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A Clear Horizon in Plaque Psoriasis: Exploring the Role of Investigational Oral Therapies

Dr. Papp:
What challenges do you have with currently available therapies for treating plaque psoriasis?

This is CME on ReachMD, and I'm Dr. Kim Papp.

Dr. Bagel:
And I'm Dr. Jerry Bagel.

Dr. Papp:
Jerry, good to meet with you again. Just to start things off, what are some of the challenges and limitations that we have with currently available therapies for plaque psoriasis?

Dr. Bagel:
Well, I believe some of the challenges we have are not seeing all the people that have moderate to severe psoriasis. And I think part of that reason is because what we see here, at least in the United States, between the end of World News and the beginning of Jeopardy, are 3 commercials that talk about different agents for treatment of psoriasis.

And although they say they're efficacious, they also show how much problems there could be with different drugs. And I think they overestimate that somehow, and it scares people away. I think we would be better off if we just advertised about disease awareness.

Dr. Papp:
So what are your views on the differences and the efficacy profiles between the various agents, whether we're looking at the TYK2 or 17 inhibitors, 23 inhibitors, PDE4, for example?

Dr. Bagel:
I think, starting from where I came from 40 years ago at the Columbia Presbyterian Medical Center, where people were hospitalized for Goeckerman therapy for 1 month at a time, only to come back every 6 months to 1 year later, I think that we have these IL-23s that are amazing right now, like 4 shots a year in which 70% of people can be 90% better. Sometimes, 75% of people can be 90% better. I think it's an amazing thing that for 361 days out of the year, people with psoriasis don't have to think about their disease at all.

Dr. Papp:
Yeah, I would agree. I think we have a large number of patients who can do very well, but we still have, I think, a number of patients who do not respond well or lose response. We have those patients who are not fond of taking injections or may have high anxiety related to taking injections.

And then there are those patients who appear to be resistant to biologic therapy. So I think we're always looking for additional mechanisms of action, possibly, but certainly other methods of delivery. So going from injectables to orals, I think, makes a lot of sense.

And then there's the perspective of tolerability or safety that may be pathway dependent. May also be agent dependent. So I think there are a lot of factors that are involved, and these are definitely pushing to expanding our repertoire of therapies.

Dr. Bagel:
I find that as far as injections and orals, I always offer an oral medication now because I think the deucravacitinib is an effective modality. I didn't feel that way about apremilast, but I do offer deucravacitinib. I do believe we need better oral medications because the efficacy of deucravacitinib is not the same as that of the IL-23s.

Dr. Papp:
Yeah, I think so. But nonetheless, we're still looking for new modalities and oral therapies. So you know what? I'm just going to take a second here and talk about some of the more recent developments because we have some late-stage investigational medications that are designed and being assessed for the treatment of plaque psoriasis.

I'm going to lead off by talking first about FRONTIER-1 and FRONTIER-2. So FRONTIER-1 was published this year in New England Journal, and FRONTIER-2 also this year. And both of them present, I think, complementary perspectives on a new agent: icotrokinra. It's a small oral peptide, IL-23-targeted, and what we saw in FRONTIER-1 is that at week 16, we had a very high PASI 75 response, so it was dose dependent. So as we would expect from a phase 2 study, where we're looking at, I'll say, well-behaved molecule. So we see PASI 75 in an NRI population, pushing closer with 80% in the higher-dose rang, PASI 90s pushing 60%, and PASI 100s approaching 100%.

And then, as we get into the phase 2, sorry, the long-term extension, that runs out to 1 year, we saw that the response profiles for all of those, PASI 75, PASI 90, and PASI 100, were essentially sustained, so flatlined. Flatline in medicine, always scary except when you're talking about sustained response, where we see this flat line of response for PASI 75, pretty much the same at week 16 and 52.

Actually, no appreciable difference when we're looking at PASI 90s. It's similarly no appreciable difference between what was seen at week 16 and week 52. And PASI 100, there's little fluctuations, but those fluctuations all fall well within the error bars. And at the end, we had 40.5% at week 52 and we had 40.5% at week 16, which suggests that we're getting remarkable maintenance or response.

One of the other measures, of course, is the IgA01, which is a co-primary, and that, too, between week 16 and week 52, was just flat line. So I think it's a beautiful profile indicating that we not only have a potential therapy that's going to be highly effective, but it's also going to maintain that efficacy over the long term.

Dr. Papp:
Another interesting observation is ICONIC trial. This is a phase 3 study with icotrokinra, or JNJ-2113, and the results that were just recently released show that at week 16, we had almost 65% of patients achieving clear or almost clear, compared to a placebo rate of 8.3%. And that's measuring, of course, using the IgA. Co-primary PASI 90, we had almost 50% of patients achieving a PASI 90, which is really significant. And that compares to a placebo rate of about 4%, which is kind of what we would expect.

