Vitiligo

Victor Huang, MD, Nada Elbuluk, MD, and Vaneeta Sheth, MD
Interviewed by M. Laurin Council, MD

M. LAURIN COUNCIL, MD: Hello and welcome to *Dialogues in Dermatology*. I am Laurin Council, from Washington University in St. Louis, Missouri. And I have the pleasure today of speaking with three outstanding dermatologists: Dr. Victor Huang, Assistant Professor of Dermatology at the University of California in Davis; Nada Elbuluk, Clinical Assistant Professor of Dermatology at Keck School of Medicine of the University of Southern California; and Vaneeta Sheth, Clinical Dermatologist and founder of the Vitiligo Clinic at Brigham and Women's Hospital. Drs. Huang, Elbuluk, and Sheth, welcome.

ALL: Thank you.

M. LAURIN COUNCIL, MD: So vitiligo is an important disease, mainly because of the psychosocial impairment. Let's start by discussing why this topic is so important for our patients.

VICTOR HUANG, MD: So I think that there's been a lot of advances recently, just quantifying the amount of psychic stress that goes along with the diagnosis of vitiligo in our patients. And it's been associated with not only depression and other psychiatric things, but mood disorders and whatnot. I think it's also important to recognize that up to 20 percent of patients will report physical symptoms, in terms of itching and discomfort with vitiligo, as well.

So I think one of the important messages to get across is vitiligo is not just a cosmetic disorder, it is truly a medical disorder that can be impactful on the quality of life of our patients.

M. LAURIN COUNCIL, MD: That certainly is true. When thinking about how to treat a patient who has vitiligo, it's really important to know what the disease state is, how active is the disease. What are some of the clinical signs that are used to determine activity?

VICTOR HUANG, MD: Yeah. So this is an area that's been a struggle for us, in terms of defining and stratifying our patients in terms of their activity and their prognosis. Recent advances in terms of clinical observations have given us some extra handles to understand this. So there are classic signs, such as Koebner's phenomenon, inflammatory vitiligo which is relatively rare. But in addition, the recognition of trichrome vitiligo as a sign of activity.

And even more recently, the recognition of confetti vitiligo, which is a form of vitiligo that's made up of 1 to 5 mm small macules that are acuminated around an area is often associated with rapid progression of vitiligo.

M. LAURIN COUNCIL, MD: Are there any emerging technologies that can help better assess disease activity?

VICTOR HUANG, MD: So there have been several approaches to trying to get a handle on that, as well. One area that has been developing over the course of the past ten years and is now reaching a critical point, where clinically useful tools are becoming available, is computer-assisted imaging. By using and leveraging the advances in computer vision, we're hoping that we'll be able to not only give an assessment of better, same, or worse, but give a truly granular assessment of here are a 10.5 cm area of involvement.

Three months later, there's a 9.5 cm^2 area of involvement and truly be able to say whether a patient is getting better or not. In addition, there have been improvements done on a biochemical level, as well. Using a technique that was pioneered by John Harris, sampling booster fluid, there are emerging biomarkers that are becoming available and are being validated now that should be able to give us a better handle on activity and prognosis for our patients.

M. LAURIN COUNCIL, MD: Well, that certainly is promising. And I understand there are also some fairly new treatments that have demonstrated success. Can you elaborate a bit on those?

VICTOR HUANG, MD: Yeah. So again, stemming from a lot of the advances that have come from our understanding of the underlying immunology that causes vitiligo, there's been a recognition of the importance of the interferon-gamma pathway in the pathogenesis. And this recognition has led to the use of JAK inhibitors in the treatment of vitiligo, both systemically and topically. And it's shown a lot of promise, both in treatment-naïve patients, as well as patients who have been treatment-refractory in the past.

M. LAURIN COUNCIL, MD: Once you have helped a patient to maintain a stable disease, I think at that point, sometimes they may ask about procedures that may help further relieve their symptoms. What patients are ideal candidates for procedural therapies? And what procedures can play a role in the treatment of vitiligo?

NADA ELBULUK, MD: That's a great question. So the ideal patient for procedural therapies is really someone with segmental vitiligo. That's where we're seeing the highest re-pigmentation rates. With that said, individuals with focal vitiligo or those with refractory vitiligo that have not responded to other more traditional treatments can all be considered for procedural therapies.

Now, there are numerous procedural therapies. I'll highlight sort of the more common one now which is being done currently in several places in the U.S., as well as internationally, which is cellular grafting. More specifically, there's a procedure called melanocyte-keratinocyte transplantation. And this is a procedure where you can take a donor site, and a very small one, and there's a 1 to 10 ratio of sort of donor to recipient site, and treat a larger area of vitiligo.

