the world it does have an atopic derm indication, making everything even more complex. So we do have a lot to learn. I don't know the status of that, beyond the fact that it's not available yet. And it does make it a little bit trickier though even to have two agents right now. Which one should I pick? Who is the appropriate patient for this? When should we use them as opposed to the biologics or opposed to the conventional immunosuppressants?—

--And, of course, even the labeling of the JAK inhibitors in the United States, including our topical ruxolitinib which was approved at the end of September last year, they are pretty scary. They all have black box warnings that list everything quite boldly, all these concerning things: malignancy and major adverse cardiovascular events and so on. So I think there's a lot of patient handholding and shared decision making that we have to make. And really good patient selection. I never want to push this on a patient, because the risks are potentially much higher than, for example, a topical agent that we've used in the past.

JACQUELYN DOSAL, MD, FAAD: So let's take a step back. Because if you're new to the JAK inhibitors, you may not even know what's approved yet. So what has so far been FDA approved, let's say for any dermatologic condition?

PETER LIO, MD, FAAD: So we have three total. So we have our topical ruxolitinib, that was approved at the end of September. And that is a topical JAK inhibitor. It's in kind of a light cream base. It has a number of warnings on there, but pretty exciting because, unlike a steroid, not going to thin the skin, not going to have issues around some of the sensitive areas, like ocular issues or in the folds. So that's been out for a couple of months. And then in January, we got two of the oral agents. Both are dosed at once daily dosing. And they actually both come in a couple different dosage strengths.—

--But we have abrocitinib and that's the one that was by Pfizer. And then we have upadacitinib and that's the one by Abbvie. By the way, the topical ruxolitinib is from a company called Incyte. So these are the three that we have, the two orals and the one topical. And the abrocitinib comes in 100 mg and 200 mg tablets. And upadacitinib comes in 15 mg and 30 mg tablets. But in general, we'd start with that lower dose and then if a patient weren't doing well on that dose, we have that flexibility to increase.—

--Which is also, to my knowledge, the first time I've ever seen this in an FDA-approved way. Clearly, we escalate doses of things all the time in an off-label way, but it's kind of neat, both of these drugs have on their label, if the patient is not achieving where you want them, you actually can go to that higher dose. And I think it's pretty neat, actually.

JACQUELYN DOSAL, MD, FAAD: So continuing with the topical, it's so nice to have another non-cortisone medication for our patients. And tell me what type of patient you're using this for and how you address what's on their black box warning with your patients.

PETER LIO, MD, FAAD: I have a pretty crazy clinic, in that it's very enriched with patients who are struggling. So in a way, I feel lucky, if you can feel lucky with this, I mean I feel bad for all these poor patients that are struggling, but I feel lucky because my patients really need new stuff. I'm not really worried about "did they fail this and this?," they failed everything. So I can kind of jump into the new treatments. I literally, truly have a waiting list in my office of when new drugs are being developed, I'm saying, "Okay, Mr. So-and-So, we're going to put you on this list. This is supposed to come out in February. I'll call you as soon as it's out," because that's the level of unmet need, they failed all these things.—

--That being said, so the first people are the people who are really severe and miserable and have failed everything else. But as we learn more about these treatments, I think then they start to find their niche a little bit more. And I think a good example is with dupilumab. That, of course,

came out originally in March of 2017. Initial indication was for adults with atopic dermatitis. Now, we've seen it drop to the 12 to 17-year-old range and now down to 6 years of age indication for AD. But also, we know that they've submitted the data down to 6 months. So we may actually see that medication approved from 6 months and up.—

--And what's neat is when that first came out, I had the same scenario: a bunch of patients who had failed everything we had so far. But now, I find that, for example, for dupilumab I don't feel like I have to wait until they've failed a number of other things. If they've had trouble with topicals, in some ways it's become my first systemic agent, although I'm a big fan of phototherapy. So I might mention phototherapy first, but a lot of patients can't functionally do it, it becomes a little bit of a logistical issue. So that has become one of my top lines.—

--With our JAK inhibitors right now, especially I was talking about our oral ones in particular, I'm kind of reserving them for these endstage cases. But maybe in time we're going to be able to say, "Golly, if a patient has really bad disease and they're having tons of acute issues, nothing seems to work faster than these oral JAK inhibitors." So that could be a really huge boon. Not only is the depth of their effect, the magnitude of their efficacy honestly among the best things we've ever seen for atopic dermatitis. But their speed, the rapidity, it's staggering.—

--Some of the studies, you see in the approved slide decks, you're looking at these studies where two days you can actually see measurable significant change. And that's different, that's something new for us.

