Depression? It's the Disease NOT the Drug

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Research into the immunopathological mechanisms of plaque psoriasis has produced increasingly targeted biologic therapies. The specificity of these agents allows for high rates of efficacy and decreased adverse events, most notably reduced immune system suppression. In recent years, the recognition of interleukin (IL)-17 as an important component in the pathogenesis of psoriasis has led to the development of a new class of biologics

Brodalumab (SILIQ®, Valeant, Bridgewater, New Jersey) is a human monoclonal IgG2 antibody that selectively binds to the IL-17 receptor. It was approved in 2017 for the treatment of adult patients with moderate-to-severe plaque psoriasis. In contrast to other anti-IL-17 agents, brodalumab targets the IL-17 pathway through its receptor, rather than its ligand. This binding leads to blockade of not only the IL-17A cytokine, but also IL-17C, IL-17F, the IL17A/F heterodimer, and IL-25.

In clinical trials, brodalumab demonstrated higher rates of disease clearance than both placebo and ustekinumab. Indeed, measurements of the Psoriasis Area and Severity Index response rates for brodalumab are among the highest of any available therapy for patients with moderate-to-severe psoriasis.

However, brodalumab is also notable for its box warning regarding possible increases in suicidal ideation and behavior (SIB). This labeling was mandated by the U.S. Food and Drug Administration (FDA) due to the occurrence of four completed suicides in clinical trial development, one of which was later adjudicated as indeterminate. Since the FDA decision, there has been close re-evaluation of the SIB warning by the dermatology community in an effort to better understand its rationale and relevance. In the ensuing article, we critically investigate the link between brodalumab and SIB, with full review of the clinical trial data.

There are several factors that warrant consideration when evaluating the box warning. Paramount is the increasingly recognized link between psoriasis and depression. Several large-scale, epidemiological studies have demonstrated that patients with psoriasis face an increased risk of depression, even after controlling for other comorbidities. Several psychological stressors likely play a role, such as functional disability, social stigmatization, difficulties with intimacy, and poor self-image. Importantly, the design of the brodalumab clinical trials was such that subjects were not excluded based on prior psychiatric history. While this decision allowed investigators to more accurately evaluate the psoriasis population, it undoubtedly raised the likelihood of SIB events occurring during the trial period.

Close inspection of the clinical trial data also fails to support a causal link between brodalumab and SIB. A systematic review of the 52-week controlled phases of the trials has shown that comparable rates of SIB events were reported between brodalumab and ustekinumab. In fact, during portions of the brodalumab trial where measurements of anxiety and depression were captured, subjects on brodalumab experienced greater improvements in psychiatric symptoms relative to controls. When the few cases of completed suicide were carefully examined, each subject was found to have an underlying psychiatric disorder or significant stressors.

Due to its high rates of clinical efficacy and overall favorable safety profile, brodalumab represents an important treatment option for patients with moderate-to-severe plaque psoriasis, therefore the dermatology community is strongly encouraged to critically evaluate the benefits versus the risks of this very efficacious treatment in the appropriate psoriasis population.

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Disclosures

Dr. Kircik has received compensation for his editorial support from JDD.

Dr. Kircik serves as either an investigator, consultant, an advisory board member, or a speaker for OrthoDermatologics, Amgen, Celgene, BMS, Cellceutix, Leo, Taro, Eli Lilly, Novartis, Abbvie, BI.