Depression and Suicidality in Psoriasis and Clinical Studies of Brodalumab: A Narrative Review

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Psoriasis is a chronic inflammatory skin disorder that affects patients’ quality of life and social interactions. Several studies have shown a strong consistent association between psoriasis and depression as well as possible suicidal ideation and behavior (SIB). Notable findings from a 2018 review found depression prevalence ranged from 2.1% to 33.7% among patients with psoriasis vs 0% to 22.7% among unaffected patients. In a 2017 meta-analysis, Singh et al found increased odds of SIB (odds ratio [OR], 2.05), attempted suicide (OR, 1.32), and completed suicide (OR, 1.20) in patients with psoriasis compared to those without psoriasis. In 2018, Wu and colleagues reported that odds of SIB among patients with psoriasis ranged from 1.01 to 1.94 times those of patients without psoriasis, and SIB and suicide attempts were more common than in patients with other dermatologic conditions. Koo and colleagues reached similar conclusions. At the same time, the occurrence of attempted and completed suicides among patients in psoriasis clinical trials has raised concerns about whether psoriasis medications also may increase the risk for SIB.

We review research on the effects of psoriasis treatment on patients’ symptoms of depression and SIB, with a focus on recent analyses of depressive symptoms and SIB among patients with psoriasis who received brodalumab in clinical trials. Finally, we suggest approaches clinicians may consider when caring for patients with psoriasis who may be at risk for depression and SIB.

Patients with psoriasis have high rates of depression and may be at increased risk for suicidal ideation and behavior (SIB). Attempted and completed suicides during clinical trials and other studies of psoriasis therapies, including brodalumab, highlight the importance of understanding psychiatric risk factors in patients with psoriasis. Recent meta-analyses, research studies, and published data from brodalumab clinical studies were reviewed. We also summarize research on effects of brodalumab on depression symptoms and occurrences of SIB in brodalumab clinical trials. Psoriasis elevates the risk for depression and possible suicide. Brodalumab has a boxed suicide warning; however, it states that there is no established causal association between treatment with brodalumab and increased risk for SIB. Clinicians are urged to evaluate patients with psoriasis for psychiatric risk factors regardless of their therapy and to consider the package insert and a comprehensive evaluation of relevant literature to make a well-balanced decision.


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MATERIALS AND METHODS

We reviewed research on the effects of biologic therapy for psoriasis on depression and SIB, with a primary focus on recent large meta-analyses. Published findings on the pattern of SIB in brodalumab clinical trials and effects of brodalumab treatment on symptoms of depression and anxiety are summarized. The most recent evidence (January 2014–December 2018) regarding the mental health comorbidities of psoriasis was assessed using published English-language research data and review articles according to a PubMed search of articles indexed for MEDLINE using the following terms: depression, anxiety, suicide, suicidal ideation and behavior, SIB, brodalumab, or psoriasis. We also reviewed citations within articles to identify relevant sources. Implications for clinical care of patients with psoriasis are discussed based on expert recommendations and the authors’ clinical experience.

RESULTS

Effects of Psoriasis Treatment on Symptoms of Depression and Suicidality

Occurrences of attempted suicide and completed suicide have been reported during treatment with several psoriasis medications,7,9 raising concerns about whether these medications increase the risk for depression and SIB in an already vulnerable population. Wu and colleagues2 reviewed 11 studies published from 2006 to 2017 reporting the effects of medications for the treatment of psoriasis—adalimumab, apremilast, brodalumab, etanercept, and ustekinumab—on measures of depression and anxiety such as the Beck Depression Inventory, the Hospital Anxiety and Depression Scale (HADS), and the Patient Health Questionnaire (PHQ) 8. In each of the 11 studies, symptoms of depression improved after treatment, over time, or compared to placebo. Notably, the magnitude of improvement in symptoms of depression was not strongly linked to the magnitude of clinical improvement.7 Other recent studies have reported reductions in symptoms of depression with biologic therapies, including adalimumab, etanercept, guselkumab, ixekizumab, secukinumab, and ustekinumab.14-21

With respect to suicidality, an analysis of publicly available data found low rates of completed and attempted suicides (point estimates of 0.0–0.15 per 100 patient-years) in clinical development programs of apremilast, brodalumab, ixekizumab, and secukinumab. Patient suicidality in these trials often occurred in the context of risk factors or stressors such as work, financial difficulties, depression, and substance abuse.7 In a detailed 2016 analysis of suicidal behaviors during clinical trials of apremilast, brodalumab, etanercept, infliximab, ixekizumab, secukinumab, tofacitinib, ustekinumab, and other investigational agents, Gooderham and colleagues8 concluded that the behaviors may have resulted from the disease or patients’ psychosocial status rather than from treatment and that treatment with biologic does not increase the risk for SIB. Improvements in symptoms of depression during treatment suggest the potential to improve patients’ psychiatric outcomes with biologic treatment.9

