

CLINICAL MANAGEMENT RECOMMENDATIONS

Expert Panel Discussion among Psoriasis and Psychodermatology Specialists: How Best to Manage Depressed Psoriasis Patients with Brodalumab

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INTRODUCTION

Depression is a well-established comorbidity of psoriasis. Recent epidemiologic studies have consistently found elevated rates of depression in psoriatic populations when compared to control groups.^{1,2} Despite its prevalence, dealing with depression may be unfamiliar territory for many dermatologists. When treating a psoriasis patient with depression, some providers may be overly conservative in treatment, in that they may utilize slower-acting systemic agents or rely on only topical medications or phototherapy for moderate-to-severe disease. However, patients who are severely impacted psychologically by their psoriasis may warrant more aggressive therapy, utilizing one of the highly effective and rapidly-acting agents available. To help practitioners better manage this common therapeutic challenge, a group of psoriasis and psychodermatology

experts convened to formulate a set of recommendations on how patients with psoriasis and depression may be better cared for in a dermatologic setting. This group included a board-certified psychiatrist, a licensed clinical psychologist, and multiple dermatologists with expertise in treating psoriatic disease and who have studied mental health issues related to psoriasis. To the authors' knowledge, this type of multidisciplinary workgroup focusing on psoriasis and depression has never before been assembled. The following recommendations are intended to be practical, realistic, and targeted to busy dermatology practitioners. They are not intended to be guidelines, but instead represent the consensus opinions of this diverse panel of experts.

RECOMMENDATION 1

If the presence of significant depression is suspected in a patient with psoriasis, how do we broach the topic and when do we consider referral?

One approach to inquiring about depression is to take a similar strategy as with other psoriatic comorbidities. For example, psoriatic arthritis is a common comorbid disorder for which patients are frequently screened, and the same should be true for depression. Several screening questionnaires are available for depression, including the Hospital Anxiety and Depression Scale (HADS), Patient Health Questionnaire-9 (PHQ-9), and Hamilton Depression Rating Scale (HAM-D); however, these questionnaires are often impractical in a hectic dermatology practice. One of the easiest screening tools is a review-of-systems questionnaire that allows patients to report their depression, joint pain, or other symptoms prior to being seen. If practitioners note a check in the “depressed” or “altered mood” box, or if they suspect depression for any other reason, a direct and to the point inquiry is recommended to initiate discussion. Although not necessarily required of dermatologists, it may be helpful to ask patients if their depression is secondary to psoriasis, or if there are other underlying factors involved which may predate their psoriasis. If the depression is purely secondary to psoriasis, then more aggressive treatment may be warranted; however, if the depression is primary or a combination of primary and secondary, then consultation with a mental health provider could also be helpful.

It is the consensus of the panel that the role of the dermatologist is to properly screen

patients in order to identify the cases where depression is relevant, but not to officially diagnose or treat depression. Dermatologists are ideally situated to screen and properly refer for the formal management of psoriatic comorbidities. An identical strategy should be taken with depression as is already common practice for psoriatic arthritis. If a patient with psoriasis endorses joint pain, swelling, or stiffness, a dermatologist considering systemic therapy will likely take this into account when choosing a therapeutic agent, in addition to suggesting a rheumatologic referral. In the analogous case of coexistent depression, the treating dermatologist should take into account the patient’s psychological wellbeing when considering therapy options, in addition to discussing referral to a mental health provider. The initiation of an agent that is highly effective with a quick onset of action is most desirable, especially if the patients’ depressive symptoms are purely secondary to their psoriatic disease. This strategy of timely referral and rapidly improving symptoms is most critical when a patient’s psoriatic disease is contributing to severe depression or if there is any suggestion of suicidality, including suicidal ideations, behaviors, or plans.

RECOMMENDATION 2

After a proper referral has been considered, how do we choose the best therapeutic option?