And this is exciting because for some people, particularly those with segmental, you can have re-pigmentation rates of over 90 percent, even 100 percent in some patients. So it's almost the

closest thing to a cure that we can see at this time. Those rates are a little bit lower for those who have generalized vitiligo vulgaris. And obviously, you can only do a certain amount of area at one time. The other thing is that it's a time-consuming procedure, so it takes several hours. And it's currently not covered by insurance.

So it's not for everybody. I also want to add, anyone who undergoes the procedure should have stable vitiligo, which means no new or worsening lesions in six months minimum.

M. LAURIN COUNCIL, MD: And as a general dermatologist, how can you help your patients find the right person to perform these treatments? Certainly, they're not available everywhere. How can a patient with vitiligo identify a good provider?

NADA ELBULUK, MD: Right, so that's a great question. And we have an organization that was actually founded out of Henry Ford, called the Global Vitiligo Foundation. And on that website, one can find providers within the U.S. who specialize in vitiligo and can find out more about finding someone closer to their area that specializes in vitiligo and those that perform the procedure.

M. LAURIN COUNCIL, MD: Thank you, that's very helpful. You mentioned cellular grafts. What are some of the other procedures that historically have been used?

NADA ELBULUK, MD: Great question. So traditionally, tissue grafts had been used in prior years. And so that includes punch grafting, suction blister grafting, and split thickness grafting. So with punch grafting, you know, it's a little bit more tedious, in that you're literally taking small 1 to 2 mm punch biopsies from an area of normal skin and transplanting them into an area of vitiliginous skin. There's also an issue with some cobblestoning sometimes, so cosmetically the appearance is not as good as the MKTP procedure that I just mentioned.—

Suction blister grafting also has had some nice results. It's also quite time consuming. You're literally creating blisters on an individual and then separating the epidermis from dermis and transplanting those. And then split thickness grafting is also not typically as cosmetically beneficial as the MKTP procedure. So we're not seeing that being done as much, now that MKTP has been so refined, but definitely those are traditional procedural treatments.

M. LAURIN COUNCIL, MD: And some other things that have been described in the medical literature include microneedling, platelet-rich plasma, tattooing of the affected skin, and even lasers. Are some of those treatments more accessible for patients?

NADA ELBULUK, MD: Well, I think for those areas, we're starting to slowly see more studies being done. I mean, we really can't call them part of our traditional treatment armamentarium right now. But there is promise for some of them. With microneedling, there have been some mixed studies, some showing benefit, some not showing benefit. Certainly, it depends on what topical is being combined with the microneedling. So they have tried various things, like 5-fluorouracil, topical steroids, topical immunomodulators like tacrolimus.

And some of them have shown benefit but others have not. So we need more formal studies for that. Same with PRP, there's only a handful of studies that have been done. So I think we're going to be seeing more of that over time, because a lot of these procedures are more accessible in local dermatology offices. And so hopefully if we see benefit, it will be something that more providers can also start providing to their patients.

M. LAURIN COUNCIL, MD: And are these techniques ever covered by insurance?

NADA ELBULUK, MD: So far, the procedural treatments for vitiligo have not been covered by insurance. We do hope that over time, as we can really prove that vitiligo is not a cosmetic disease and really push the idea of it being an autoimmune disease, that we'll get more

coverage for all procedural therapies, including even phototherapy, which we still struggle to sometimes get covered.

M. LAURIN COUNCIL, MD: Are there any downside to pursuing aggressive therapy?

NADA ELBULUK, MD: So with procedural therapies, there's always risk that you can get with a lot of procedures, such as skin infection, some pain with anesthesia, scarring, and you can get Koebnerization, as well. And so it's really important obviously to go over all of the stuff preoperatively with the patient, because it is possible.

M. LAURIN COUNCIL, MD: Sometimes when we face a disease that's as challenging as vitiligo, patients are willing to try just about anything to improve their condition. And many times, they have tried several things before they even present to a dermatologist. Let's talk about some of the alternative therapies that have been tried, starting with nutritional supplements.

VANEETA SHETH, MD: Sure. So there's a range of nutritional supplements that come up, especially when patients start doing their own online research. One of the most common would be things like vitamin B12, because of the purported link between vitiligo and another autoimmune condition like pernicious anemia. But the data really suggests that just having vitiligo alone doesn't put you at risk naturally for having lower B12 levels, so there's no strong data, currently at least, to suggest that patients should be monitored or supplemented.

