

## **Update on Therapeutics**

Caitriona Ryan, MD, interviewed by Saami Khalifan, MD

**SAAMI KHALIFAN, MD:** This is Saami Khalifan from Harvard Combined Dermatology program, interviewing today Dr. Caitriona Ryan, from St. Vincent Hospital in Dublin, Ireland. She is an expert in psoriasis, eczema, and hidradenitis suppurativa, with a special interest also in genital psoriasis, here to talk to us today about treatment and updates for psoriasis and its management in a variety of settings. Thank you so much for being with us today, Dr. Ryan. So, Dr. Ryan, I know you recently published an interesting paper on the Delphi approach, sort of thinking about the treatment algorithms around psoriasis. So we wanted to hear how that came about and tell us a little more about that.

**CAITRIONA RYAN, MD:** Well, that was a project headed up by April Armstrong with the medical board members of the National Psoriasis Foundation. And really looking at treatment targets in psoriasis. There was treatment targets published in other – in Europe and in Canada, with no real guidance or treatment recommendations in psoriasis for the goals they were trying to achieve for their patients. So this was a big undertaking for the group, especially the key authors. And they really looked at what as – there was a group of psoriasis experts. And what we considered to be the best way for clinicians in the community to measure psoriasis and that could be streamlined. And I think the consensus there was that the percentage BSA was the one that was easiest to do in the clinic, in busy dermatology clinics like we have today, to look at baseline of psoriasis severity and then where patients were at when we're looking at their treatment targets. Looking at targets, we looked at what was acceptable and then also what was our goal. So we were treating patients with a new treatment. What were we hoping to achieve and what did we think the lowest cutoff was at 12 weeks? And that was considered by everyone the best

time to initially decide how treatment was working, three months of treatment. And then what were we aiming for. And the consensus throughout the entire panel was 3% BSA was the acceptable target but really what we were looking to achieve at 12 weeks was patients having 1% or less body surface area involvement. Looking at when we – further on in treatment, again 1% body surface area involvement was considered to be the goal of maintenance treatment with our psoriasis patients. I think now we've got such a large repertoire of fantastic treatments for psoriasis, this is what psoriasis patients deserve to achieving with their treatment. So that now we're helping to give a guidance for when to change treatment. So if your patient hasn't achieved at least a reduction in psoriasis to 3% of their body surface area or less, and hopefully 1%, it's time to change treatments. A lot of patients are on biologic treatments but aren't happy with the level that they have. And now we've got something to help us along with when to change.

**SAAMI KHALIFAN, MD:** So you bring up an interesting issue that I myself oftentimes struggle with. Is that there's so many different options out there now. And so thinking about all the new biologics that are available and the ones that are coming through the pipeline even, how do you decide what's your first, second, third line agent? How do you stratify various agents in terms of what would be best for the patient that you have in front of you today?

**CAITRIONA RYAN, MD:** Okay, I think that's a tough question because I don't think the same treatment is always – I don't have a definite algorithm. I always try to individualize a patient's treatment plan. Put patients who have joint disease, patients who are larger, of higher BMI, patients who have history of inflammatory bowel disease, my algorithm will be slightly different for all of them. But I think, you know, looking as, you know, in general, typically where I start with patients who have moderate to severe disease, that haven't

been on an agent before, and if they have stable disease, I tend to go to the agents where we have the most safety data to date and that would be the TNF-alpha agents, and that's where I would start. And this can differ a little bit, if a very – if a larger patient sometimes ustekinumab can be a good choice to make. If they have the greater than 100 – if they're greater than 100 kg, because we can use the higher dose in those patients in the U.S. Or if patients are needle-phobic, ustekinumab can be a good choice because it's only every three months. Or if there is compliance issues. I think then when it comes to patients who have very severe disease or need a fast onset of action, infliximab can be one that works very well. And now also the new IL-17 drugs. When it comes to patients who have joint disease, I think that's a really, really important category of patients. I often say to my patients their skin won't scar, their joints won't, so if there's any evidence of joint disease, I think the sooner we get our patients on the appropriate biologics, and when I say appropriate, the ones that have been shown to inhibit structural damage, that they – we have to choose those agents and choose them quickly. And the longer a patient is left off the appropriate treatments, the more the scarring is going to occur. So for me, that would be a TNF-alpha agent or the newer IL-17 drugs. If a patient has a history of inflammatory bowel disease, then we're going to go with the anti-TNF-alpha agents with ustekinumab and that's now been approved for use in inflammatory bowel disease. Or now the newer agents, the IL-23, so the anti-P13 drugs will be a great new option and they haven't come to market yet, so they're not yet FDA approved. But I think that that will be a category of patients that these drugs will be really useful in.

