IN-DEPTH REVIEWS

Review of suicide and depression in psoriasis and management of suicide warnings in patients treated with psoriasis drugs

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ABSTRACT

Patients with psoriasis are thought to be at increased risk of depression, anxiety and suicidality predominantly as a result of the psychosocial impact of this disease. Studies have shown that the pro-inflammatory cytokines that are elevated in psoriasis and targeted by biologics have also been identified in patients with depression. It is therefore thought that anti-cytokine therapies may improve patients' quality of life not only by reducing their disease burden but also by modulating the inflammatory pathways implicated in depression. While depression is mentioned in the package inserts of brodalumab and apremilast, only brodalumab has a black box warning requiring discussion of suicidality prior to prescribing the drug. In clinical trials, the majority of patients receiving brodalumab experience a reduction in symptoms of depression and anxiety. The package insert for brodalumab points out that no causal association has been established between brodalumab and suicide, and the FDA-mandated Risk Evaluation and Mitigation Strategies (REMS) program for brodalumab takes only minutes to complete. Brodalumab and apremilast may therefore be considered for patients in whom depression is caused by psoriasis, provided that patients and their providers have a mutual understanding of the risks and benefits of these therapies and the REMS program is followed.

INTRODUCTION

Multiple studies have found that patients with psoriasis are at risk for depression.(1-6) A recent meta-analysis reported the prevalence of major depression to be 9% to 28% among patients with this disease.(2) The authors of a population-based cohort study in the United Kingdom found that patients with psoriasis had an increased risk of depression, anxiety and suicidality,(1) and the authors of a cohort study in the USA found that psoriasis was associated with major depression even after adjusting for demographic factors and medical comorbidities such as cardiovascular disease.(4) While the dermatologic symptoms of pruritus, burning and pain can independently have a negative impact on overall quality of life,(7) the psychosocial impact of psoriasis has increasingly received greater attention. Patients have reported feeling stigmatized and embarrassed due to their physical appearance,(4, 8) and patients' perception of their disease severity, regardless of the objective extent of skin involvement, may correlate with depression risk.(1)

Studies have demonstrated that patients treated with TNF-alpha inhibitors (etanercept, infliximab, and adalimumab), interleukin (IL)-17 inhibitors (ixekizumab), and IL-12/IL-23 inhibitors (ustekinumab) for psoriasis can experience notable improvement in symptoms of depression and anxiety.(9-13) Brodalumab, an IL-17 receptor antibody, and apremilast, an oral medication that inhibits phosphodiesterase 4 (PDE4), have also been shown to improve symptoms of depression in patients with psoriasis.(14) (15) However, the package inserts for these two therapies mention depression, suicidal ideation and behavior (SIB) or suicide. In this article, we review the data that led to the concern for psychiatric adverse events during treatment with brodalumab and apremilast and we summarize the evidence for their clinical efficacy. We also summarize data on the psychiatric effects of biologic therapies overall on patients with psoriasis and discuss the possible connection between psoriasis, depression, and systemic inflammation.

BRODALUMAB

IL-17A, IL-17C and IL-17F are cytokines that promote inflammation in psoriasis, and IL-17-producing T cells have been localized to the dermis of psoriatic skin lesions.(16, 17) Brodalumab is a fully human anti-IL-17 receptor monoclonal antibody which has demonstrated success in treating patients with moderate-to-severe plaque psoriasis in randomized clinical trials.(14, 18) In a 12-week, phase 2, dose-ranging study,(18) patients were randomized to receive placebo or subcutaneous injection of brodalumab. Patients in the treatment group received brodalumab either at a dose of 70 mg, 140 mg, or 210 mg on day 1 and at weeks 1, 2, 4, 6, 8, and 10, or at a dose of 280 mg on day 1 and at weeks 4 and 8. Mean improvements in psoriasis area-and-severity index (PASI) scores were 86.3%, 85.9%, and 76.0% among those receiving 210 mg, 140 mg, and 280 mg of brodalumab, respectively, in comparison to 16% among those receiving placebo. In a phase 3, double-blind, randomized, placebo-controlled study of brodalumab (AMAGINE-1),(14) patients in both treatment groups (140 mg and 210 mg) were found to have significantly greater improvements in their PASI scores. Additionally, a greater proportion of patients receiving brodalumab as opposed to placebo reported resolution of psoriasis symptoms such as itching, burning, redness and pain.