With vitamin D, there's a little more of a larger body of research, showing that these patients may have lower vitamin D levels, and we don't know how much of that is because they're more strongly photo-protecting their skin versus being related to something innate to their vitiligo. But recent studies, especially looking at patients who have gone through narrow band phototherapy, do suggest that vitamin D may play a bigger role than we thought, because studies have found

recently that in patients that have re-pigmenting lesions, those areas tend to have greater vitamin D receptor expression.

And that patients undergoing treatment with narrow band do have higher vitamin D levels and tend to respond better. So there may be more of a link that needs to be teased out.

M. LAURIN COUNCIL, MD: Is there any evidence that antioxidants can be beneficial?

VANEETA SHETH, MD: So at this point, I would say the data is limited but encouraging. Most of the studies that have been done usually use a cocktail of antioxidants, usually vitamin C and E, as well as alpha lipoic acid. And it's given often more as an adjunct to narrow band phototherapy. But there have been some small but decent studies that suggest that if you take the antioxidants, either pretreatment and then during phototherapy, that those patients do have better rates of re-pigmentation. And in general, the downside or risk is fairly low, pretty well tolerated.

M. LAURIN COUNCIL, MD: And there are some other treatments that patients may ask about, treatment with melagenia or pseudocatalase. Can you elaborate a bit on those?

VANEETA SHETH, MD: Sure. So these are things that have been purported from other countries. Melagenia is based on a human placental extract that's obtained from a group in Cuba. And it's a solution that you are supposed to apply to the vitiligo and use in combination with a phototherapy regimen. But when outside groups have tried to replicate the results that have been reported, there really haven't been found to be any significant benefits to using it.—

And same thing with pseudocatalase. The theory behind it is supposed to be that it's supposed to prevent oxidative damage from melanocytes. But when it's been studied by independent groups, it really has not been shown to work any better than placebo.

M. LAURIN COUNCIL, MD: Have any dietary modifications been proven efficacious?

VANEETA SHETH, MD: So this is a question that comes up a lot with my patients. I know especially with gluten, it's a hot topic right now. And patients will often ask if going gluten-free would help their vitiligo. And at this point, there's really only a handful of case reports suggesting that if you don't have a diagnosis of celiac there's any benefit to going gluten-free. So by and large, I would say that there is really no strong evidence that going gluten-free has any beneficial effect on vitiligo.

There is, however, related to green tea, an ingredient that's been found, in vitro at least, to have some very promising results with their influence on melanocytes in vitiligo. Specifically, a compound called epigallocatechin 3 gallate, or EGCG for short. And it's been found in vitro to work on a number of different ways, including decreasing JAK-2 expression, decreasing a cytokine called CXCL-10, which we know is important for the pathogenesis of vitiligo, and also having some beneficial effects in terms of decreasing reactive oxygen species. So no in vivo studies yet, but I think it could be a promising treatment.

M. LAURIN COUNCIL, MD: It does seem though that the overarching theme is that many of these supplements, at best, have very limited data to support their use, while others clearly show no difference. What do we know about the potential adverse effects of these alternative therapies?

VANEETA SHETH, MD: So depending on the therapy, by and large there's not a lot of downside. But there are certain ingredients you do want to be careful about. So vitamin E and gingko in particular do have mild anticoagulant effects. So in patients who are also on other blood thinners or with certain comorbidities, you do want to be a little bit cautious. For some of the treatments that are out there that are used in combination with phototherapy, one in particular called khellin that's used for UVA treatment, that you do have to be a little bit careful

about because it has been reported to cause transaminitis, so it does require a little bit of lab monitoring, as well.

M. LAURIN COUNCIL, MD: Thank you. Dr. Huang, Elbuluk, and Sheth, you certainly have given our listeners a lot to think about when approaching the patient with vitiligo, what treatments are available, and whom these may be most appropriate. What therapies are important to discourage, at least until further evidence emerges. Are there any final thoughts with which you'd like to leave our listeners?

NADA ELBULUK, MD: Yes, I would say that for providers who feel that, you know, they've sort of hit a wall or their patients aren't improving or getting any better, I think there are a lot of new and emerging therapies. And it's an exciting time for vitiligo. So, you know, I think one should definitely, you know, reach out to a colleague in their area who may specialize more, and not be afraid to refer patients, you know, to someone who may have more experience that could offer some of these newer therapies. And we just want to continue to give hope to our patients and the dermatologists who are treating them that really are a lot of, you know, exciting new areas of research for vitiligo and hopefully more treatments on the horizon.

VICTOR HUANG, MD: Absolutely. I think another area that I would encourage providers to be aware of are the advocacy and support groups that are out there. Within the vitiligo community, we've been very, very self-conscious about wanting to make sure that the outcome measures that we develop and the studies that we design are directly reflective of the needs and desires of our patients. And these patient groups are incredible in terms of their passion and their support that they give to one another. As well as the advocacy that they bring to our peers and legislators, to continue support for research and treatment of vitiligo.

