Hyperpigmentation in 2025:
Current and Evolving Approaches to Treatment

Andrew F. Alexis, MD, MPH, FAAD, interviewed by Hassan Galadari, MD, FAAD

HASSAN GALADARI, MD, FAAD: Hello, everyone. My name is Dr. Hassan Galadari. I'm an Associate Professor of Dermatology at the UAE University. Welcome to a new episode of *Dialogues in Dermatology*. With me today is Dr. Andrew Alexis, who is a Professor of Clinical Dermatology at Weill Cornell. Dr. Alexis, how are you feeling today, how are you doing?

ANDREW F. ALEXIS, MD, MPH, FAAD: Doing great. It's great to be with you, Hassan.

HASSAN GALADARI, MD, FAAD: Same here. So our topic for today is going to be on hyperpigmentation. So we're going to kind of delve into the pathogenesis of it. And then we really want to kind of understand the new therapeutic aspects of the condition. So let's start off with hyperpigmentation. What is it? Why does it happen? And what can we do about it?

ANDREW F. ALEXIS, MD, MPH, FAAD: Hyperpigmentation, as we all know, is such a broad spectrum of disorders that present with hyperpigmentation. But let's take one very common sort of model disorder of hyperpigmentation, like melasma. We're gaining more and more knowledge about the etiology of melasma being more complex than previously understood. In addition to increased melanin production, there is also increased vascularity in lesional skin of melasma and this might contribute to the pathogenesis and have implications for treatment, which we can talk about.—

--It's also been proposed that melasma may be a phenotype of photoaging, as histologically there are many similarities to manifestations of photoaging and melasma.

HASSAN GALADARI, MD, FAAD: So who gets melasma? People talk about melasma, who gets it? Who is at high risk, let's say for example?

ANDREW F. ALEXIS, MD, MPH, FAAD: While melasma can affect really anyone of any background, we do see a higher prevalence in populations with more darkly pigmented skin, including Fitzpatrick skin types III, IV, and V, and also VI. But I find in my experience probably the greatest prevalence is in my patients with more sort of intermediate pigmentation, as in III or IV even more so than the higher ends of the spectrum.

HASSAN GALADARI, MD, FAAD: Is there like a risk factor that we would kind of know that these people will probably develop melasma at one point in their lives? Are there any?

ANDREW F. ALEXIS, MD, MPH, FAAD: There have been some nice global epidemiologic studies that have tried to identify potential risk factors. There is an association with having a positive family history, the use of oral contraceptives or other hormonal therapies are certainly associated, but certainly need more research to have better predictors of who is more likely to get melasma. But these are the ones that we know: hormonal factors, family history, and of course as an environmental factor, sun exposure.

HASSAN GALADARI, MD, FAAD: So we talked about a little bit of the risk factors here. Before we delve into the therapeutics, how can we avoid developing melasma? So for example, if a person has a family history of it, is there a way in which this person can avoid, for example, developing it? Are there certain steps that this person can take? Or once it happens, then you know we're going to start with a treatment?

ANDREW F. ALEXIS, MD, MPH, FAAD: I think that as a first step for anyone who either has melasma or is at risk for melasma, photoprotection is step one, that's the foundation. We know exposure to the sun, and that's not just UV but including the visible light spectrum, can exacerbate melasma. So having daily photoprotection is really a key first step to prevention and even as a component of treatment.

HASSAN GALADARI, MD, FAAD: So we're talking avoiding the sun mainly through sun protection. Are there any certain things or any certain filters that a person has to look for in terms of basically when applying certain sunscreens?

ANDREW F. ALEXIS, MD, MPH, FAAD: The gold standard when it comes to protecting against hyperpigmentation, including melasma is, with respect to sunscreens that are available, it's the broad spectrum sunscreens that protect against UVA and UVB, but also protect against visible light using tint or iron oxide being the most common ingredient to give that extra visible light protection. That can go a step further, add oral antioxidant therapy such as polypodium leucotomos, which is derived from the tropical fern plant.—

--Has been shown in, well there's mixed data actually. There's one study by Pandya and colleagues that was published a number of years ago in *JAMA Dermatology*, which did not show greater efficacy over placebo, was not statistically significant. But there is another study out of Singapore showing that patients who took polypodium leucotomos orally in combination with hydroquinone 4% did better than patients who took placebo in combination with 4% hydroquinone.