Depression and suicidality:

3066 patients with psoriasis were treated with brodalumab over the course of the following clinical trials: a phase 2, randomized, double-blinded, placebo-controlled, dose-ranging study, an open-label extension of this phase 2 study, and three phase 3, double-blind, randomized controlled trials (AMAGINE-1[NCT01708590], AMAGINE-2 [NCT0170863], AMAGINE 3 [NCT01708629]) along with their open-label long-term extensions.(14, 19) In a pooled analysis of these 5 clinical trials,(19) 1.0% of patients receiving placebo and 0.8% of patients receiving brodalumab reported depression during the 12-week controlled treatment period. During the 52-week active-controlled treatment period, SIB occurred in four patients (0.11%) treated with brodalumab. Two patients completed suicide, one attempted suicide, and one engaged in intentional self-injury. Cumulatively, over the course of the controlled treatment periods and open-label extensions of these studies, SIB in the form of intentional self-injury, unspecified suicidal behavior, suicide attempt or completed suicide occurred in 15 (0.16%) patients. Six patients (0.07%) attempted suicide and four (0.04%) completed suicide—

all four were men ranging from 39 to 59 years of age. One of these events was later deemed indeterminate in the Columbia Classification Algorithm for Suicide Assessment review.(19)

Across the phase 2 and 3 clinical trials for brodalumab, the risk of SIB during brodalumab treatment was found to be higher among those with a prior history of depression or suicidality.(19) After approximately 260 weeks of follow-up, including the period after which treatment was discontinued, 3.21% of patients with a history of suicidality exhibited suicidal behavior in comparison to 0.20% of patients with no history of suicidality.

Approach to the patient starting Brodalumab:

Due to the observed events of suicidal ideation and completion during treatment with brodalumab in clinical trials, this therapy is available in the United States only through a Risk Evaluation and Mitigation Strategy (REMS) program. Both prescribers and pharmacies must be certified with the REMS program. The FDA requires that patients register with REMS only once; this process takes a short time to complete (less than 5 minutes) and requires a very brief explanation. Patients must also sign a Patient-Prescriber Agreement Form prior to starting brodalumab that indicates they are aware of the risks associated with the medication and that they will seek medical attention should feelings of depression or suicidality develop.

A definitive association between brodalumab and suicidality has not been established,(19, 20) and the FDA points out no causal relationship between brodalumab and suicide. However, brodalumab is the only biologic therapy with a black box requirement

Figure 1: Boxed-warning regarding suicidal ideation and behavior in the prescribing information for Brodalumab.

WARNING: SUICIDAL IDEATION AND BEHAVIOR

See full prescribing information for complete boxed warning.

- **Suicidal ideation and behavior, including completed suicides, have occurred in patients treated with SILIQ. (5.1, 6.1)**
- **Prior to prescribing, weigh potential risks and benefits in patients with a history of depression and/or suicidal ideation or behavior. (5.1)**
- **Patients with new or worsening suicidal thoughts and behavior should be referred to a mental health professional, as appropriate. (5.1)**
- **Advise patients and caregivers to seek medical attention for manifestations of suicidal ideation or behavior, new onset or worsening depression, anxiety, or other mood changes. (5.1)**
- **SILIQ is available only through a restricted program called the SILIQ REMS Program. (5.2)**

for providers to discuss suicide and depression with patients initiating treatment (Figure 1). The REMS program, in addition to this black box warning, are two safety precautions that ensure this very effective treatment can continue to be offered to patients with psoriasis.

SECUKINUMAB & IXEKIZUMAB

Additional biologic therapies targeting the IL-17 cytokine family are available for patients with psoriasis. Secukinumab, a human monoclonal anti-IL-17A antibody, and ixekizumab, a recombinant, humanized monoclonal antibody that also selectively targets IL-17A, are two biologics that have proven efficacious for the treatment of moderate-to-severe plaque psoriasis.(21, 22) In a phase 3, double-blind, 52-week trial investigating the efficacy of secukinumab versus etanercept, 77.1% of patients receiving 300 mg of subcutaneous secukinumab (administered once weekly for 5 weeks, then every 4 weeks) achieved reductions in PASI scores of at least 75%, in comparison to 44.0% of those receiving 50 mg of etanercept (administered twice weekly

for 12 weeks, then once weekly) and 4.9% of those receiving placebo.(21) In a phase 3 clinical trial investigating ixekizumab in the treatment of moderate-to-severe psoriasis, 89.1% of patients receiving 80 mg of subcutaneous ixekizumab (administered twice weekly for 12 weeks following a starting dose of 160 mg) achieved 75% or greater reductions in PASI scores in comparison to 3.9% of patients in the placebo group. (23)