JACQUELYN DOSAL, MD, FAAD: That's great. Our patients are going to be thrilled with that, too, because there's really nothing that rivals that.

PETER LIO, MD, FAAD: One of the hardest parts about these medications though is that they really do have these very stern warnings that can really strike fear into the hearts of anybody,

even the most desperate patients. So I think a big part of our job is to avoid the 10:30 p.m. phone call. What I mean by that is in the past, sometimes even with things like tacrolimus, topical tacrolimus has been out since 2001 or so, and I don't often talk about the black box. I'll often say, "You may see some warnings, we'll talk about it," I'm so used to it.—

--But occasionally, the patient fills the prescription after work at the pharmacy. They go home, they're about to put it on their kid or on themselves and they read the black box. And they say, "Wait a minute," and I get the call. So I feel like in a way, that means I failed. And I still am guilty sometimes, I try my hardest not to, but sometimes I forget. It's a busy visit, we're talking about so many things. And I think that can really shake the patient. So for these, I try to be extremely preemptive and proactive. I try to say, "Okay, listen. These are very powerful medicines." Let's start with our topical ruxolitinib, because that one I think many people are going to be able to use or experiment with and try, because it really has a broader indication and overall I think is less cumbersome to use than the oral medicines.—

--So for that, you'll notice the black box warnings are the same. They really do say essentially the exact same thing. And a lot of that data is based on a very important study, a post-marketing study, that was done in rheumatoid arthritis patients using, as we were talking about before, tofacitinib, so a different JAK inhibitor, in a group of patients that by definition had to be at least 50 years of age and had to have at least one major cardiovascular risk factor. So this makes it really hard. It's sort of like if you're trying to compare apples to apples and you have a group of patients that has a whole separate disease, and using a different drugs, and has different risk factors, what can you say to a 28-year-old guy with atopic dermatitis who is feeling great, but is miserable except for the skin? I don't know.—

--The truth is, I think as scientists we have to say we don't know. We don't know how to translate this on an individual level. All we can say is that these medicines as a class have some

serious side effects. We've got to let you know, because we don't want surprises. And they're all new enough that we really don't know. I'd like to think that ours are safer and our population group is safer. And from what we see in the trials, and there's hundreds and hundreds and hundreds of patients, thousands even, we look at the trials for all of these medicines together, that's still not enough. There still may be a signal that we can't see.—

--So how do I tell my patients? I say, I'm really trying to make sure we pick the right patient. And I always say, "We're not rushing into this. You've done your due diligence. You've done your topicals. You've done probably some other systemic agent or we couldn't do it for one reason or another. And you're suffering, you're suffering a lot." So one of the things I love is something called the Atopic Dermatitis Control Tool, the ADCT. It's free online, it's non-sponsored, it's fabulous. It's six questions, it takes under one minute. A patient can do it, answer six questions about their disease, and they get a number.—

--And that number is pretty powerful because you can track it. It's a validated scale, you can track it. And basically, you want them under 7. If they're 7 or less, you feel like, alright, you're in pretty good control. But if they're more than that, that means they're probably not well controlled. And I had a patient this morning, she was 21 I think, and it was very striking. Because she said, "You know, I think I'm okay. I'm doing alright with what I'm doing." I said, "Let's do this together," we just did it together live. And she couldn't believe it.—

--And I said, "Yeah, you're really not. Three, four nights of the week, you're having trouble with your sleep. This is a huge problem, this is not okay, it's not normal." But people become inure to it over time. So picking the right patient. Explaining that this is an extremely powerful class of medications that does have some potential risks. And then for the topical version I like to say, "Listen, I think if we're careful with our amount of usage, we're going to be using it to targeted body areas, we're not going to be using it continuously for long periods of time. We're certainly

not going to be able to use more than 60 grams a week," which is actually one of the things they put in the label, because you can't afford it, it's expensive.—

