

What Lies Beneath the Face Value of a BOX WARNING: A Deeper Look at Brodalumab

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ABSTRACT

Brodalumab, a fully human antibody of the interleukin-17 receptor, is highly effective in the treatment of moderate-to-severe plaque psoriasis. However, based on safety signals identified in clinical trials, brodalumab carries a boxed warning regarding possible risks of suicidal ideation and behavior (SIB). The validity of this link remains controversial, especially in the context of the psoriasis population as well as clinical trial data from other recently approved treatments. Herein, we critically examine the association between brodalumab and SIB.

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INTRODUCTION

Psoriasis is a chronic, immune-mediated, inflammatory skin condition that affects 2-3% of the world's population.[1,2] Plaque psoriasis is the most common form of the disease, characterized by the presence of well-demarcated, erythematous, and scaly plaques. Several co-morbid conditions are linked to psoriasis, including inflammatory arthritides, inflammatory bowel disease, and cardio-metabolic disease.[3]

Importantly, studies have shown that psoriasis patients suffer from a multitude of psychological stressors, as the disease burden can lead to functional disability, social stigmatization, and poor self-image.[4] Compared to the general population, patients with psoriasis are at an increased risk of depression—a risk factor for suicidality—even after controlling for other co-morbidities.[5-8] The presence of systemic inflammation may also contribute to depression and psychological symptoms due to pro-inflammatory cytokines such as tumor necrosis factor(TNF)-α, which are increased in both major depressive disorder and psoriasis.[9,10]

Over one quarter of psoriasis cases are categorized as moderate-to-severe, with the disease severity often necessitating systemic treatment agents.[11] The development of biologic therapies has vastly improved the treatment outlook for these patients, and research continues to explore increasingly specific disease mediators and targeted approaches. In particular, the identification of interleukin (IL)-17 as a fundamental component in the pathogenesis of psoriasis has led to the approval of several new biologics. The currently approved anti-IL-17 agents are secukinumab (COSENTYX®, Novartis, East Hanover, New Jersey), ixekizumab (TALTZ®, Eli Lily, Indianapolis, Indiana), and brodalumab (SILIQ®, Valeant, Bridgewater, New Jersey).

Notably, brodalumab carries a boxed warning regarding possible increases in suicidal ideation and behavior (SIB). However, brodalumab demonstrated higher rates of clinical response relative to both placebo and ustekinumab.[12] Given the significant capacity of brodalumab to improve disease states in psoriasis patients, there has been close evaluation of the nature and validity of its SIB warning. In this article, we explore the possible link between brodalumab and SIB in the context of its clinical trial data as well as data from other recently approved agents.

Psychiatric Co-morbidity in Psoriasis

Over the past decade, the risk of psychiatric disease in psoriasis patients has been increasingly recognized and explored. Given the complexity in identifying psychiatric disorders, the most applicable data can be garnered from large scale epidemiological studies.

A population-based study from the National Health and Nutrition Examination Survey examined the association between psoriasis and major depression in 12,382 US citizens.[5] Among patients with self-reported psoriasis (2.8% of the study population), 16.5% met the criteria for major depression, which was over double the 7.8% prevalence found in the general study population. Psoriasis was significantly associated with major depression even after adjustment for sex, age, race, body mass index (BMI), physical activity, smoking history, alcohol use, history of myocardial infarction, history of stroke, and history of diabetes mellitus (OR 2.09, 95% CI 1.41-3.11).

In another large-scale study, 4,994 participants were surveyed regarding skin disease and psychological disorders.[6] Depression was present in 13.8% of patients with psoriasis compared with 4.3% of healthy controls (OR 3.02; 95% CI 1.86–4.90). Among all reported skin disorders –including non-melanoma skin cancer, eczema, and acne—only psoriasis showed a significant association with suicidal ideation (OR 1.94, 95% CI 1.33–2.82).

A meta-analysis of 98 studies has supported the connection between psoriasis and depression.[13] Patients with psoriasis were found to be one and a half times more likely to demonstrate signs of depression relative to non-affected controls (OR 1.57; 95% CI 1.40–1.76) and were also more likely to use anti-depressant medications (OR 4.24, 95% CI 1.53–11.76). Overall, 28% (95% CI 22–34%) of the psoriasis patients showed symptoms of depression; 19% (95% CI 12-29%) and 12% (95% CI 8-18%) demonstrated signs of clinical depression based on criteria from the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) and the International Classification of Disease (ICD), respectively.

