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Journal Club: Efficacy of Systemics After Discontinuation

Dr. Neal Bhatia:
Hi, I am Dr. Neal Bhatia. I'm the Chief Medical Editor for Practical Dermatology and welcome to another edition of Atopic Dermatitis Journal Club. And I am proud to introduce my good friend, Dr. Naiem Issa. We make the joke of the falling star and the rising star. Dr. Issa's a supernova of rising stars, if you want to call it that. Naiem, tell us where you practice and your academic affiliations.

Dr. Naiem Issa:
Thanks for having me, Neal. It is a pleasure to be here with all of you guys, and thank you to Practical Dermatology for being here. So my name is Naiem Issa. I'm also a board certified dermatologist. I am with Forefront Dermatology where I am working as the clinical director of clinical trials and academics. And I'm a professor of dermatology at University of Miami, as well as George Washington University and West Virginia University.

Dr. Neal Bhatia:
Naiem's being humble. He has a very good research background. He has a PhD in kinases and he understands ins and outs of MOA. Which is why this is actually a good topic about systemic therapies and the efficacy of them after they are discontinued.

So we were talking a little bit about the importance of maintenance of the gains, once patients get clear and then after they stop the drug. Then we think about how important is it to get patients to a point they can stop or take a holiday, and how do we maintain that efficacy? What are some strategies you have?

Dr. Naiem Issa:
Right. So the thing is as you and probably all of our colleagues have to deal with is this question of, well, how long do I take said medication for my eczema, right? Do we have any data to help guide us with answering that question, right? And especially for parents and their kids, probably the first thing that they ask after you discuss with them, you're taking like 10, 15 minutes in the room and they're saying, okay, look, I'm on board with the mechanism, this and that and the safety, but is this a forever drug?

Dr. Neal Bhatia:
Exactly. And a lot of these trials, they don't have recapture data, they don't have holiday time, but it is kind of built into maybe a 52-week study where you say, okay, I could probably take a break at this point.

Dr. Naiem Issa:
Right.

Dr. Neal Bhatia:

So is there some sweet spot that you like?

Dr. Naiem Issa:
Right. Right, exactly. And so this is the whole underpinning for the paper that I've got to publish with Dr. Sean Kwatra as well, and Dr. Del Rosso, and so that just came out a couple of weeks ago in the Journal of Clinical and Aesthetic Dermatology. So basically the crux of what we were looking at in this part one of a two-part series is what happens with biologics after you discontinue them, according to the pivotal trials with that 52 week extension where you go to a withdrawal arm after achieving clear or almost clear or an EASI 75. And so there is some great data to help guide that. So for dupilumab, we have data from the SOLO-CONTINUE study, but in that study you have weekly injection as well as the on-label every two weeks. Yeah. Exactly.

Dr. Neal Bhatia:
Makes sense.

Dr. Naiem Issa:
So they're grouped together before they are then switched to the placebo withdrawal arm. And then you also have, for tralokinumab, you have kind a step-down where you have those who were clear at week 16, were re-randomized to either every two weeks or every four weeks.

Dr. Neal Bhatia:
Every four weeks, right.

Dr. Naiem Issa:
Or the placebo arm. And based on that data, that's why on-label there was the every four week on-label injection pattern as well.

Dr. Neal Bhatia:
That's very real world.

Dr. Naiem Issa:
Right. Exactly. Very real world. And on top of that, for lebrikizumab, there's a similar story there. However, so while the data is there and it is published and publicly available, the more important thing that we have to note is that the clinical trials were heterogeneous. And that's oftentimes something that is not really talked about. And granted, we're making direct comparisons here. But the setup and the demographics of these patients and what were washout periods were different, different topical washout periods, different systemic washout periods, whether you're looking at non-responder imputation or multiple imputation, this, that and the other thing. So these are all things that we have to really consider besides just the number that we see ultimately on the graph.

Dr. Neal Bhatia:
Yeah. And that's what twists around research from real world, right? Because here we're washing it on doing monotherapy, whereas in the real world we're adding, right?

Dr. Naiem Issa:
Exactly.

Dr. Neal Bhatia:
We're thinking about and instead of or like we always talk about. Think about now if you put your research hat on, if you had to design a

trial differently, would you put it as you've quoted or would you try to tweak the data, or not tweak the data, tweak the trial so that you can capture different data points?