HASSAN GALADARI, MD, FAAD: Now this is a nice little segue, because you just mentioned hydroquinone. We want to talk now a little bit about the treatments. In terms of avoiding it, you're applying basically your SPF, your sun protection, and so forth. Now say, for example, you do develop it. Now you need to kind of treat it. You've mentioned one of them which is hydroquinone. Is it still the gold standard in 2025? Does it stand as the gold standard?

ANDREW F. ALEXIS, MD, MPH, FAAD: That's a great question and it's title is being challenged, that's for sure in 2025. But yes, it remains our first line still. Typically 4% concentration is the usual starting point. But for more severe melasma or for it to be more

aggressive, to get a faster response, many of our colleagues are using 6%, 8%, sometimes even higher. My personal preference is still just start at 4%.

HASSAN GALADARI, MD, FAAD: And how often?

ANDREW F. ALEXIS, MD, MPH, FAAD: My preferred agent would be the classified modified Kligman Willis formula, so containing hydroquinone 4%, a corticosteroid like fluocinolone 0.01%, and tretinoin 0.05%. So the classic triple combination formula. But for patients who don't respond to that, I will compound up to 6% or even 8%, but that's my limit. Because I do find that higher concentrations, higher risk of irritant contact dermatitis, I then begin to start worrying about longer term use and exogenous ochronosis as a complication.

HASSAN GALADARI, MD, FAAD: If you start a person on hydroquinone-containing topicals, how long would you keep them on them before saying we're at risk of developing ochronosis, we need to kind of stop it?

ANDREW F. ALEXIS, MD, MPH, FAAD: When I'm using a 4% modified Kligman Willis formula, I'm comfortable treating for up to six consecutive months before rotating off to a non-hydroquinone agent. Where does that six months come from? There are actually some studies that use that specific fixed combination, three ingredient formula that's approved for melasma for six months without evidence of any significant atrophy from the corticosteroid and no exogenous ochronosis in that cohort. So six months is my comfort zone and then I'll transition. If I'm using the higher concentration of hydroquinone, I might shorten the six months.

HASSAN GALADARI, MD, FAAD: So if you do stop it or you give them a break or a holiday, how long is that holiday? When do you go back to using it again?

ANDREW F. ALEXIS, MD, MPH, FAAD: If I'm going to go back to hydroquinone, again given that this is a chronic relapsing disorder, of course that scenario is quite common to have to go

back to hydroquinone at some point, I'm comfortable with a six month hiatus. So it's like a six month on, six month off type of routine. However, in 2025 we now have more, and not only more numerous but also more effective non-hydroquinone alternatives, such that we can more confidently switch over to a non-hydroquinone and maintain.

HASSAN GALADARI, MD, FAAD: And just keep them on it. So this is quite important, because the AAD now has a lot of international members. These international members don't have access to hydroquinone, people from Europe, for example, where hydroquinone is banned. And you've mentioned the non-hydroquinone medications or topicals. Which ones are you alluding to and if you could tell us what their mechanism of action is?

ANDREW F. ALEXIS, MD, MPH, FAAD: I can highlight, and there's more than three, but I'll highlight three of the newer, most exciting developments in the recent past as far as non-hydroquinone therapies. One would be thiamidol, which of course has been available outside the United States for a number of years but in the US, it is now just becoming available. But in any event, thiamidol has actually been studied in a randomized controlled study for melasma, demonstrating efficacy. So an agent cosmeceutical formulation containing thiamidol.—

--The next agent is cysteamine, which when it first emerged as a topical agent was 5% and now we have a formulation that's 7.5% cysteamine with greater efficacy. It's a short contact therapy. Patients apply it to the face for 15 minutes and wash off. The third sort of novel non-hydroquinone agent that I'd like to talk about today is called 2-MNG, also known as Melasyl. And this ingredient is found in a cosmeceutical agent that also has niacinamide and some other ingredients.—

--That has been studied in postinflammatory hyperpigmentation, in melasma. And it's even been compared to 4% hydroquinone. It's been compared to thiamidol and found to be comparable. There's even a study comparing it to cysteamine. So we now have comparative studies.