Patients with concomitant psoriatic arthritis may represent an especially vulnerable population. In a prospective cohort study of 50,750 US female nurses, the risk of depression was found to be higher in individuals with psoriasis relative to non-affected controls (RR 1.29, 95% CI 1.10-1.52), after controlling for BMI, physical activity, smoking, and the presence of major chronic conditions.[14] When individuals with psoriasis were further examined for the presence of psoriatic arthritis, those with concomitant psoriatic arthritis had a higher risk of clinical depression (RR 1.52, 95% CI 1.06–2.19) than those without (RR 1.25, 95% CI 1.05–1.49). Similarly, a smaller study of 607 individuals with psoriasis found that patients who also carried a diagnosis of psoriatic arthritis were at an increased risk for depression (OR 2.1, 95% CI 1.29-3.45) as well as anxiety (OR 1.92, 95% CI 1.24-2.98).[15]

Brodalumab and Observations of SIB

Brodalumab is a human monoclonal IgG2 antibody that selectively binds to the IL-17 receptor A, thereby inhibiting its interactions with cytokines IL-17A, IL-17C, IL-17F, IL17A/F heterodimer, and IL-25. It was approved in 2017 for the treatment of adult patients with moderate-to-severe plaque psoriasis. Due to the perceived heightened level of psychiatric risk associated with brodalumab, the drug was recommended by FDA reviewers for use as a second-line therapy, with the need to reassess treatment in patients who do not achieve adequate response within 12 weeks, as well as the incorporation of a risk evaluation and mitigation strategy program that requires certification from both prescribers and pharmacies.[16]

During the clinical development program for plaque psoriasis, there were 4 completed suicides and 10 suicide attempts in brodalumab-treated subjects, the majority of which occurred during the long-term, open-label phase of the study.[17] One case of completed suicide was later adjudicated as indeterminate according to the Columbia Classification Algorithm of Suicide Assessment (C-CASA).[17] In each case of completed suicide, confounding risk factors were present, including a history of depression, substance abuse, significant financial and legal stressors, and psychosocial stressors.[17] While there is not a compelling reason to attribute these deaths to brodalumab, as opposed to comorbid psychiatric disorders or life circumstances, the number of events was of concern. The details of these events are summarized in Table 1.

With the goal of improved SIB evaluation, the electronic Columbia Suicide Severity Rating Scale (eC-SSRS) and Patient Health Questionnaire-8 (PHQ-8) were implanted for prospective evaluation during the studies. Importantly, at this point, most patients had already entered the long-term extension phase, which resulted in the lack of an adequate randomized comparison group (the double-blind phase had been completed for most patients).

There are several factors that may have created an exaggerated suicidality signal in the brodalumab trials. Unlike the clinical trials for other recently approved biologics, there was not a specific exclusion of subjection with a history of psychiatric events or prior suicide attempts.[17] Subjects in the brodalumab trials were also predominantly middle-aged white males, who represent the demographic at greatest risk for suicide.[18,19] The rate of suicides in this group has increased in recent years, from 20.7 suicides per 100,000 in 2007 to 23.4 per 100,000 in 2013.[19] During the pre-recession time period of 1999-2007, suicide mortality increased by 0.12 per 100,000 per year; however, the recession period from 2008-2010 saw an additional 0.51 deaths per 100,000 per year (which translates to an additional 1580 suicides annually).[18]

In an analysis by Lebwohl et al.,[20] the psychiatric data from five brodalumab clinical trials (one phase II trial, one phase II long-term extension, and three phase III trials) was collectively examined. The set included 4464 patients with 9161.8 patient-years of brodalumab exposure, and the analysis focused on controlled periods of the studies where comparator data was available. There was no observed increase in brodalumab SIB rates relative to either ustekinumab or placebo, although the comparator periods were not powered to detect rare events such as suicides. Overall, the authors did not find a causal relationship between brodalumab treatment and SIB.

Notably, the AMAGINE-1 trial included measurements of anxiety and depression between baseline and week 12, during which a greater proportion of brodalumab-treated patients experienced improvements in psychiatric symptoms relative to placebo (likely linked to their improving skin disease). Positive effects on psychiatric well-being have also been identified in the clinical trials of another highly effective anti-IL-17 agent, ixekizumab (discussed later).

TABLE 1.

Completed Suicides During Clinical Trials With Brodalumab Treatment	
Age, y/Sex/Race	**Clinical Information**
58/male/White	-Originally from Poland -Also carried diagnosis of psoriatic arthritis -Completed suicide 58 days after his last dose of brodalumab (210 mg), which was 329 days after starting treatment -Suicide occurred by hanging -Subject reported to the investigator that he had significant financial stresses, primarily caused by the loss of disability payments after his positive response to brodalumab
39/male/White	-Originally from US -Completed suicide 27 days after his last dose of brodalumab (210 mg), which was 140 days after starting treatment -Method of suicide was unknown, and his death was reported by family members -Subject disclosed to the investigator that he had legal difficulties and was likely facing impending incarceration
56/male/White	-Originally from US -History of depression and anxiety, for which he was being treated with trazodone -Completed suicide 19 days after his last dose of brodalumab (210 mg), which was 845 days after starting treatment -Suicide occurred by jumping from the roof of his apartment building -Subject reported to the investigator that he had recently relocated and was feeling isolated and stressed
56/male/Asian	-Case was later adjudicated to be "indeterminate" regarding suicidal intent by C-CASA -History of depression and anxiety, for which he was being treated with citalopram and alprazolam -Also had an unclear history of alcohol abuse -Subject died 14 days after his last dose of brodalumab (210 mg), which was 97 days after starting treatment -Found dead in his vehicle, and toxicology results showed the presence of heroin and alcohol, as well as citalopram and alprazolam

