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Brodalumab: 4-Year US Pharmacovigilance Report

Mark Lebwohl MD,[a] John Koo MD,[b] Craig Leonardi MD,[c] April Armstrong MD MPH,[d] Nicole Rawnsley PharmD BSc,[e] Earl Goehring Jr,[f] Abby Jacobson MS PA-C[e]

[a]Icahn School of Medicine at Mount Sinai, New York, NY
[b]Psoriasis and Skin Treatment Center, University of California, San Francisco, San Francisco, CA
[c]Central Dermatology, St. Louis, MO
[d]University of Southern California, Los Angeles, CA
[e]Ortho Dermatologics (a division of Bausch Health US, LLC), Bridgewater, NJ
[f]Bausch Health, Bridgewater, NJ

ABSTRACT

Brodalumab is an interleukin-17 receptor A antagonist approved for the treatment of moderate-to-severe psoriasis in adults without response or with loss of response to other systemic therapies. Brodalumab carries a boxed warning in the United States regarding suicidal ideation and behavior, though no causal relationship has been established. Here, we summarize 4 years of pharmacovigilance data, from August 15, 2017, through August 14, 2021, reported to Ortho Dermatologics by US patients and healthcare providers. The most common AEs listed in the brodalumab package insert (incidence ≥1%) and AEs of special interest are described. Brodalumab exposure estimates were calculated using the time between the first prescription-dispensing authorization date and last prescription-dispensing authorization date. Data were collected from 4019 patients with an estimated brodalumab exposure of 4563 patient-years. The most common AE was arthralgia (115 events; 2.52 events per 100 patient-years). No completed suicides and no new suicidal attempts were reported. There were 102 cases with serious infections; however, no serious fungal infections (including no new cases of oral candidiasis) were reported. There were 26 COVID-19 cases, and 3 of the cases with comorbid conditions were fatal. There were no new cases of Crohn's disease. Of 37 reported malignancies among 32 cases, none were deemed related to brodalumab. Four-year pharmacovigilance data are consistent with the established safety profile reported in long-term clinical trials and 3-year pharmacovigilance data.

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INTRODUCTION

Brodalumab is an interleukin-17 receptor A antagonist indicated for the systemic treatment of moderate-to-severe plaque psoriasis in adult patients who have lost response or failed to respond to other systemic therapies.[1] Although the safety profile of brodalumab has been characterized in one phase 2 study, multiple phase 3 studies, and US pharmacovigilance reports for years 1 through 3, a boxed warning is included in the US package insert regarding suicidal ideation and behavior.[1-8] In brodalumab clinical trials, screening/exclusion of candidates was not based on a history of suicidal behavior or depression, and no causal relationship between brodalumab and suicidal behavior has been demonstrated.[1,9]

Because of the chronic nature of psoriasis, it is necessary to assess long-term data regarding adverse events (AEs) in a real-world setting. This report provides an update based on 4-year pharmacovigilance data, building upon the 3-year pharmacovigilance report.[4]

MATERIALS AND METHODS

This analysis summarizes pharmacovigilance data reported to Ortho Dermatologics by US patients and healthcare providers (HCPs) from August 15, 2017, through August 14, 2021. The most common AEs (with an incidence ≥1%) listed on the brodalumab package insert[1] and other AEs of clinical interest are summarized with descriptive statistics and assessed as exposure-adjusted rates per 100 patient-years (PYs).

Brodalumab exposure was calculated as the time from the first prescription-dispensing authorization date to last prescription-dispensing authorization date. Patients with the same initial and last prescription-dispensing authorization date were excluded from the analysis. Detailed patient medical histories, including prior psoriatic medications and time between prior therapy and brodalumab initiation, were not included in pharmacovigilance reports.[5]

TABLE 1.

US Pharmacovigilance Monitoring of Common AEs Listed in the Brodalumab Package Insert Through 4 Years (August 15, 2017–August 14, 2021)

AE	Event, n (r)[a]	Event drug related, n[b]	Discontinued, n (%)[c]	Maintained, n (%)[c]	Action unknown/NA, n (%)[c]
Arthralgia	115 (2.52)	1	25 (22)	53 (46)	37 (32)
Headache	45 (0.99)	0	6 (13)	25 (56)	14 (31)
Fatigue	44 (0.96)	1	6 (14)	20 (45)	18 (41)
Injection-site reaction	35 (0.77)	3	1 (3)	18 (51)	16 (46)
Diarrhea	33 (0.72)	0	6 (18)	19 (58)	8 (24)
Myalgia	31 (0.68)	0	6 (19)	18 (58)[d]	7 (23)
Nausea	29 (0.64)	0	5 (17)	17 (59)	7 (24)
Influenza	23 (0.50)	1	9 (39)	7 (30)	7 (30)
Oropharyngeal pain	21 (0.46)	0	2 (10)	11 (52)[e]	8 (38)
Neutropenia	1 (0.02)	0	0	1 (100)	0
Tinea infection	0	--	--	--	--