**SAAMI KHALIFAN, MD:** So, you know, I recognize there's a lot of nuance in the treatment of these. And, you know, I know you also have some specialty area in treating, for example, like genital psoriasis. So is your approach different when you're treating

someone say with inverse psoriasis or genital psoriasis than when you're treating someone with regular plaque psoriasis?

**CAITRIONA RYAN, MD:** Well, unfortunately we just don't have the evidence available yet and it's an area I'm very interested in. I did a big study between Ireland and the U.S., looking at the prevalence of genital psoriasis and also its impact on quality of life and sexual health. And both centers, in Ireland and in the U.S., showed the same prevalence of genital involvement and that was across all severities of psoriasis, with 38% having current genital psoriasis on clinical examination. We examined every single patient in the study, that was over 300 patients. Its presence had a profound impact on quality of life, independent of disease severity. And even more profound impact on their sexual health and sexual functioning. One of the reasons we did the study was to first of all create awareness. Often, patients, you know, when you discover a patient has genital disease, they don't know it was genital psoriasis kind of – because it can often look different there. They say that nobody's ever asked them before and it turns out they've been using their super-potent steroids in the area, as well. And often, the patients unfortunately are ashamed to bring it up or embarrassed. So when the doctor actually asks, they don't volunteer the information. So disease awareness is important for us. But also to highlight how no studies have been done so far in the treatment of genital psoriasis with non-topical agents. So unfortunately, despite all the great randomized clinical trials we have on the biologic agents, until very recently, none looked specifically genital involvement and the improvement of genital involvement over time. So we have no good research in the effect of traditional systemic treatments or of biologic treatments in that area. And it does appear to be different – have different characteristics to whether (INAUDIBLE) psoriasis. But one

of the drug companies right now is looking at the effective in IL-17 agent in genital psoriasis, so I'm really looking forward to seeing those results.

**SAAMI KHALIFAN, MD:** You bring up an interesting topic on awareness. And so it sounds like from your experience, even physicians are not particularly aware of the problem. So how does one quantify, for example, or how does one go about even broaching that topic? How do you do it when you have your patients, specifically about like genital psoriasis and things like that?

**CAITRIONA RYAN, MD:** Well, in the study we actually examined everyone. But typically in my clinical practice, I ask every single patient did they have any involvement in the genital area. I also ask them about the perianal area, as well. And patients will typically tell you at that point. And then if they do have it present, I go ahead and examine, first of all to confirm that it's genital psoriasis and they don't have any other superimposed type of condition, and then also to prescribe the appropriate treatments, whatever it is for them. And then to counsel them on taking care of the area, how important the Koebner phenomena is there, use of lubricants during intercourse, to stop the Koebner effect from making things worse. That was something we certainly saw in questioning patients in the study.

**SAAMI KHALIFAN, MD:** And so going back a little bit to something you touched on earlier, with the horizon for new therapeutics, for example, which – you mentioned about the P19s. Is there one that you're particularly excited about? I think now the PASI scores are, you know, getting into like PASI 100s even that are pretty, you know, pretty remarkable. What are your thoughts on the ones that are coming out? You know, how

does one go about monitoring or screening patients for these agents that are coming out? What are your thoughts on that?

**CAITRIONA RYAN, MD:** Yeah, I do agree. I think PASI 90 is the new PASI 75. Or indeed PASI 100, which is really what we should be aiming for in our patients. Our patients deserve to be clear. The IL-17 inhibitors were the newest to market. The PASI 90 and PASI 100 scores, the patients were achieving in those studies was through the roof. Now, the IL-23 inhibitors, we have guselkumab and risankizumab. We already have the initial phase III results presented at the ADV this year for guselkumab. And that was guselkumab and when it was compared to adalimumab. The PASI 90 scores, over 70% of patients were achieving a PASI 90 score in those studies. And then I think 37% achieving full clearance or more. And we haven't yet seen the risankizumab (s/l molecule), which is the one that was shared between Boehringer Ingelheim and now AbbVie is taking over its production. And I'm very, very excited to see the results of that study. Certainly when we saw the phase II results, patients with even a single injection were staying clear months and months later. So I'm very excited to see those results, too. What I'm even more excited to see is how they perform in the joints. So it's very important with our biologic agents to see, for the ones that are really achieving amazing skin efficacy, are they doing the same in the joints? So that information will become apparent very shortly. I think they will certainly have a significant role to play, especially in patients who have problems with the bowels. It looks like the IL-17 agents aren't a good choice in patients with active inflammatory bowel disease.

