ORIGINAL ARTICLE

Psychiatric adverse events during treatment with brodalumab: Analysis of psoriasis clinical trials

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Background: Individuals with psoriasis are at increased risk for psychiatric comorbidities, including suicidal ideation and behavior (SIB).

Objective: To distinguish between the underlying risk and potential for treatment-induced psychiatric adverse events in patients with psoriasis being treated with brodalumab, a fully human anti−interleukin 17 receptor A monoclonal antibody.

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Methods: Data were evaluated from a placebo-controlled, phase 2 clinical trial; the open-label, long-term extension of the phase 2 clinical trial; and three phase 3, randomized, double-blind, controlled clinical trials (AMAGINE-1, AMAGINE-2, and AMAGINE-3) and their open-label, long-term extensions of patients with moderate-to-severe psoriasis.

Results: The analysis included 4464 patients with 9161.8 patient-years of brodalumab exposure. The follow-up time–adjusted incidence rates of SIB events were comparable between the brodalumab and ustekinumab groups throughout the 52-week controlled phases (0.20 vs 0.60 per 100 patient-years). In the brodalumab group, 4 completed suicides were reported, 1 of which was later adjudicated as indeterminate; all patients had underlying psychiatric disorders or stressors.

Limitations: There was no comparator arm past week 52. Controlled study periods were not powered to detect differences in rare events such as suicide.

Conclusions: Comparison with controls and the timing of events do not indicate a causal relationship between SIB and brodalumab treatment. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2017.08.024.)

Key words: adverse events; depression; mental health; psoriasis; psychiatric; psychiatry; suicidal ideation and behavior.

CAPSULE SUMMARY

- Patients with psoriasis are at increased risk for psychiatric comorbidities, including suicidal ideation and behavior.
- This study compared the incidence of psychiatric adverse events in patients treated with brodalumab, placebo, and ustekinumab.
- Data from 5 clinical trials did not reveal a causal relationship between suicidality and brodalumab treatment.

The burden of psoriasis reaches beyond skin manifestations to encompass disability, impaired quality of life, and disease-related morbidity.[1] These impediments arise from psoriasis symptoms as well as from coexisting inflammatory conditions (eg, cardiometabolic disease, inflammatory bowel disease) and psychiatric comorbidities and their sequelae.[2-4] Higher rates of depression, anxiety, self-harm, and suicidality have been detected in patients with psoriasis compared with in the general population or individuals with other dermatologic conditions.[5-8] Stress, social stigma, and physical limitations contribute to the psychiatric symptoms experienced by patients with psoriasis.[9] Underlying inflammatory mediators that are upregulated in psoriasis may also contribute to high rates of depression. Elevated levels of proinflammatory cytokines such as tumor necrosis factor-α, interleukin (IL)-6, and IL-17–A have been found in both psoriasis and psychiatric disorders, including depression and post-traumatic stress disorder.[10-14]

Brodalumab, a fully human anti–IL-17 receptor A monoclonal antibody, is the first biologic to treat psoriasis that acts directly as an IL-17 receptor antagonist.[15] Brodalumab demonstrated efficacy in 3 large phase 3 psoriasis clinical trials in which Psoriasis Area and Severity Index 100 response rates were significantly higher than with placebo or active control (ustekinumab) at week 12.[16,17]

Brodalumab was generally well tolerated, with no imbalance in psychiatric adverse events (AEs) and suicidal ideation and behavior (SIB) events compared with placebo or ustekinumab at week 12 or ustekinumab at week 52.[16,17] SIB was identified as a potential risk in the phase 3 brodalumab psoriasis program after most patients had completed 52 weeks on the study.[18] Psychiatric AEs were observed, including depression and anxiety, and SIB incidents were reported.[16,17,19] Although there is no known biologic basis for brodalumab to induce psychiatric AEs, the possibility of drug-mediated effects on patient behavior warranted further investigation. An exploratory analysis was conducted to identify psychiatric AE occurrences (including SIB) across late-stage clinical trials of brodalumab in patients with psoriasis and to explore the possibility of a causal relationship with study drug treatment.

METHODS

Clinical studies

Psychiatric AE data were gathered from 5 psoriasis clinical trials in the brodalumab development program: a phase 2, randomized, double-blinded, placebo-controlled, dose-ranging