A 60-Year-Old Man With Facial Vitiligo

What's the Take Home?

Ronald N. Rubin, MD
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Introduction. A 60-year-old man presents to his internist requesting a discussion on treatment options for his facial vitiligo.

Patient history. The patient recently saw TV advertisements heralding a cream that is now FDA approved for vitiligo, and he was curious about the cream's efficacy for his facial vitiligo, which has never been treated previously.

The patient first presented with vitiligo when he was about 15 years of age. At that time, he had experienced mouth trauma requiring several dental extractions and surgical repairs in the months prior. He always questioned whether the repairs or the trauma triggered the vitiligo, which involved an area near and above his left upper lip and paranasal region (measureing at roughly 6 x 4 cm arear). He recalls the lesion had an abrupt onset to its approximate current size with quick stabilization and no progression then or since.

The patient noted that there is no personal or family history of other autoimmune disorders. When asked, he noted that neither he nor his family (he is married with grown children) or friends essentially "notice" the vitiligo anymore, and he does not believe it ever impacted his quality of life.

Physical examination. The patient's physical examination is entirely within normal limits. The only notable finding during his physical examination was the unpigmented area on his skin, which otherwise has a dark, Mediterranean complexion consistent with his family's background.

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Correct Answer: D. Treatment with topical ruxolitinib will offer visible and quantifiable improvement in facial and non-facial areas.

Discussion. The presented patient is known to have vitiligo, specifically the so-called segmental variant. As a general condition, vitiligo is a depigmenting disorder, with an estimated worldwide prevalence of 0.5%.[1,2] Other demographics include absence of ethnic or racial variation, equality of prevalence by sex, and a more than 50% age of onset before 21 years of age.[1] There is, however, a very marked separation of vitiligo variants with the rather interesting nomenclature of "segmental" (10% of cases) and "non-segmental" forms. Segmental vitiligo has lesions, which are localized and involves smaller total skin areas, whereas the non-segmental form involves large and diffuse areas of all forms of skin.[1,2] Experienced dermatologists' examinations will reveal well-defined discretely bordered, homogeneous macules in the non-segmental (generalized) form, with much less pigment homogeneity and discrete border edging in the segmental (focal) form of disease.[1]

Segmental forms of vitiligo have characteristics that include: (1) frequent childhood onset; (2) early involvement of hair compartments of the skin; (3) frequent facial involvement; and (4) lack of combining with other autoimmune diseases.

Conversely, non-segmental (generalized) vitiligo manifests: (1) usual adult onset; (2) progressive rather than fixed, stable skin involvement; and (3) frequent association with personal or familial history of other autoimmune diseases.[1,2]

Confirming the diagnosis begins with presentation of skin depigmentation, which should fit into either the segmental or non-segmental clinical profiles. The patient fits the characteristics associated with the segmental form of vitiligo.

There are a variety of systems, which attempt to quantitate the extent of vitiligo (somewhat akin to burn surface area quantitation) and importantly, to assess effects of vitiligo on quality of life, which can be a challenging parameter to measure. Still, the pathophysiology of vitiligo has recently come into focus. The general components are known and resemble many other autoimmune disorders. Thus findings of destruction of epidermal melanocytes as targets; mononuclear lymphoid infiltrates found at the active borders of vitiligo lesions and recruitments of CD8+ cytotoxic T cell lymphocytes with destruction of melanocytes are known components of the vitiligo process.

Several more specific pathophysiology mechanisms have been elucidated,[3] including: (1) intrinsic defects in melanocytes, which renders the patients' melanocytes being selectively targeted for immune destruction; (2) abnormal activation of INF-gamma(interferon) and JAK kinase immunity pathways, which draw CD8 "killer" lymphocytes to the vitiligo areas; and (3) a full innate immune response, wherein the

combination of the intrinsically abnormal, now immunogenic, melanocytes are targets being attacked by an activated effector system of cytokines drawing destructive lymphocytes to the area.[4]