--And you're generally going to get one a month, if you're lucky. So I really tell my patients, "I don't think these are going to apply to us in the same way, but you should know about the class." Now, for the orals I say the same thing, "This was done in a different population. We think their risks are probably higher than what yours will be. They're not zero but there's a risk to having eczema that's untreated. There's a risk to driving in to see me this morning, especially in Chicago. You could get in a car accident, you could get carjacked." There's all these things, we deal with risk all the time. So trying to put that in perspective is very difficult.—

--But I think part of it is the strength of that relationship and making it a shared decision. I present these options to the patient and let them really sort of tell me when they're ready. And sometimes, we end the visit, it can be a long visit and I say, "I don't want you to decide right now. No, I want you to go home, think about it. Let's talk tomorrow. Read about it. Talk to your family. Make sure you feel comfortable." Because the one thing I don't want is someone who feels like I pushed it on them and then they have a bad effect and they're saying, "Oh, my gosh, this guy told me to do this." I like it to be more we're going to come to this together.

JACQUELYN DOSAL, MD, FAAD: That's such great advice. I do just want to be clear though, what actually are the black box warnings on these? Because we talked about it but we didn't directly say. And are they the same, I think you did say that they are, but are they the same exact conditions for each of the JAK inhibitors, the topical and two orals?

PETER LIO, MD, FAAD: They are extremely similar, yes. The actual prescribing information does vary a little bit on each product. And I would encourage everybody to spend a few minutes to look at it, because our patients get it in every single package. Most of them don't read it but some of them do, so it is good to spend some time. But there are a couple of major things they

talk about. They mention first of all this major adverse cardiovascular event. And these include things like myocardial infarction and stroke. They talk about clotting, so deep vein thrombosis, arterial thrombosis. They talk about mortality risk, so there really did seem to be a higher risk of mortality, especially in patients who are current smokers or former smokers.—

--They also talk about malignancy, so both skin cancers, that's elevated. And in fact, some of the labels actually say, "Recommend to your patients skin screening," and that's something we all do, we know how to do that better than anybody, "and sun protection," because there's a skin cancer increase but also non-skin cancer elevation, especially in that rheumatoid arthritis study that was seen. So we have a number of different serious issues. And then we have the lab abnormalities. Now again, for the topical, ruxolitinib, they're not indicated necessarily for this, but for the two orals that are approved, they are.—

--And the big issues are there have been cases of hyperlipidemia. There have been cases of thrombocytopenia, anemia, lymphopenia. So you really do have to keep an eye. And liver enzyme elevation and CPK elevation. So kind of keeping an eye on these labs. Also, of course, we're going to want to do, like we would maybe a psoriasis biologic or any immunosuppressive medicine, a TB test at baseline, hepatitis panel at baseline. And I'm actually doing an HIV test at baseline, too, just to be sure. And I'm repeating that level of intensity every year, so that I make sure.—

--And then I'm doing labs usually the first month, and then the third month, and then quarterly if things are looking good. But there's some nuance there and I'm still trying to find my footing on it, as well.

JACQUELYN DOSAL, MD, FAAD: Do you check a pregnancy test?

PETER LIO, MD, FAAD: Thank you, yes, that's an interesting point. These are definitely contraindicated in pregnancy. We really do suspect that they could cause fetal harm. But I haven't. In general, I'm talking to the patients. I explain that to them. I don't think it's a bad idea. But I'm also not prepared to treat it, like I would isotretinoin, seeing them every month. So I think just kind of explaining that if they found out they were pregnant, then we'd want to stop it immediately and talk about it.—

--There's actually a registry, as well, if they were going to stay on it. But in general, I just make it very clear and talk to the patients directly.

JACQUELYN DOSAL, MD, FAAD: What about drug interactions? Do I have to worry about anything when I'm prescribing?

PETER LIO, MD, FAAD: You definitely do. And that also makes their life very tricky. And I will be honest with you, a lot of them are kind of tricky. Like there's a whole special section about antithrombotic agents. In the first few months, you're not supposed to be on any antiplatelet agents except for low dose aspirin. Then in theory you could go back on it and there's a whole bunch of things that could potentially interact. So I do recommend reading it. This is a time where I really love my little pocket computer and I could punch it in and say, "Hmm," but I will tell you already, I've had to talk to several primary care doctors and say, "Okay, can we hold this one? This is a cardiac medicine. How can we do it?"—

--Because I'm not comfortable messing around with their medicines. The indication will say "lower the dose" or "monitor it." It's like I don't know how to do that for their other medicines. Obviously, I can do it with our stuff but it really does take a team approach. And this is very different than the biologics, which delightfully don't have really any drug-drug interactions, so you can just sort of use it willy-nilly.