A recent phase II clinical trial in Japanese subjects supports the lack of SIB associated with brodalumab.[21] In the open label trial, 145 subjects were treated with either brodalumab 210 mg or 140 mg subcutaneously every 2 weeks. After 52 weeks, the Psoriasis Area and Severity Index (PASI)-75 rates, PASI-90 rates, and PASI-100 rates were 94.4%, 87.5%, and 55.6%, respectively, in the 210-mg group, and 78.1%, 71.2%, and 43.8% in the 140-mg group. There were no reports of suicidal ideation or suicidal behavior.

Other Recent Approvals and Observations of SIB

The SIB data from other recently approved agents provides additional context for the evaluation of brodalumab. Reports of SIB have been observed among several medications, most pronounced with ixekizumab (Table 2).

Ixekizumab

Ixekizumab is a humanized IgG4 monoclonal antibody that binds with high affinity and specificity to IL-17A, thereby

TABLE 2.

Recent Approvals and Observations of SIB			
Product	**Events**	**Rate Per 100 PY**	**95% CI**
Apremilast†	1 completed on placebo	0.052-0.062	(0.002, 0.345) to (0.001, 0.288)
Secukinumab‡	1 completed in screening	0.034	(0.001, 0.190)
Ixekizumab	10 attempts on active	0.15*	(0.072, 0.276)
	1 attempt on placebo	0.55*	(0.014, 3.064)
Brodalumab	4 completed on active	0.044	(0.012, 0.112)
	10 attempts on active	0.11	(0.052, 0.201)

†Apremilast Medical Review, Psoriasis, 2014, Table 29 (Placebo 0-16w and apremilast 30 mg BID 0-52w) was used to estimate the incidence rate range, while the apremilast Prescribing Information, 2015, Section 5, indicated 1 suicide occurred in the psoriasis program.
‡Secukinumab Advisory Committee Briefing Book, 2014, Table 5-14 (Pool B, through ≥52w) was used to estimate the exposure, and Section 5.5.6 indicated 1 suicide in the psoriasis program.
¶Ixekizumab Summary Review, Draft, 2016 p15 describes rates for attempted suicide during the psoriasis program. No completed suicides were noted.
*Patient year not provided but instead back-calculated from the rate and the number of attempts.

inhibiting its interaction with the IL-17 receptor. Ixekizumab was approved for the treatment of moderate-to-severe plaque psoriasis in 2016 and psoriatic arthritis in 2017.

During the clinical development program of ixekizumab for psoriasis, there were 10 reports of suicide attempts in ixekizumab-treated patients, including those identified through retrospective analysis using C-CASA: 2 attempts during the induction period, 1 attempt during the maintenance period, 6 attempts during the long-term extension period, and 1 attempt during post-treatment follow-up (Table 3).[22] There were additionally two reports of serious depression requiring hospitalization. There were no reports of completed suicides in patients treated with ixekizumab.

All events of suicide attempts were determined by the investigator to be not related to ixekizumab due to the presence of risk factors such as undisclosed history of prior suicide attempt, depression, bipolar disorder, anxiety, alcohol/substance use or abuse, and the presence of major, acute psychosocial triggers.[22] Depressive symptoms throughout the trial were captured primarily through administration of the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR16). An analysis of QIDS-SR16 scores demonstrated significant reductions from baseline in depressive symptoms in patients treated with ixekizumab as compared to placebo, both at the end of the induction period and at the end of maintenance period.[22,23]

Importantly, subjects with a history of prior suicide attempts, significant uncontrolled neuropsychiatric disorders, or frequent active suicidal ideation as assessed by the QIDS-SR16 were excluded from study participation. In contrast, the brodalumab trials allowed patients with SIB risk factors at baseline to participate, thereby capturing safety data more reflective of the psoriasis population, but also impacting SIB results.