Dr. Naiem Issa:
So it's interesting. So for the research hat on, if you're reviewing a grant or what have you, you want as clean and pure a signal as you possibly can, and that's really hard to do. So if it was up to me I would love to do a trial where patients did not have a topical before enrolling patients who were never on a systemic such as an immunosuppressant or a prior biologic, like the more later studies or phototherapy or what have you. Just a clean atopic derm patient. But are you ever going to find that?

Dr. Neal Bhatia:
Right. Well, that's the problem.

Dr. Naiem Issa:
Yeah, it'll never happen.

Dr. Neal Bhatia:
There are also those who want to still treat outside in.

Dr. Naiem Issa:
Exactly.

Dr. Neal Bhatia:
They still want something to do with their hands, right?

Dr. Naiem Issa:
Right.

Dr. Neal Bhatia:
And again, the data points are going to come out, but is there a way to take that and say this is the realistic way of treating those patients that you just discussed?

Dr. Naiem Issa:
Right, absolutely. One of the numbers that comes off the top of my head is for tralokinumab, for example, for that 52 week maintenance period where at every two weeks and then they have the withdrawal arm to placebo. By week 52, patients maintained clear or almost clear or EASI 75 approximately 33% of the time, give or take, or almost a third of the time. So I use a data point like that to say to my patients or the parents of my patients that say, look, if we got you to clearance and you chose to either reduce the dose to every month or to get off of it, you have a one in three chance of potentially staying clear for the rest of the year. And that's a data point that resonates with everybody.

Dr. Neal Bhatia:
Absolutely. It also reminds them of the marathon. That it's not going to get better overnight, it's also going to take time. But now that we have this conversation piece, you could say, are we better off stopping the drug, giving them a holiday? Or is there ease of having that conversation? Because take average Joe dermatologist, just to get them to write biologics is enough, you give them an endpoint where they can say, sure, you can stop at this point, give them a holiday. Would that make that writing a little bit more reassuring?

Dr. Naiem Issa:
Yes, absolutely. And I always tell and advise folks to put themselves in the shoes of the patient. What would you want to hear yourself? And so for me, I would love to know that there's a potential that I can get off of drug and maintain some sort of efficacy because I'm going to travel or I just don't want to keep medication in my system or whatever. That makes the conversation even more palpable and tolerable for the patients. So it's not like pulling teeth to try to convince someone that they need medication. Here we're trying to say this, well, you need medication right now. Let's go ahead and get your disease under control. Then you have the choice. You're empowering your patients.

Dr. Neal Bhatia:
And then I think these are all targets. They're not blanketing immunosuppressants, they're not doing anything that way. But you brought up some of the TH2 side, 4, 13, some of those targets. Is there another MOA that we should be looking at?

Dr. Naiem Issa:
Yes, absolutely. So also within the same manuscript that I have, I also look at the OX40s. Granted, this was at the time where the phase 2data, it had just come out for both of the OX40s, such as rocatinlimab. And so those studies were very different also than the canonical AD studies that were done because there's a whole different dosing strategy, there's a longer maintenance period, and then all the different dose ranges were then put onto a placebo withdrawal arm.

Dr. Neal Bhatia:
Absolutely. No, you see that in both the design of roca, of amletilumab, and I think there was another OX40s still in early phase-

Dr. Naiem Issa:
yeah.

Dr. Neal Bhatia:
And all of them have that different design, which is good for us because then we see where that gap could be that fill the regimens that we need.

Dr. Naiem Issa:
Right.

Dr. Neal Bhatia:
Yeah, absolutely.

Dr. Naiem Issa:
So the whole point is to show that there's heterogeneity in all of these, so it's hard to make blanket statements, hard to make indirect comparisons. But just to raise awareness that this is the playing field that we are in, so we have to be smart in how we are interpreting data and to not misinterpret the data.

Dr. Neal Bhatia:
Absolutely.

Dr. Naiem Issa:
That's the call to action here.

Dr. Neal Bhatia:
Well, that's the joy of talking to you, Naiem, because you're the one who writes the books, you're the one who does the work, and it's always a joy.

Dr. Naiem Issa:
It's a pleasure.

Dr. Neal Bhatia:
Absolutely. Thank you for doing this. This is another edition of Atopic Dermatitis Journal Club, and we'll see you next time.

Dr. Naiem Issa:
Thank you.