HASSAN GALADARI, MD, FAAD: What is the mechanism of action? Thiamidol is a tyrosinase inhibitor but the cysteamines here, for example, how does it work?

ANDREW F. ALEXIS, MD, MPH, FAAD: As you pointed out, thiamidol does inhibit tyrosinase. In fact, it was found in one study to be the most potent inhibitor of human tyrosinase in the study. Cysteamine is a little bit more complex in terms of its mechanism of action. Tyrosinase inhibition is certainly one of the mechanisms. But another mechanism maybe too, it likely increases intracellular glutathione and leads to a shift in melanin synthesis from eumelanin to pheomelanin, so that might be another component of its mechanism of action.—

--I will just, before I forget in terms of comparative studies, cysteamine too does have the comparative studies compared to hydroquinone 4%, compared to the modified Kligman formula, showing comparable results to the gold standard of triple combination. So again, we have more confidence in these newer non-hydroquinone agents versus our gold standard.—

--Back to mechanism of action. 2-MNG, or Melasyl, very novel mechanism. It's not a tyrosinase inhibitor but what it does do is it actually binds to precursors of melanin synthesis. So it removes precursors from the pathway, hence reducing the production of eumelanin and pheomelanin combined.

HASSAN GALADARI, MD, FAAD: Melasma has also other components in terms of the vascularity and so forth. Is there anything that's new there? It's not just stopping the pigmentation but it's also stopping the inflammation, the vascular component of it. Are there any ingredients that a person has to look for?

ANDREW F. ALEXIS, MD, MPH, FAAD: With the vascular component, one real transformative or gamechanger in terms of therapeutics is, and I'm sure you have a lot of experience with it, is

tranexamic acid, of course. It's believed that part of its mechanism of action might have to do with reducing the vascular component.

HASSAN GALADARI, MD, FAAD: The long lasting debate has always been whether it's used topically or orally, so which one is more effective and which one would you go for?

ANDREW F. ALEXIS, MD, MPH, FAAD: In my opinion, there's no doubt that the oral therapy is the most efficacious. I've not seen comparable results with topical tranexamic acid. So that's not to say that topical tranexamic acid is not effective, but compared to oral it's to the same. But things that we can do to enhance the efficacy of topical tranexamic acid, not only higher concentrations but also combining with microneedling or laser-assisted drug delivery. These would be some other techniques to enhance the effect.—

--But oral, in the US we have a 650 mg tablet. So I generally have patients cut that in half and then they take 325 b.i.d. orally. The trouble is we know that this is very much off-label. Oral tranexamic acid is not approved for melasma or any dermatologic condition. It's a thrombotic agent that's used for bleeding diathesis and other indications. So we have to carefully select our patients who we put this on, ensuring that they don't have any personal risk factors or strong family history of thromboembolic events.

HASSAN GALADARI, MD, FAAD: Are there any set of questions that you would ask the patients before you put them on, for example, oral tranexamic acid?

ANDREW F. ALEXIS, MD, MPH, FAAD: I will carefully screen for factors like cigarette smoking, being on estrogen therapy, having any personal or family history of deep vein thrombosis or stroke, myocardial infarction, other thrombotic events and I'll take that into consideration. One question that comes up is do we do labs? I don't do labs across the board on every single

patient but if there are some questions about their risk factors that aren't clear, just from taking a normal history, then I will order protein CNS and PT, PTT, etc., to check for any coagulopathy.

HASSAN GALADARI, MD, FAAD: For how long do you put them on the medication? You've got to stop somewhere.