When considering a therapeutic agent for the depressed psoriasis patient, highly effective and quickly acting treatment options are preferred. For many patients, depression is to a large extent due to the

disfiguration and reduction in quality of life caused by their psoriasis. In some cases, psoriasis may in fact be the entire underlying reason for their depression. Separating depression secondary to psoriasis from primary, intrinsic depression is often as simple as asking the patient. Direct questions such as “How does your psoriasis make you feel?” or “Do you think your depression is related to your psoriasis?” are typically well-received by patients and will offer the provider some insight into the nature of the patient’s psychological comorbidity.

Regardless of the primary or secondary nature of depression, the more psychologically distressed the patient, the more essential it is that his or her psoriasis symptoms are resolved quickly. The IL-17 inhibitors are some of the most effective and fastest acting therapeutic options available and are all useful for rapidly controlling psoriatic disease. One agent in this group, brodalumab (Siliq™), has a black box warning regarding suicidal ideation and behavior, which may dissuade some practitioners from prescribing it to a potentially depressed patient. However, as long as the patient has previously failed another systemic agent for psoriasis, brodalumab can be an excellent choice due to its speed of onset and high rates of clearance. In regard to the three cases of adjudicated suicide (i.e. the deaths that a panel of independent experts determined were consistent with suicide after reviewing all available data) that occurred during clinical development, the United States Food and Drug Administration states in the brodalumab package insert that the “causal association between treatment with SILIQ and increased risk of suicidal ideation and behavior has not been established.”³ This consensus panel of psoriasis and psychodermatology experts concur with the

FDA’s assessment and conclusion for the following reasons:

1. The box warning was developed in response to three confirmed suicides that occurred from a total of 4,464 exposed patients throughout brodalumab’s psoriasis development program.⁴ Two additional suicides occurred in 1,168 patients in trials for other conditions.⁵
2. There was no chronological association between initiation of brodalumab and the completion of suicide, with the acts occurring 140, 329, and 845 days after the subjects’ first dose.⁴
3. Over the first 12 weeks of one of the pivotal phase 3 trials, treatment with brodalumab reduced patients’ depression and anxiety, as documented by their Hospital Anxiety and Depression Scores. This response was statistically significant when compared to placebo groups.⁶
4. The three subjects who completed suicide had significant concurrent life stressors that may have contributed to their actions, including financial hardship, acute social isolation, and likely pending incarceration.⁴ A fourth overdose occurred in a patient who mixed opiates and alcohol; however, this patient did not leave a suicide note or any other indication that the overdose was intentional.
5. Throughout the 52-week, controlled, head-to-head comparison period of the phase 3 trials, numerically higher rates of suicidal ideation and behavior (SIB) were seen in the ustekinumab-treated group than in the brodalumab-treated group.⁴

6. IL-17 and the brodalumab molecule have very little ability to cross the blood-brain barrier. Brodalumab has a molecular weight of 144 KDa, and it is generally accepted that molecules larger than 0.4 KDa are unable to cross the blood-brain barrier.⁷
7. No link between the blockade of IL-17 signaling and depression has been established, and human studies show no consistent association between IL-17 and suicidal ideation and behavior.⁸
8. The brodalumab development program did not exclude patients with a history of psychiatric disorders or other risk factors for suicidality, in contrast to the development programs for many other therapeutic agents for psoriasis.
9. Despite the inclusion of patients with psychiatric disorders and SIB risk factors, rates of serious psychiatric adverse events in the brodalumab clinical trials are comparable to the rates reported for other psoriasis treatments.⁹
10. During the clinical trials of brodalumab in the treatment of rheumatoid arthritis and Crohn's disease, no convincing signals regarding depression or SIB have arisen; however, one case of attempted suicide was reported during the phase 2 trial for rheumatoid arthritis.^{10,11}

CONCLUSION

This panel of psychodermatology and psoriasis experts have collaborated to release the following consensus statement:

Depression is prevalent in psoriasis. Multiple studies have shown that suicidality is increased in patients with

psoriasis. Depression, suicidal ideation, and suicide are prevalent and increasing problems in society. It's the disease, not the drug. We should always evaluate and consider the mental health of our patients. It is our conclusion that treatment of psoriasis does not increase or cause depression but instead plays an important role in ameliorating depression. Timely institution of highly and rapidly effective treatment may be critical in patients with significant negative psychological consequences of psoriasis.