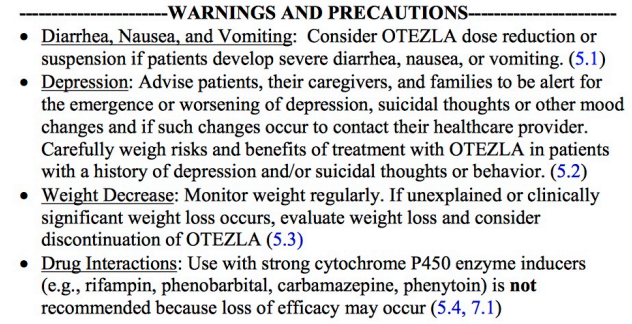
In a pooled analysis of 10 clinical trials of secukinumab, the most commonly reported adverse effects were nasopharyngitis, headaches, and upper respiratory tract infections.(24) These studies did not report an association between secukinumab and increased risk of SIB or depression. Ixekizumab has also not been linked to an increased risk of depression or suicidal behavior and has been demonstrated to improve symptoms of depression in patients with psoriasis. (12) If suicidal ideation and depression are of particular concern when starting a patient on an anti-IL-17 therapy, it is important to recognize that alternative options such as secukinumab and ixekizumab may be considered.

APREMILAST

Apremilast is an oral medication that inhibits phosphodiesterase 4 (PDE4) and leads to the downregulation of tumor necrosis factor (TNF)-alpha, IL-12, and IL-23, pro-inflammatory cytokines that are elevated in psoriasis.(25) In a phase 2b, randomized, placebo-controlled, dose-ranging trial of apremilast for the treatment of moderate-to-severe psoriasis,(26) a greater proportion of patients receiving apremilast versus placebo achieved significant improvement, as determined by 75% reduction from baseline PASI scores. In a phase 3 randomized controlled trial of apremilast in patients with moderate-to-severe plaque psoriasis (ESTEEM 1),(27) a significantly higher percentage of patients randomized to apremilast versus placebo achieved 75% or greater reduction in psoriasis severity. Additionally, the majority of patients initially in the placebo group and re-randomized to apremilast also achieved significant reduction in disease severity. Apremilast was further demonstrated to be effective in biologic-naïve patients with moderate plaque psoriasis involving 5 to 10% of the body surface area, with improvements sustained after 52 weeks of follow-up.(28)

Depression and suicidality:
A total of 832 patients were treated with apremilast across two phase 3 clinical trials.(29) At baseline, 13.4% of patients in the placebo group and 13.7% of patients in the treatment group reported depression (respectively). During the placebo-controlled phase of the trial, patient-reported depression occurred in 12/832 (1.4%) patients being treated with apremilast and 2/418 (0.5%) patients receiving placebo. At week 16 of the trial, patient-reported depression was noted to be higher in the apremilast group; psychiatric adverse events (specifically depression) in this group did not continue to increase over subsequent weeks. At the completion of the study there had been one suicide attempt and no completed suicides in the apremilast group. One patient in the placebo arm of ESTEEM 1 attempted and completed suicide. In additional retrospective cohort studies of apremilast for the treatment of psoriasis, patient-reported rates of depression and mood lability have ranged from 0.8% to 3.9%.(30-32) None of these studies have reported instances of suicidal attempts or completions.

Figure 2: Depression specified as a precaution in prescribing Apremilast.



----------WARNINGS AND PRECAUTIONS----------

- Diarrhea, Nausea, and Vomiting: Consider OTEZLA dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting. (5.1)
- Depression: Advise patients, their caregivers, and families to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes and if such changes occur to contact their healthcare provider. Carefully weigh risks and benefits of treatment with OTEZLA in patients with a history of depression and/or suicidal thoughts or behavior. (5.2)
- Weight Decrease: Monitor weight regularly. If unexplained or clinically significant weight loss occurs, evaluate weight loss and consider discontinuation of OTEZLA (5.3)
- Drug Interactions: Use with strong cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) is **not** recommended because loss of efficacy may occur (5.4, 7.1)

Approach to the patient starting apremilast:

In the prescribing information for apremilast, depression is listed under "Warnings and Precautions" (Figure 2). At week 16 of the phase 3 placebo-controlled trials, 1.3% of patients treated with apremilast reported feelings of depression in comparison to 0.4% of patients treated with placebo. One patient (0.1%) experienced treatment-limiting depression that led to discontinuation of apremilast, while none of the patients in the placebo group discontinued treatment as a result of depression. Due to this imbalance of patient-reported depression at this point in the trial, it is therefore recommended that the risks and benefits of initiating apremilast be weighed, particularly in patients with a history of psychiatric comorbidities or suicidal behavior. As with brodalumab, patients starting apremilast should be appropriately counseled to seek medical assistance should they develop symptoms of depression or suicidal ideation.