ANDREW F. ALEXIS, MD, MPH, FAAD: Exactly. So I'm most comfortable with three months. In three months, you tend to get the response that we're looking for, pretty significant clearance in three months. Then I like to take a hiatus for at least six months.

HASSAN GALADARI, MD, FAAD: I've had a few patients, I don't know if this has been reported or not, but I've had a few patients who have been on tranexamic acid and developed, for example, hair loss.

ANDREW F. ALEXIS, MD, MPH, FAAD: Interesting, I have not seen that.

HASSAN GALADARI, MD, FAAD: I was wondering if there's any mechanism of action that would cause something like this? But it's been a number of them. If you haven't seen it, then probably it's just anecdotal hopefully.

ANDREW F. ALEXIS, MD, MPH, FAAD: I haven't but now that you've said it, it's certainly something I'm going to look for to see if it's been reported in the literature, too. I was going to add one thing about treating the vascular component. So we started with the potential role of tranexamic acid working by that mechanism, at least in part. But other strategies would be using our lasers.

HASSAN GALADARI, MD, FAAD: I wanted to kind of allude to this. I like interviewing you, Andrew, because you really kind of guide me through the whole interview process. We talked about the topicals, we talked about the oral, and now we want to talk a little bit about the

energy-based devices. Is there any space for the use of energy based devices in the treatment of melasma?

ANDREW F. ALEXIS, MD, MPH, FAAD: Increasingly so. Historically, we have generally shied away. By we, I just mean collectively the world of dermatologists and other practitioners who treat melasma have hesitated to use lasers because of the risk of exacerbating the melasma. But more and more, we have newer devices that have greater efficacy and equally important, greater safety than historic approaches. And so yes, I do think there is a role for lasers in energy-based devices.—

--Which ones? In my hands, I'm most comfortable with the 1927 nanometer nonablative fractional lasers. In particular, I use a nonablative fractional diode laser. It has very low energy and low density, low treatment density, and hence is extremely low risk. So I don't see exacerbation of melasma using this. I do see enhanced efficacy when using it in combination with my topical therapies.

HASSAN GALADARI, MD, FAAD: So you usually combine? So you combine your energy-based devices. Do you add also probably oral tranexamic acid, in addition to topicals, all at the same time?

ANDREW F. ALEXIS, MD, MPH, FAAD: Depending on the patient. The key is though, you've just hit the nail right on the head, it's combination therapy. I am not using lasers alone. I am not using other procedures, like chemical peels, alone. I'm using it in combination with topical therapies. In a typical scenario, I still lead with topicals as a starting point. But after a period of several months, usually approximately three months, we reassess the patient. If the results are falling short of the patient's treatment goals, then we can introduce procedures to enhance efficacy.—

--Procedures within the range of procedures I might consider would be superficial peeling agents or nonablative fractional lasers. I do know, of course, there are other lasers that can be used but for me, my top choice of lasers in my practice for this patient population is that 1927 nonablative fractional.

HASSAN GALADARI, MD, FAAD: One of the risk factors, as you had mentioned, of developing melasma is pregnancy. Now, what topical agents would you use, for example? Or would you even treat a pregnant woman who has melasma and you wanted to kind of prevent the worsening of her condition?

ANDREW F. ALEXIS, MD, MPH, FAAD: Great question and very common, real world scenario. I'm most comfortable with topical azelaic acid in that context.

HASSAN GALADARI, MD, FAAD: You're going old school, azelaic acid.

ANDREW F. ALEXIS, MD, MPH, FAAD: Azelaic acid, still a role for it in melasma. And that's a perfect place for it, too, in the patients who are pregnant or breastfeeding, I think that's a pretty safe choice. If I was compelled to do a procedure, even though I shy away from doing any medically unnecessary procedures during pregnancy, but if there was a scenario where we, through shared decision making, there was a need to add a procedure, that would be glycolic acid peels. I would be comfortable with that, if I had to do a procedure.