So I think this just speaks to the effectiveness of icotrokinra. Something that we kind of expected based upon the mechanism of action, but you don't know because so much of the effectiveness is really based on the properties of the drug itself. And icotrokinra shows that it's got good properties. It's got good legs.

So for anyone who's just tuning in, you're listening to CME on ReachMD. I'm Dr. Kim Papp, and with me today is Dr. Jerry Bagel. We are discussing the investigational oral therapies for plaque psoriasis.

I would like to turn it around a little bit, if I could, and get back to you and just ask a question. How do you see some of these newer oral agents potentially fitting into our treatment planning?

Dr. Bagel:
Well, I find the data somewhat consistent, at least for the long-term maintenance of response with deucravacitinib. I mean, remember, these are not monoclonal antibodies that induce a monoclonal antibody against them. So with these oral medications, these small molecules, you don't lose that kind of efficacy. It seems like it's maintained.

The interesting thing about this molecule is that it's a small protein, and you think it's going to get all dissolved, let's say, in the gastric acid. But enough gets through, and maybe 1% or 2% to have a receptor antagonist to IL-23. And yes, we did the clinical trials with this molecule, and it worked very, very well.

I mean, as the oral molecules become closer in efficacy to the shots, I think they could take over. But they have to get closer, and with this molecule, it's getting closer. So I'll be frank. I offer, like I said before, I offer deucravacitinib whenever someone is either initiating or switching a biologic. And I'd say about 15% of the patients are taking me up on it because the efficacy is not as high.

Dr. Papp:
Yep. I'm going to just step back a little second, so I focused on icotrokinra. But I think I'll just mention the others. You had already talked

about deucravacitinib, and April was the lead author on a publication a couple a years ago that reviewed deucravacitinib. And we see that it has certainly respectable efficacy and long-term durability.

There is a newer TYK2 inhibitor, zasocitinib, that April also is the lead author on, that was just published this year. And we're seeing results that are pretty good, so in line with icotrokinra. We don't yet have the long-term efficacy for zasocitinib, but I guess we'll wait and see.

I think all of this is very exciting. Very exciting because we have, for a long time, been looking at the need for oral therapies that are both safe and effective and tolerable. So when we're talking about tolerability, that's always been the weak point of the PDE4 inhibitors, and that's kind of limited the doses that we can explore. Though, the efficacy is also muted by the fact that we have that tolerability.

Compliance, I think, is pretty high with an oral because it's one of those things that patients can take responsibility for. And I think the other advantage of oral therapies that is sometimes forgotten and is, I would say, still somewhat of a theoretical concern, but a real concern for patients, is if you do have any drug-related issues, any safety issues, for example, then you stop taking the drug, and it's out of your system in a hurry. Whereas, the biologics, because of the long half-life, it's going to stick around for some time.

So I think there is still a lot of fear amongst many patients over the biologics, founded or otherwise. I mean, that's not necessarily our decision, and both of us agree and you even alluded to these are very safe drugs, but there's still a lot of concern that these biologics are very potent. They are very highly effective, and therefore, they are definitely impacting immune response somewhere, somehow. And so in the back of people's minds, they're concerned about the potential for side effects.

Dr. Papp:
Well, this has been absolutely fascinating, Jerry. I really appreciate it. It's wonderful speaking with you again, and just before we wrap things up here, I want to put you on the spot. I know almost nothing puts you on the spot. You're one of the coolest cats I've ever met.

One thing. Just a take-home message to our audience. What is your view? Your final word on the promise of —

Dr. Bagel:
Look. Look. I would —

Dr. Papp:
— these investigational oral meds for plaque psoriasis?

Dr. Bagel:
I appreciate, Kim, you saying that. And look, I was one of the authors on the National Psoriasis Foundation Treat to Target, and we're looking to treat 1% or less body surface area. I think these newer oral medications are going to hit the spot there. I think they're going to get up to a 1% or less body surface area in 60%-70% of the people.

Once that happens, then they become on pretty much equal footing with the subcutaneous biologics, and people will have to then make a choice. And I think many more will start going towards an oral medication, which they really wanted from the very beginning.

I mean, dermatology has always been an oral cream type. It wasn't always into shots. And I think If we can get the efficacy and safety back there, which it looks like we're getting to, then we're going to get back to oral medications. And I like your idea about the half-lives. People getting out of it if they have to. If they get a strep infection, if they get a pneumonia, they can stop it right away.

Dr. Papp:
Yeah. Well, I have to say that I concur. So I think, yeah. The promise here is that we are getting back to orals. So they're now real contenders in treatment of plaque psoriasis.

Well, Jerry, I'd like to thank you very much. This has been a really great, wonderful conversation. And it was just an absolute delight speaking with you today.

Dr. Bagel:
I always learn from you, Kim. Always. Thank you very much. I love working with you.

Dr. Papp:
Thanks. You're very kind. Likewise.