Evidence From Brodalumab Studies

Intensive efforts have been made to assess the effect of brodalumab, a fully human anti–IL-17RA monoclonal antibody shown to be efficacious in the treatment of moderate to severe plaque psoriasis, on symptoms of depression and to understand the incidence of SIB among patients receiving brodalumab in clinical trials.22-27

Depression and Anxiety in Studies of Brodalumab—To examine the effects of brodalumab on symptoms of depression, the HADS questionnaire22 was administered to patients in 1 of 3 phase 3 clinical trials of brodalumab.23 A HADS score of 0 to 7 is considered normal, 8 to 10 is mild, 11 to 14 is moderate, and 15 to 21 is severe.23 The HADS questionnaire was administered to evaluate the presence and severity of depression and anxiety symptoms at baseline and at weeks 12, 24, 36, and 52.23 This scale was not used in the other 2 phase 3 studies of brodalumab because at the time those studies were initiated, there was no indication to include mental health screenings as part of the study protocol.

Patients were initially randomized to placebo (n = 220), brodalumab 140 mg every 2 weeks (Q2W; n = 219), or brodalumab 210 mg Q2W (the eventual approved dose; n = 222) for 12 weeks.23 At week 12, patients initially randomized to placebo were switched to brodalumab through week 52. Patients initially randomized to brodalumab 210 mg Q2W were re-randomized to either placebo or brodalumab 210 mg Q2W.23 Depression and anxiety were common at baseline. Based on HADS scores, depression occurred among 27% and 26% of patients randomized to brodalumab and placebo, respectively; anxiety occurred in 36% of patients in each group.22 Among patients receiving brodalumab 210 mg Q2W from baseline to week 12, HADS depression scores improved in 67% of patients and worsened in 19%. In contrast, the proportion of patients receiving placebo whose depression scores improved (45%) was similar to the proportion whose scores worsened (38%). Hospital Anxiety and Depression Scale anxiety scores also improved more often with brodalumab than with placebo.22

Furthermore, among patients who had moderate or severe depression or anxiety at baseline, a greater percentage experienced improvement with brodalumab than placebo.23 Among 30 patients with moderate to severe HADS depression scores at baseline who were treated with brodalumab 210 mg Q2W, 22 (73%) improved by at least 1 depression category by week 12; in the placebo group, 10 of 22 (45%) improved. Among patients with moderate or severe anxiety scores, 28 of 42 patients (67%) treated with brodalumab 210 mg Q2W improved by at least 1 anxiety category compared to 8 of 27 (30%) placebo–treated patients.23
Over 52 weeks, HADS depression and anxiety scores continued to show a pattern of improvement among patients receiving brodalumab vs placebo. Among patients initially receiving placebo, mean HADS depression scores were unchanged from baseline (5.3) to week 12 (5.5). After patients were switched to brodalumab 210 mg Q2W, there was a trend toward improvement between week 12 (5.4) and week 52 (3.1). Among patients initially treated with brodalumab 210 mg Q2W, mean depression scores fell from baseline (5.5) to week 12 (3.4), then rose again between weeks 12 (2.9) and 52 (3.5) in patients switched to placebo (Figure, A). The pattern of findings was similar for HADS anxiety scores (Figure, B). Overall, brodalumab treatment appears to improve symptoms of depression and anxiety in patients being treated for psoriasis. This finding is consistent with the effects reported for other biologic therapies previously discussed.

SIB in Studies of Brodalumab—In addition to assessing the effect of brodalumab treatment on symptoms of depression and anxiety in patients with psoriasis, the brodalumab clinical trial program also tracked patterns of SIB among enrolled patients. In contrast with other clinical trials in which patients with a history of psychiatric disorders or substance abuse were excluded, clinical trials of brodalumab did not exclude patients with psychiatric disorders (eg, SIB, depression) and were therefore reflective of the real-world population of patients with moderate to severe psoriasis.