JACQUELYN DOSAL, MD, FAAD: The one that I read about was fluconazole and ketoconazole, which would be more in our wheelhouse that we might be concurrently prescribing for some other reason. So that was one, I guess because of the CYP interactions, so I certainly took note of that. The one other thing that I wanted to ask you about was when I was reading about the topicals, I read that acne could be a potential side effect. Do you have experience with that?

PETER LIO, MD, FAAD: Yes. And in fact, in a number of different oral JAK inhibitor trials, acne was one of the more common of the adverse events. In fact, I believe it was even as high as like 15 or 16 percent in one of the trials in patients. Now, the vast majority of those cases seemed to be really mild and usually are able to be treated with conventional acne type approaches. But there are a few patients who dropped out of the trials because of the acne. So I think that is something worth talking about.—

--One of the things that's already come up is if they're using the topical ruxolitinib, the topical JAK on their face, would that increase the risk for acne? And the answer is I don't know, I don't know yet, I'm watching carefully. And for these oral agents, I think it is something we're going to see. Weirdly enough, I will say it, and I was involved in one of the trials, knock on wood, I have not seen it personally, I've just heard about it. So I haven't seen it personally but hopefully I won't have to, but I presume we will, if the numbers really are more than 10 percent, I think we're all bound to see it eventually.

JACQUELYN DOSAL, MD, FAAD: So let's say you're starting you're atopic dermatitis patient on one of the oral JAK inhibitors. What do you counsel or what can we expect as far as duration of therapy? Is this like a biologic that's sort of indefinite? Do you try to take them off? How do you approach it? And I know that there's FDA labels, too, so some of this will be off-label, I'm sure.

PETER LIO, MD, FAAD: Yes. No, and I love the question because right, that's something that the FDA sort of doesn't really put much about and the companies don't talk much about how do we get them off, but our patients ask a lot about that. The number one thing people ask me is, "Is this forever?" And I think my response generally, again this is just me so take this as you will, I'm speaking only for myself, but I often say, "No, I don't think anything should be forever. I think we need to get this under control, because it's crazy out of control, and it's hurting you, and hurting your life, and damaging your skin further, and creating a vicious cycle of disease, so we need to stop it. And I think we need to hold it down for a while. We need to get you from this vicious cycle of flaring to a virtuous cycle of healing."—

--And how long does that take? I usually tell patients in my experience, on the order of six months to a year for many patients. But if you're doing great in that timeframe and feeling really well, I don't think it's crazy to think we could potentially start weaning or coming off of a medicine. Now, for certain conditions in certain patients, you do that and it comes right back. Fine, I believe that, I'm not denying that. But I will tell you, I've written papers about it, too. For some patients, when you hold them in this state for a while and you stop, they enter a relative remission.—

--And that, to me, is powerful, that's deep healing. And I really do think, well, we have some of the data because in some of the trials for these oral JAKs, they've randomized people back to placebo at some point. And actually, there is a proportion of the patients who actually stay relatively clear. They maintain their clear or almost clear EASI-75 status. So there's no doubt that it's a real thing. The question is, can we be clever? Can we predict who is the right patient to do this? And I think part of it again, it's a give-and-take. How are you feeling? I have some patients who say, "Please do not take me off. I love my life now. I am doing everything I wanted to do."—

--I always tell a story, I had a cardiothoracic surgeon several years ago. He was on permanent disability. And I had to write something I'd never wrote. I had to try to write a reversal of permanent disability, because when he went on one of the new agents, he could operate again. He could actually do it. So it changed his entire life and he's now operating. It's completely crazy, right? So that's the kind of thing that we can potentially offer with some of these more powerful treatments, something that truly we didn't have in the past.

JACQUELYN DOSAL, MD, FAAD: That's amazing. We are starting to run out of time. We could talk about this forever, but I do just want to mention a couple of conditions that I've read about that had been reported as off-label use. I love reading this stuff, because I think dermatologists are the most creative and smart people. But, of course, it's been used off-label, there's reports about alopecia areata, dermatomyositis, granuloma annulare, sarcoidosis, lichen planus, morphea, just overall pruritus which it sounds like works very well for itching, psoriasis, vitiligo, and others. I mean, it's really remarkable.—

--So when I hear things like that, I just think we're on the cusp of something really fantastic. And I found myself debating this in my mind as I've been learning about them. Should we be really excited about these, which it sounds like the answer is yes, or should we be scared?