M. LAURIN COUNCIL, MD: Thank you.

Commentary

Authors: Lisa Guo and M. Laurin Council, MD

Vitiligo is a chronic disease characterized by depigmentation of the skin and hair follicles due to the destruction of melanocytes. Far more than just a cosmetic condition, vitiligo has a profound impact on the quality of life of patients and is associated with substantial psychosocial impairment1. Fortunately, various therapeutic options do exist with more in development, however there is still much uncertainty surrounding the disease. In this podcast of Dialogues in Dermatology, Drs. Victor Huang, Nada Elbuluk and Vaneeta Sheth and I discuss the management of vitiligo, new and exciting treatments for the disease as well as alternative therapies that patients may inquire about.

The treatment strategy for vitiligo depends on the type of vitiligo, extent of body surface involved, response to previous therapies, and disease activity1,2. It can be difficult to assess stability of disease, but Dr. Huang notes various clinical signs associated with activity and/or rapid progression, including Koebnerization, inflammatory vitiligo, and trichrome and confetti patterns, in which small macules dot the borders of a larger lesion3. Initial management for patients with limited body surface area involvement is to stabilize depigmentation through local application of topicals such as corticosteroids or calcineurin inhibitors. For more widespread disease, the mainstay of therapy is phototherapy with narrow band UVB light, which can be combined with topicals as well2. Several new and promising medical treatments are also currently under study. Dr. Huang discusses the exciting potential of JAK inhibitors (both topical and systemic) in the treatment of vitiligo. This class of drugs downregulates the interferon-gamma pathway, which is thought to be involved in the inflammatory pathophysiology of this complex disease. In particular, both tofacitinib and ruxolitinib have demonstrated clinical improvement for a small number of patients4,5. Once a patient's disease has stabilized, defined as no new or worsening lesions for at least 12 months, surgical options can be considered for repigmentation. Broadly, these procedures involve the transfer of melanocytes from normal, pigmented skin to affected areas. Traditional procedures involve tissue grafts, including punch grafting, suction blister grafting and split thickness grafting. Dr. Elbuluk also describes the newer and increasingly more common procedure of cellular grafting, or melanocyte-keratinocyte transplantation. This technique can achieve better cosmetic results than traditional methods, in particular punch and split thickness grafting, and a very small donor site can treat a much larger area of vitiligo. This treatment is particularly effective in patients with segmental vitiligo, achieving repigmentation rates of over 90%, however it may also be helpful for patients with nonsegmental vitiligo recalcitrant to other medical therapies6. Other treatments mentioned include microneedling, platelet-rich plasma tattooing and lasers, however Dr. Elbuluk states that the results from the few studies that do exist on these procedures are mixed, therefore further research is required before these techniques are used more widely.

Given the frustrating and at times difficult to treat nature of vitiligo, patients may seek out treatments that have not necessarily demonstrated convincing clinical benefit in research studies. Dr. Sheth discusses the evidence surrounding several of these alternative therapies, including vitamin supplementation. The purported therapeutic effect of some vitamins such as B12 is not supported by data. On the other hand, preliminary research suggests that vitamin D may be involved in the disease process of vitiligo, but its role as a potential therapeutic agent is still unclear. Dr. Sheth also points out that other supplements such as antioxidants may be promising, particularly when used together with phototherapy, as oxidative stress may contribute to the immune-mediated attack on melanocytes1. In a double-blind placebo-controlled trial using alpha-lipoic acid and vitamins C and E, combining phototherapy with this antioxidant cocktail improved rates of repigmentation7. Again, the data is still too limited to definitively support their prescription, but initial studies are encouraging. There are also treatments such as melangenia (based on a human placental extract) and pseudocatalase with claims of benefit from other countries, but Dr. Sheth cautions that positive results have not been able to be replicated by other groups. Finally, regarding dietary modifications, Dr. Sheth reports that there is no strong evidence to suggest that trendy diets such as the gluten-free diet are helpful. Overall, the predominant theme surrounding these alternative therapies is that the evidence, if any, to support their use is currently limited.

Vitiligo is a lifelong disease that can be very difficult to manage. The landscape of vitiligo is challenged by the prevalence of potential misinformation and alternative therapies with inadequate evidence to support their use. It is important for clinicians to be familiar with these various therapies in order to better advise patients on appropriate options for treatment. Fortunately, patients and clinicians alike can be encouraged by the multitude of new and emerging therapies that have shown success, with many more in the pipeline.

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