And yet, the precise activation trigger (e.g. genetics, chemical exposures, or other factors) for these processes remains unclear. Despite the lack of clarity on the activation trigger, the latest therapeutics provide significant efficacy for patients with vitiligo. All lines of therapy are judged upon the degree of repigmentation. Generally, 50% to 75% repigmentation is an acceptable response to treatment.[1]

There are two types of core therapies: ultraviolet (UV) light and topical agents. For generalized (non-segmental) forms of vitiligo, the first-line treatment option is narrow-band ultraviolet phototherapy. If this treatment does not yield a response, topical steroids and immunosuppressives are used.[1,5,6] For the more localized segmental forms, localized phototherapy is an appropriate option. When both treatment options, ultraviolet light and topical agents, fail to provide re-pigmentation, surgical techniques with grafting of healthy skin can be performed, particularly with facial lesions.[1,4]

Additionally, a targeted Janus kinase (JAK) inhibitor, ruxolitinib, yielded good results in two large (more than 550 patients) randomized trials when compared with placebo for generalized non-focal vitiligo covering up to 10% of total body skin surface area. There was statistical separation from placebo by week 12 of therapy, and at 24 weeks, ruxolitinib had more than 50% responses compared with less than 10% with patients treated with placebo.[7] Importantly, toxicity and adverse event profiles were good, with less than 1% hematopoietic adverse effects and low plasma concentrations of the agent in treated cases. Indeed, the most common adverse events were site acne (4%) and pruritis (5%). This safety profile may indicate that more extensive skin area therapy is possible. This data also makes Answer A incorrect.

These study results may also lead to topical biologic immunosuppressives in combination with UV phototherapy in both segmental and non-segmental forms of disease. Whatever therapies are utilized, the re-pigmentation process is lengthy—often requiring 6 or more months, which makes answer B incorrect.

Another important issue is the fact that re-pigmentation requires not just controlling and stabilizing the autoimmune process, but also a source of new melanocytes in the disease areas, like hair follicles, which contain a reservoir of melanocytes that can re-populate the skin area. These follicle melanocytes are immune protected much like the retina and CSF, so they have not been destroyed by the pathological immune process. Notably, the hair follicle must have pigment in it. White hairs have lost theirs and cannot provide this reservoir. These facts explain why re-pigmentation is rare in the hands and knuckles (no hair follicles).

For this patient population, sunscreens should be used only to prevent sunburns in appropriate settings (e.g. a day at the beach) since they screen out UV radiation, which, in moderate amounts, is helpful in vitiligo. Indeed, routine and ongoing use of sunscreens, answer C, is not recommended, and therefore, incorrect.

Patient follow-up. The patient was referred to a dermatologist for an opinion regarding the use of these novel biologics, which are now available. He was briefed in detail regarding efficacy, adverse events, toxicity, and costs, which are not at all trivial. As of this writing, the patient noted that he has lived with his localized vitiligo for many years, and it has remained stable. He already routinely maps and measures the affected area using his cell phone camera and will continue to do so. If there is change in progression, which would not be usual in localized, long-term stable facial, segmental vitiligo, he will reconsider. But for now, he has opted against using ruxolitinib for his facial vitiligo.

What's the take home? Vitiligo is an autoimmune skin condition, wherein the autoimmune process causes destruction of epidermal melanocytes with resultant depigmentation of the skin. The condition's prevalence is estimated to be 0.5% worldwide with demographics of equal sex and racial ratio, and frequent onset in those younger than 20 years of age.[1,2] The condition manifests two basic clinical syndromes: the non-segmental generalized form (80% to 90% cases) and the less common segmental form (~10% of cases). Although data exists noting the involvement of the JAK2 pathway, ultimately leading to a T cell-mediated melanocyte destruction, more details regarding the biochemical pathophysiology of vitiligo remain elusive.

Treatment generally involves the use of ultraviolet light, yielding re-pigmentation in roughly 50% of impacted areas. Previous studies[4] have aimed therapeutics at the JAK pathway. One such agent, ruxolitinib, applied locally, resulted in greater than 50% re-pigmentation, and even greater than 75% re-pigmentation response in more than half of treated patients with vitiligo.[7]

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