PETER LIO, MD, FAAD: I think you're right on. And probably the wisest answer is a little bit of both. We know that with any great technology, it can be helpful and harmful. And the sword always cuts both ways, the sharper the sword the more dangerous it is. So these are incredibly powerful. And there's no doubt. I always tell my patients, too, we're not trying to put this in the water. You don't see my face plastered on the side of a bus, saying, "Come over and I'll give you this medicine." No, no, no. You're coming to us because you're suffering.—

--That's the only people I really am saying these are for. If you are healthy and do not need these medicines or medicine in general, that's better. I don't want people on stuff that they don't

need. That's our first to do no harm, that's our major objective and our prime directive, if you will. But for those patients who are really, really suffering, and I've seen suffering to me in my practice, atopic dermatitis is the worst. It causes the most suffering cases, not only the patient, it's the whole family unit. It affects the school and society and even us.—

--Like there are days I come home, I depressed. I feel like I have not helped anybody as much as I wish I could. People are sobbing on the phone, it's just terrible. So to have some new powerful things for those patients, I really think that can change the narrative for these people. But it can be scary, too. And we're going to cause some harm as we try to help. But that comes with the territory and that's why we have to have that relationship. They're not a client, they're a patient. And we really have that patient/doctor connection because they have to believe that I'm really trying to help and even if bad things happen, certainly we didn't want that.—

--But we all know, if we're going to take those risks, some bad things are going to happen. And for the right patient and the right setup, I think it's worth it. It's worth it to take those risks because we can get an awful lot of people better.

JACQUELYN DOSAL, MD, FAAD: I love it. Such a great message of hope, too. So thank you so much. Anything that we missed, anything else you want to leave us with?

PETER LIO, MD, FAAD: Gosh, I think that's it. I just hope everybody spends a little time learning about them and is not afraid to use them. I know they're kind of scary. I think my big concern is just that there's so many patients with bad atopic dermatitis who really feel undertreated and feel kind of unsatisfied, because they get the same message over and over. "Here's a one pound jar of steroid, good luck." And I think it would just be so great, even if you're not comfortable prescribing it, refer to somebody who is. Get comfortable or have one person in the group or in the neighborhood that says, "You know what? I'll take care of this."—

--I just think that's a powerful thing. And I say that speaking with my National Eczema Association hat on. I'm a board member. So I just hear over and over and over for patients who are feeling unheard and sort of uncared for. And I know we have the power. That's why I love dermatology so much. We have the power to actually help them and now we have the tools, as well as the talent.

JACQUELYN DOSAL, MD, FAAD: Love it. Thank you so much, Dr. Lio.

PETER LIO, MD, FAAD: Thank you again for having me, this has been great.

Commentary

Angelia L. Stepien, DO with Todd Schlesinger, MD, FAAD (ed.)

Janus kinase (JAK) inhibitors were first introduced as therapeutics for myelofibrosis and rheumatoid arthritis.[1] More recently this class of medications has been studied for the treatment of a wide range of dermatologic conditions. The Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway of intracellular signaling mediates several immune-mediated inflammatory dermatoses. The scope of this pathway is constantly evolving. Understanding the complexities of this therapeutic class is essential for practical disease management. In this episode of Dialogues in Dermatology, Drs Peter Lio and Jacquelyn Dosal discuss the newly approved JAK inhibitors and their use in dermatology.

There are 4 members of the JAK family: JAK1, JAK2, JAK3, and Tyk2.[1] These cytoplasmic tyrosine kinases are phosphorylated and dimerize in response to specific cytokines, chemokines, growth factors, and growth hormones.[1,2] These then phosphorylate STAT transcription factors ultimately resulting to gene transcription.[1,2,3] JAK inhibitors are small molecule drugs that act as targeted immunosuppressant agents and through inhibition of the JAK-STAT pathway regulate immune responses and cell growth.[3] For therapeutic effects, these drugs inhibit specific JAK targets. Dr. Lio highlights the role of JAK1 in allergic and atopic diseases.