HASSAN GALADARI, MD, FAAD: Is there a certain concentration you would want to cap it off at? Or which concentration of glycolic acid would you say is enough?

ANDREW F. ALEXIS, MD, MPH, FAAD: I generally start with 30% and then increase up to 50%, if tolerated. I actually rarely go up to 70% anymore. In my early days, I was a bit more aggressive and yeah, I would go up to 70% quite a bit, but I did experience some complications. So really to have a very sort of reliable safety profile, 30 to 50% is my sweet spot.

HASSAN GALADARI, MD, FAAD: How about the non-hydroquinone ones that you just mentioned? Because a lot of them are actually found, as you said, in active cosmeceuticals. So any person can walk into the pharmacy and just get them. Are they safe during pregnancy?

ANDREW F. ALEXIS, MD, MPH, FAAD: Great question. We don't have an answer to that. Since there's no data to answer that question and no experience, I generally don't recommend those during pregnancy. So I just stick to what we know, because the older label, which of course the FDA has abandoned the ABCD system of pregnancy safety, but in the old traditional classification, azelaic acid used to be pregnancy category B.

HASSAN GALADARI, MD, FAAD: Dr. Alexis, thank you so much. This was really truly wonderful. We kind of really dissected melasma through all the different processes, it's pathogenesis, its treatments. If there are any final words that you would like to tell us, little pointers for the listeners out there?

ANDREW F. ALEXIS, MD, MPH, FAAD: It's really been a pleasure speaking with you about this today. I'd like to say that we can really do so much more with melasma than what we've been able to do historically. There used to be a compromise when not being able to use our traditional gold standard of hydroquinone. But now we have multiple agents that don't have hydroquinone and that can rival the efficacy of hydroquinone and we can use them long term.—

--In terms of procedures, we have gained more and more confidence in using superficial peeling agents, like glycolic acid and some lasers, including the nonablative fractional, but also picosecond lasers and even microsecond pulsed 1064 Nd:YAG has been used as a strategy to get both the pigment and the vascular component. So we have a broader range of treating melasma in a multimodal fashion to get better efficacy and still maintain safety.

HASSAN GALADARI, MD, FAAD: Thank you again. Thank you so much for being with us. Hopefully, we get to see you once again.

ANDREW F. ALEXIS, MD, MPH, FAAD: Thank you so much.

Commentary

Josee Smith, MD with Jules Lipoff, MD, FAAD (ed.)

Disorders of Hyperpigmentation are numerous, with a wide variety of causes, including post inflammatory, melasma, genetic predisposition, and environmental influences such as sun exposure. This interview with Dr. Andrew Alexis reviewed his latest perspectives on the pathogenesis and treatment of hyperpigmentation, including several key points:

1. Melasma remains incompletely understood. We have thought melasma to involve an interplay of hormonal influences, family history, and environmental triggers like sun exposure. New evidence shows this condition is even more complex and that increased vascularity in the pathogenesis of melasma may provide new treatment avenues.

2. **Hydroquinone** remains a first-line therapy for hyperpigmentation for up to 6 months at a time. Following that period transition to a non-hydroquinone therapy is recommended to avoid paradoxical ochronosis.

   One area of interest is more development of non-hydroquinone therapies, with varying levels of evidence supporting their use. Thiamidol has long been available outside the U.S., acts as a potent inhibitor of human tyrosinase. Cysteamine has a less understood method of tyrosinase inhibition and thought to possibly increase intracellular glutathione. It is used as a short-contact therapy—applied for 15 minutes and then washed off.2-MNG (Melasyl) does not inhibit tyrosinase but binds to melanin precursors. It may be found in a cosmeceutical formulation alongside niacinamide and other ingredients.
3. **Tranexamic Acid (TXA) is** a thrombolytic agent, that may address hyperpigmentation due to its vascular-modulating effects. Though off label, it seems most efficacious when used orally, but can also be used in topical formulations. It can be used topically alone or in conjunction with microneedling or laser-assisted delivery. Cautious patient selection and discussion remains important given potential increase risk for thromboembolic events.

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