**SAAMI KHALIFAN, MD:** Ah.

**CAITRIONA RYAN, MD:** I know.

**SAAMI KHALIFAN, MD:** So they certainly aren't making these drugs easier to say. So but one thing that we didn't talk about was monitoring. Which of these drugs require ongoing like monitoring of blood levels or, you know, CBCs, things like that? And what are like safety profiles between the various agents? Which ones are you most concerned about when you start a patient? And which are you more comfortable having them come back 6, 12 months later, without ongoing monitoring?

**CAITRIONA RYAN, MD:** Well, I think the nice thing about the biologic agents for us, especially those of us who used a lot of methotrexate and cyclosporin in the past, is the systemic toxicities, particularly when it comes to the renal or liver profile, are very low. So when it comes to monitoring their CMP, their CBC, it's very rare that we see any abnormalities at all. And they're usually caused by something else. So typically with all of the newer biologics, I do labs every six months thing in particular I'm looking out for in them. The important labs I think at baseline though, particularly when using a TNF-alpha agent, is making sure that they don't have latent TB. And that seems to be more important for the TNF inhibitors. I do it for all my patients on biologic treatments. And then to screen for hepatitis B or C and then HIV at baseline.

**SAAMI KHALIFAN, MD:** And so if they – and let's say they have a history of hepatitis, do you not start any biologics? Do you go on to treat their hepatitis? Or is that for you like an absolute contraindication?

**CAITRIONA RYAN, MD:** No. So and for hepatitis C, it's actually been shown that combining the treatment with TNF-alpha inhibitors can improve the viral load. Hepatitis B treatment with biologics is contraindicated, so I would refer those patients on for treatment of their disease first and then go ahead and treat them. And once they have been treated,

I would always check if it was successfully treated. I would continue to check their hepatitis B viral load at six monthly intervals.

**SAAMI KHALIFAN, MD:** Okay, alright. And so, you know, we talked a little about treat to target. So it sounds like the treat to target that you mentioned at the beginning of this interview was body surface area ideally less than 1%. And so over what period of time are you seeing patients on biologics, for example, achieving that? And contrast that with let's say more of the traditional agents that we use for psoriasis, how long, if ever, are you seeing that amount of improvement?

**CAITRIONA RYAN, MD:** With the biologic agents, 12 weeks is our cutoff for deciding if the treatment is improving the patient or not. Although with a lot of the biologic agents, we see them improve and improve over the first six months. With the newer agents, particularly with the IL-17s, see dramatic improvements even in the first two weeks. And so quicker than the TNF-alpha inhibitors and ustekinumab. In looking at the IL-23 profile, it seems to be a little bit slower than the IL-17s, although it may go on to achieve a slightly higher PASI 90 or PASI 100 week 12 or week 16. With the traditional agents, cyclosporin is one of my rescue drugs. So it works very quickly. You can see an improvement in patients within the first week to two weeks. I usually only use it as a bridging agent or when to rescue patients because of the systemic toxicities over time. Methotrexate I give longer, to achieve a maximal effect. So really with methotrexate, I think you have to give it at least four months, to give a trial of at least four months before you decide that it's not working. We see patients achieve a PASI 75 response about 40% of the time.

**SAAMI KHALIFAN, MD:** You know, this is something that you may not know the answer to. I had a discussion recently about the use of tacrolimus or tacrolimus, FK506, as



opposed to cyclosporin, you know, both are calcineurin inhibitors, but in dermatology we almost never use it. Do you have any experience using it or if so, you know, what has that experience been?