Apremilast and Secukinumab

Clinical trials for apremilast and secukinumab have also demonstrated signals for SIB (Table 2). Among secukinumab trials, there was one completed suicide that occurred during the screening period (prior to any study drug being administered).[24]

Among apremilast trials, one completed suicide occurred in the placebo group, with no completed suicides in the treatment group.[25] There was, however, one suicide attempt with apremilast treatment (0 to ≤52 weeks).[26] Post-marketing data recorded up to March 2016 showed 65 reported cases of SIB: 5 completed suicides, 4 suicide attempts, 50 cases of suicidal ideation, 5 cases of depression, and 1 case of suicidal behavior.[27] In 32 of 65 cases, patients reported improvement after discontinuation of apremilast. A retrospective analysis was performed using three large patient databases (the US Food and Drug Administration Adverse Event Reporting System database, the European Medicine Agency's EudraVigilance database, and the Northwestern Medicine Enterprise

TABLE 3.

Attempted Suicides During Clinical Trials With Ixekizumab Treatment

Age, y/Sex/Race	Prior History of Depression	Reported Stressors	Method of Attempted Suicide
69/male/White	No	-Diagnosed with severe depression during the trial after the death of a friend -Financial problems -Difficulty coping with recent retirement	Slashed his throat, leading to hospitalization
49/female/White	Yes	-Learned that her husband had an affair with his niece	Lacerated herself and took minor drug overdose
40/male/White	Yes	-None reported	Patient did not disclose method but did report two suicide attempts within a three-week period
55/female/White	Yes	-Learned that her close friend had died -Life partner was ending their relationship	Attempted to inject air into her veins with the trial syringes
46/male/White	No	None reported	Lacerated his wrist while under the influence of alcohol
29/male/White	Yes	-Lost his job after arriving to work two hours late -Financial issues -Girlfriend was ending their relationship	Overdose of ibuprofen and codeine
34/female/White	Yes	-Family stressors	Overdose of alcohol and exposure to carbon monoxide
45/male/White	Yes	-Domestic problems	Overdose of valium
47/female/White	Yes	-None reported	Overdose of antidepressants
26/male/Black	No	-Family dispute	Overdose of MDMA

Data Warehouse), which found no safety signal between apremilast and SIB.[28]

Adalimumab

There are rare reports of suicide while on adalimumab treatment.[29] During clinical trial development of the drug, one patient with a known history of heavy alcohol use and anxiety disorder committed suicide 40 days after his last dose of adalimumab (equaling 0.4 events per 100 patient years).[30] The patient was in the open-label treatment phase and had withdrawn consent due to lack of efficacy.

IL-17 and the Pathophysiology of Depression

Investigation has increasingly focused on the role of the immune system and systemic inflammation in the pathophysiology of depression. Studies have shown that serum levels of IL-6, TNF-α, and IL-1 are elevated in patients with depression.[10,31,32]

At present, the exact role of IL-17 in depression remains unclear. One study in patients with rheumatoid arthritis examined the levels of IL-17 among those with or without comorbid depression or anxiety.[33] Serum IL-17 levels were significantly higher in patients with both rheumatoid arthritis and anxiety relative to those without anxiety (P=0.044), and levels of IL-17 positively correlated with the severity of anxiety, even after adjustment for pain and arthritis disease severity. In contrast, a study examining plasma levels of IL-17 and IL-23 in patients with major depressive disorder found no difference in these markers relative to healthy controls.[34] There was also no significant correlation between changes in cytokine levels and changes in depression scores after 6-week treatment with an anti-depressant.

A recent study using mouse models examined the effects of increasing Th17 cell counts on depressive symptoms.[35] The administration of Th17 cells was associated with an elevation in depression-like behaviors, whereas the administration of undifferentiated CD4+ cells or vehicle was not. In addition, mice who were deficient in RORγt—the transcription factor necessary for Th17 cell development—were more resistant to the depression-like state. Further investigation is needed to evaluate the direct role IL-17 may play in pathologic conditions of the central nervous system.

CONCLUSION

It is difficult to accurately capture SIB data in clinical trials, and this challenge only increases in the post-market setting. Interpretation of SIB data is complex, especially in diseases such as psoriasis, where there exists a significant background signal of depression that itself is not well understood (and has been reported at a widely ranging prevalence). In addition, data from different development programs can be problematic to compare because of variations in patient characteristics, follow-up methods, and ascertainment of SIB.

In the case of brodalumab, several factors should be considered by prescribing dermatologists in evaluating the merit of its boxed warning. These issues include a clinical trial design that did not exclude patients based on psychiatric history, the lack of increased SIB during periods when brodalumab was actively compared to placebo or ustekinumab, as well as the known risk of SIB in the psoriasis population. In addition, the labeling decision by the FDA was heavily influenced by the fact that SIB behavior in the brodalumab trial manifested as completed suicides, despite the presence of attempted suicides in other biologic trials.

In summary, regardless of the treatment agent used, the concern over SIB in the psoriasis population remains a relevant issue. Continued research is needed to help identify vulnerable patients and to better assess risk versus benefit at the level of the individual. Importantly, the role of the physician in remaining vigilant of SIB in psoriasis patients should not be limited to solely biologic therapies or boxed warnings.

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