The United States Food and Drug Administration (FDA) approved ruxolitinib, a topical JAK inhibitor, the first in its class for atopic dermatitis in September 2021. Dermatologists have had tofacitinib available for the treatment of psoriatic arthritis but earlier this year two additional oral JAK inhibitors, upadacitinib and abrocitinib were approved for atopic dermatitis. Baricitinib is another that is currently not approved for the treatment of AD in the United States, but is within other countries. Beyond their FDA approvals, these medications have therapeutic potential in alopecia areata, vitiligo, dermatomyositis, lupus erythematosus, graft versus host disease, and psoriasis.[1-4] In his clinic, Dr. Lio has reserved these medications for his end stage atopic dermatitis patients and has seen them work with both speed and efficacy. He compares the JAK inhibitors to dupilumab when it was first approved, highlighting that there is often evolution in treatment once new medications find their niche.

Dr. Lio stresses the importance of education, shared decision-making, and good patient selection when choosing to prescribe these medications. Black box warnings for the JAK inhibitor class include serious infections, malignancy, major adverse cardiovascular events, and thrombosis.[5,6,7] More commonly, increased upper respiratory infections, acne, and lab abnormalities have been seen during therapy.[1,3,4]

Laboratory monitoring is necessary before starting an oral JAK inhibitor. Dr. Lio emphasizes keeping a close eye out for hyperlipidemia and hematologic abnormalities, as well as liver enzyme and CPK elevation. Thrombocytopenia, anemia, and lymphopenia are seen in a dose dependent manner but are reversible after treatment cessation.[1] Dr. Lio repeats these labs at the first month, third month, and then quarterly. Baseline labs are similar to other immunosuppressive medications or biologic therapies and include testing for tuberculosis and hepatitis.[6,7] Dr. Lio also tests for HIV. These medications should not be used during pregnancy or while breastfeeding.[6,7] Physicians should be aware of drug-drug interactions. Dr. Dosal and Dr. Lio discuss the importance of recognizing the medications that can interact with oral JAK inhibitors and how to work as an interdisciplinary team when managing these patients. Specifically, Dr. Lio talks about the use of antiplatelet therapy which except for low-dose aspirin is contraindicated for the first 3 months of treatment with abrocitinib.[7] When patients ask if they

will be on the medication forever, Dr. Lio emphasizes the importance of stopping the vicious cycle of disease and typically tells his patients to expect a treatment course of 6 months to 1 year.

Dr. Lio encourages listeners to spend the time to become familiar with the prescribing information for each of these novel therapies and to work with patients to make an informed decision. He emphasizes that although the JAK inhibitors come with risks, these risks can be worth it to relieve suffering in our patients.

References

1. Shreberk-Hassidim R, Ramot Y, Zlotogorski A. Janus kinase inhibitors in dermatology: A systematic review. *J Am Acad Dermatol*. 2017;76(4):745-753.e19. URL: https://www.jaad.org/article/S0190-9622(16)31187-2/fulltext

2. Paniagua RT, Fiorentino DF, Chung L, Robinson WH. Tyrosine kinases in inflammatory dermatologic disease. *J Am Acad Dermatol*. 2011;65(2):389-403. URL: https://www.jaad.org/article/S0190-9622(10)00500-1/fulltext

3. Chapman S, Kwa M, Gold LS, Lim HW. Janus kinase inhibitors in dermatology: Part I. A comprehensive review. *J Am Acad Dermatol*. 2022;86(2):406-413. URL: https://www.jaad.org/article/S0190-9622(21)02071-5/fulltext

4. Chapman S, Gold LS, Lim HW. Janus kinase inhibitors in dermatology: Part II. A comprehensive review. *J Am Acad Dermatol*. 2022;86(2):414-422. URL: https://www.jaad.org/article/S0190-9622(21)02022-3/fulltext

5. Prescribing Information Opzelura (ruxolitinib). 2022;1-2. https://www.opzelura.com/prescribing-information.pdf. Accessed April 18, 2022.

6. Highlights of Prescribing Information Rinvoq (upadacitinib). 2022;1-59. https://rxabbvie.com/pdf/rinvoq_pi.pdf. Accessed April 18, 2022.

7. Highlights of Prescribing Information Cibinqo (abrocitinib). 2022;1-3. https://labeling.pfizer.com/ShowLabeling.aspx?id=16652#S7.1. Accessed April 18, 2022.