It is our consensus that the treatment of psoriasis with medications, including brodalumab, does not increase or cause depression, but instead plays an important role in ameliorating depression. Of the recommendations expressed in this article, the most notable is that the timely institution of highly and rapidly effective treatment may be critical in patients with significant negative psychological consequences of psoriasis. As previously stated, this panel concluded that the role of the dermatologist is not to officially diagnose or treat depression, but instead to focus on proper screening and referral. It is also recommended that dermatologists tailor their treatment of depressed patients with psoriasis to include agents that are highly effective and rapidly acting. There are many factors to consider when selecting a psoriasis therapy.^{12,13} It is the hope of this panel that these recommendations will provide a practical framework for managing patients with psoriatic disease and comorbid depression.

Conflict of Interest Disclosures:

Dr. Thibodeaux has no relevant conflicts of interest.

Dr. Fried has no relevant conflicts of interest.

Dr. Goldenberg is a consultant and speaker for Abbvie, AMLA, Bayer, Celgene, Dermira, Leo, Novartis, Pharmaderm, Pfizer, and Regeneron/Sanofi. He is a consultant for Allergan, Amgen, Almirall, Castle, Eclipse, Galderma, Genentech, GSK/Stiefel, Intraderm, ISDIN, Janssen, Menlo, Ranbaxy, Scibase, Suneva, TEVA, Valeant/Ortho Dermatologic, and Verrica. He is a speaker for Merz and on the board of directors of Verrica.

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Dr. Kircik is a speaker for Abbott Laboratories, Allergan, Amgen, Assos Pharma, Astellas Pharma US, Inc., Cipher, CollaGenex, Connetics Corporation, Dermik Laboratories, Embil Pharmaceuticals, Exeltis, Genentech, Innocutis, Innovail, Johnson & Johnson, Leo, L'Oreal, 3M, Onset, OrthoNeutrogena, PediaPharm, PharmaDerm, Serono, SkinMedica, Stiefel Laboratories, SUN Pharma, Taro, Triax, UCB, Valeant Pharmaceuticals, and Warner-Chilcott. He has participated in advisory boards for Aclaris, Allergan, Almirall, Anacor, Biogen-Idec, Colbar, Celgene, Cipher, Connetics, EOS, Exeltis, Ferndale Laboratories, Genentech, Intendis, Innocutis, Isdin, Johnson & Johnson, Merz, OrthoNeutrogena, Promius, Quinnova, SkinMedica, Stiefel Laboratories, SUN Pharma, Valeant, and Warner-Chilcott. He is an investigator for Acambis, Allergan, Amgen, Anacor, Astellas, Asubio, Berlex, Biolife, Biopelle, Boehringer-Ingelheim, Breckinridge Pharma, Celgene, Centocor, Cellceutix, Coherus, CollaGenex, Combinatrix, Connetics Corporation, Coria, Dermavant, Dermira, Dow Pharmaceutical Sciences, Dusa, Eli Lilly, Exeltis, Ferdale Laboratories, Foamix, Genentech, GlaxoSmithKline, Health Point, Idera, Intendis, Johnson & Johnson, Leo, L'Oreal, 3M, Maruho, Merck, Medicis, Merz, Novartis, Noven, Nucrist, Obagi, Onset, OrthoNeutrogena, Promius, QLT, PharmaDerm, Pfizer, Quinnova, Quatrix, SkinMedica, Stiefel, SUN Pharma, TolerRx, UCB, Valeant, Warner-Chilcott, and Xenoport. He is a consultant for Allergan, Almirall, Amgen, Anacor, Colbar, Cipher, CollaGenex, Connetics, Exeltis, Genentech, Intendis, Isdin, Johnson & Johnson, Laboratory Skin Care, Leo, Medical International Technologies, Merck,

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