In a recently published, detailed analysis of psychiatric adverse events (AEs) in the brodalumab clinical trials, data related to SIB in patients with moderate depression and anxiety scores.
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to severe psoriasis were analyzed from the placebo-controlled phases and open-label, long-term extensions of a placebo-controlled phase 2 clinical trial and from the previously mentioned 3 phase 3 clinical trials. From the initiation of the clinical trial program, AEs were monitored during all trials. In response to completed suicides during some studies, additional SIB evaluations were later added at the request of the US Food and Drug Administration, including the Columbia Suicide Severity Rating Scale, the PHQ-8, and the Columbia Classification Algorithm for Suicide Assessment, to independently adjudicate SIB events.22

In total, 4464 patients in the brodalumab clinical trials received at least 1 dose of brodalumab, and 4126 of these patients received at least 1 dose of brodalumab 210 mg Q2W. Total exposure was 9174 patient-years of brodalumab, and mean exposure was 23 months. During the 52-week controlled phases of the clinical trials, 7 patients receiving brodalumab experienced any form of SIB event, representing a time-adjusted incidence rate of 0.20 events (95% confidence interval [CI], 0.08–0.41 events) per 100 patient-years of exposure. During the same 52-week period, patients receiving the comparator drug ustekinumab had an SIB rate of 0.60 events (95% CI, 0.12–1.74 events) per 100 patient-years, which was numerically higher than the rate with brodalumab. Inferential statistical analyses were not performed, but overlapping 95% CIs around these point estimates imply a similar level of SIB risk associated with each agent in these studies. During controlled and uncontrolled treatment periods in all studies, the SIB rate among brodalumab-treated patients was 0.37 events per 100 patient-years.22

Over all study phases, 3 completed suicides and 1 case adjudicated as indeterminate by the Columbia Classification Algorithm for Suicide Assessment review board were reported.22 All occurred in men aged 39 to 59 years. Of 6 patients with an AE of suicide attempt, all patients had at least 1 SIB risk factor and 3 had a history of SIB. The rate of SIB events was greater in patients with a history of depression (1.42) or suicidality (3.21) compared to those without any history of depression or suicidality (0.21 and 0.20, respectively).22 An examination of the regions in which the brodalumab studies were conducted showed generally consistent SIB incidence rates: 0.52, 0.29, 0.77, and 0 events per 100 patient-years in North America, Europe, Australia, and Russia, respectively.24

As previously described, depression and other risk factors for SIB are prevalent among patients with psoriasis. In addition, the rate of suicide mortality has increased substantially over the last decade in the general population, particularly among middle-aged white men,29 who made up much of the brodalumab clinical trial population.22 Therefore, even without treatment, it would not be surprising that SIB events occurred during the brodalumab trials. Most patients with SIB events during the trials had a history of predisposing risk factors.22

Prescribing information for brodalumab in the United States includes a boxed warning advising physicians to be aware of the risk of SIB as well as a statement that a causal relationship between SIB and brodalumab treatment has not been established.27

COMMENT

This review indicates that depression is increased among patients with psoriasis regardless of treatment regimen; however, the association between psoriasis and suicidality is unclear. In clinical trials of brodalumab, treatment resulted in improved symptoms of depression and anxiety among patients with psoriasis and was associated with lower rates of SIB compared to ustekinumab.22,23

Despite the boxed warning in the brodalumab package insert concerning suicidality, a causal relationship between brodalumab treatment and increased risk of SIB has not been firmly established.27 The US boxed warning is based on 3 completed suicides and 1 case adjudicated as indeterminate among more than 4000 patients who received at least 1 dose of brodalumab during global clinical trials (0.07% [3/4464]). Compliance in the Risk Evaluation and Mitigation Strategy (REMS) program is mandatory, and patient screening and counseling should not be minimized.27 The 3 completed suicides occurred in patients who reported a history of financial stressors, legal difficulties, or depression and anxiety, and they occurred at least 140 days after initiation of treatment with brodalumab, a chronology that does not support a strong association between brodalumab exposure and SIB.22 Taking into consideration the increased risk for depression among individuals with psoriasis and the details surrounding the 3 completed suicides, an evidence-based causal relationship between brodalumab and increased risk for suicidality cannot be concluded. However, physicians must assess risks and benefits of any therapy in the context of the individual patient’s preferences, risk factors, and response to treatment.

Dermatologists who are aware of the comorbidity between psoriasis and mood disorders play an important role in evaluating patients with psoriasis for psychiatric risk factors.30,32 The dermatologist should discuss with patients the relationship between psoriasis and depression, assess for any history of depression and SIB, and evaluate for signs and symptoms of depression and current SIB.33 Screening tools, including the HADS or the short, easily administered PHQ-234 or PHQ-4,35 can be used to assess whether patients have symptoms of depression.1,36,37 Patients at risk for depression or SIB should be referred to their primary care physician or a mental health care practitioner.37 Currently, there is a gap in knowledge in screening patients for psychiatric issues within the dermatology community,33,38 however, health care providers can give support to help bridge this gap.

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