**CAITRIONA RYAN, MD:** Tacrolimus, obviously it's a calcineurin inhibitor, but it hasn't had the same effect in psoriasis. It would be great if it did have, because it isn't as nephrotoxic as cyclosporin. But often in transplant patients who have psoriasis, we'll ask the transplant physician to opt for cyclosporin over tacrolimus in that scenario because it isn't as efficacious in psoriasis.

**SAAMI KHALIFAN, MD:** We talked about a lot of things here today. Treat to target, ideally less than 1% but at least 3% within the first 12 weeks with the new biologics. A lot of stuff coming out in the pipeline. A lot of new exciting agents. Monitoring seems to be less of an issue than with the traditional agents. There are nuances when it comes to, you know, whether the patient is overweight, whether they have arthritic – or bone involvement. And obviously screening them for genital involvement and things like that. I want to thank you for taking the time to talk with us today. Definitely taught a lot. Is there anything you want to say in closing?

**CAITRIONA RYAN, MD:** Well, I think the important thing for us to remember as dermatologists, because we're all very busy, we're seeing, you know, a new patient every couple of minutes, to really ask your patient about how psoriasis is impacting on their life. It's so important to ask that question because it can bring so much with us. And then always remember to ask your patient every time they come back if they're having joint pain or back pain, because it's often something that happens down the road and we forget about it after the initial screening sometimes.

**SAAMI KHALIFAN, MD:** Alright, well, Dr. Ryan, thank you very much.

**CAITRIONA RYAN, MD:** Thank you.

## Update on Therapeutics

Commentary by Priyanka Vedak, MD and A. Shadi Kourosh, MD, MPH

In a consensus paper with 24 other psoriasis experts Dr. Ryan examined the existing literature and put together treatment targets for managing psoriasis. When initiating a new therapy, an “acceptable” treatment response was defined as reaching a body surface area (BSA) less than 3% 12 weeks post treatment, with the “target” treatment response being a BSA of 1% or less at that time. During the maintenance period, evaluation was recommended every 6 months with BSA less than 1% as the target response. The authors of this paper hope that the establishment of these targets will help guide providers and patients, and specifically caution against the use of these targets as a method of restricting access to therapeutic options by insurance companies (1). She recommends baseline labs testing for hepatitis B and C status and for latent TB, followed by basic labs every 6 months.

In her interview, Dr. Ryan helpfully guides listeners through the different treatment options available for psoriasis today, noting that different clinical scenarios may prompt a provider to choose one therapeutic option over the other. With regards to psoriatic arthritis, she highlights the importance of choosing a therapeutic option that helps inhibit structural damage. Up to 40% of patients with psoriasis will go on to develop psoriatic arthritis, with skin disease generally preceding the diagnosis of psoriatic arthritis by 7 to 12 years. Psoriatic arthritis can be distinguished from other inflammatory arthropathies by the presence of cutaneous disease, nail changes, and full-digit swelling (dactylitis) (2). Treatment options that can be helpful for both cutaneous and joint disease include TNF alpha inhibitors and IL 17A inhibitors. In fact, the IL 17 A inhibitor secukinumab has shown efficacy even among those individuals who previously underwent TNF alpha inhibition (3). IL 17 inhibitors can also exhibit relatively quick effect, as can cyclosporine, methotrexate and infliximab. For patients with a history of inflammatory bowel disease or who weigh over 100kg, the IL12/23 inhibitor ustekinumab can be a good choice. Ustekinumab comes in two dosing formulations, 45mg or 90mg and both serum concentrations of ustekinumab and clinical improvement have both been shown to be affected by the weight of the patient (4).

Unfortunately, an important area of psoriatic involvement that has been frequently overlooked is that of genital psoriasis. A study performed by Dr. Ryan examining the effects of genital psoriasis on quality of life and sexual functioning found that 38% of patients had current genital psoriasis and that 43% reported a decreased frequency of intercourse. She emphasizes the importance of raising awareness regarding the potential for psoriasis to affect the genital area by screening patients for involvement during your office visits, noting that genital psoriasis has been associated with characteristics including younger age of psoriasis onset, more severe disease, and male sex. Consequently, this is an important area for future study with regards to the efficacy of biologics.

In summary, there are a number of new and promising treatments for psoriasis that are allowing for truly impressive disease control. Providers and patients should actively monitor disease control and discuss potential alternative treatment options at the 3-month mark after initiating a new therapy.