PSORIASIS, DEPRESSION & INFLAMMATORY CYTOKINES

Systemic inflammation in psoriasis may play a role in the development of depression,(33) as pro-inflammatory cytokines that are elevated in psoriasis-- such as IL-17, IL-23, and TNF-alpha-- have also been identified in patients with depression.(34) Inflammatory marker levels are increased in the central nervous system (CNS) of individuals with depression and suicidal behavior,(35) indicating that a pro-inflammatory state may be implicated in the pathophysiology of depressive symptoms. This connection between inflammation and depression has been illustrated in studies of anti-depressant medications. One study found that bupropion, a commonly used anti-depressant, decreased levels of TNF-alpha synthesis in mice,(36) and another study found that combination treatment with bupropion and a selective serotonin reuptake inhibitor (SSRI) was more effective in patients with higher baseline levels of IL-17.(37)

Anti-cytokine treatments have been found to decrease symptoms of depression in those with inflammatory diseases.(38) TNF-alpha antagonists in particular have been shown to reduce symptoms of depression in patients with psoriasis.(11, 39) One study demonstrated that a higher proportion of patients receiving etanercept, as opposed to placebo, achieved at least 50% improvement in symptoms of depression.(40) Therapies targeting IL-12, IL-17 and IL-23 have also been shown to impact mental health. Greater improvements in symptoms of anxiety and depression, as measured by the Hospital Anxiety and Depression Scale (HADS), were observed in patients receiving ustekinumab (IL-12/IL-23 inhibitor) and guselkumab (IL-23 inhibitor) versus those receiving placebo.(9, 41) Ixekizumab also demonstrated efficacy in this regard, leading to the remission of depression in 40% of patients who fit criteria

for moderately severe depression at baseline.(12)

PSYCHIATRIC EFFECTS OF SYSTEMIC THERAPIES

While patients with psoriasis are understood to be at increased risk of depression, the influence of systemic treatment itself on depression has not been well characterized. Recently, patients in the Psoriasis Longitudinal Assessment and Registry (PSOLAR)(42) who were being treated with biologics, other systemic therapies (such as methotrexate or cyclosporine), or phototherapy were assessed for the development of depressive symptoms.(43) The biologics ustekinumab, adalimumab, etanercept, and infliximab were included in this study. The incidence rate of depression ranged from 2.62% to 3.53% among those receiving biologics, while the incidence was 5.85% and 5.70% among those receiving phototherapy and conventional systemic therapy, respectively. A total of 21 patients demonstrated suicidal ideation and behavior, with 3 men completing suicide. Of the 11 patients who attempted or completed suicide, 7 were receiving biologic therapy and 8/11 (73%) had a history of depression at the time of enrollment in the study. The incidence rate of suicidal ideation, suicide attempt, or suicide completion was 43 per 100,000 patient years within the entire cohort; the incidence rate of suicide among patients with psoriasis is reported to be 90 per 100,000 patient years.(1) The authors of this study concluded that biologic therapy is correlated with a lower risk of depressive symptoms, in comparison to conventional systemic therapy, among patients with moderate-to-severe psoriasis. Given the unclear connection between suicidality and non-TNF-alpha biologics, additional studies might further elucidate this risk.

CONCLUSION

The negative impact of psoriasis on patients' quality of life is well established and has been explored at length in the literature. While patients with psoriasis are reported to have higher rates of depression, anxiety and suicidality, successful response to treatment has been correlated with a positive impact on mental health and overall quality of life. Therapies that target the pro-inflammatory cytokines elevated in psoriasis have demonstrated substantial clinical efficacy across a number of clinical trials and should therefore be considered for those with moderate-to-severe or recalcitrant disease. While adverse psychiatric events have been reported during treatment with brodalumab and apremilast, a causal association between these therapies and suicide has yet to be established. It is nevertheless evident that patients with known psychiatric conditions or prior histories of suicidal behavior may be at slightly increased risk of adverse psychiatric effects when starting a new biologic such as brodalumab. It is therefore imperative that careful medical histories are obtained in order to closely monitor patients and to determine whether alternative therapies should be considered.

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