AE, adverse event; NA, not applicable; r, exposure-adjusted event rate per 100 patient-years. [a]Number of patients experiencing AE, not total number of AEs. [b]Relatedness to brodalumab was based on company-determined causality. [c]Treatment action taken upon AE occurrence. Percentage is the event divided by total number of patients experiencing the event. [d]One patient increased brodalumab dose. [e]One patient temporarily stopped taking the drug but planned to resume brodalumab treatment.

Ethics approval and informed consent were not necessary, as the postmarketing data presented here were noninterventional and were not collected as part of a clinical study.

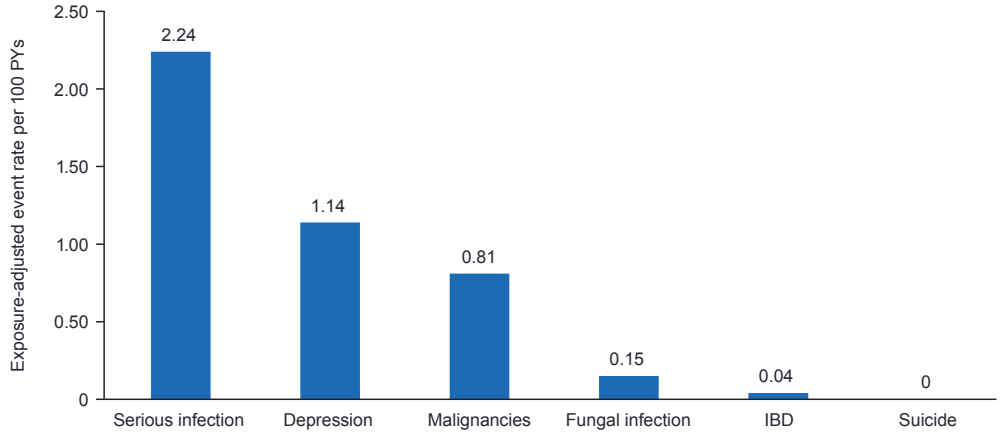
RESULTS

Common AEs Listed in Brodalumab Package Insert

Data were collected from 4019 patients in the United States who took brodalumab and reported an AE, with an estimated exposure of 4563 PYs (exposure-adjusted event rate per 100 PYs is the number of events per 45.63 PYs of exposure). Within the 4-year period, 22% of AEs were reported by HCPs and 78% were reported by patients.

Among the common AEs listed in the brodalumab package insert, arthralgia was reported the most during the 4-year pharmacovigilance monitoring (Table 1). Of 115 cases of arthralgia (2.52 events/100 PYs), 53 patients continued and 25 discontinued brodalumab; 37 actions were unknown. Of the 4

FIGURE 1. Exposure-adjusted clinical events of special interest, as deemed by the reporter or company, per 100 PYs. Exposure-adjusted event rate per 100 PYs is the number of events per 45.63 PYs of exposure. IBD, inflammatory bowel disease; MedDRA v24.1, Medical Dictionary for Regulatory Activities, version 24.1; PY, patient-year; SMQ, Standardized MedDRA Query; SOC, System Organ Class.



Definitions of Clinical Events of Special Interest (MedDRA v24.1)

Serious infection: Any MedDRA Preferred Term identified under the System Organ Class (SOC) Name "Infections and Infestations," where the SOC was indicated as "primary" and event seriousness as "serious"

Depression: Included MedDRA Preferred Terms from Depression (excluding suicide and self-injury) SMQ

Malignancies: Included MedDRA Preferred Terms from Malignancies SMQ and Malignant lymphomas SMQ

Fungal infection: Included any Preferred Term containing terms candidiasis, candida, fungal, onychomycosis, or yeast infection

Inflammatory bowel disease: Included MedDRA Preferred Terms *Inflammatory bowel disease*, *Irritable bowel syndrome*, *Crohn's disease*, *Colitis ulcerative*

Suicide: Included MedDRA Preferred Terms *Suicide attempt*, *Suicidal ideation*, *Suicidal behavior*, *Completed suicide*

new cases of arthralgia since the 3-year report, 3 patients were temporarily off brodalumab when their joint pain recurred.

Additional common AEs listed in the brodalumab package insert include headache, myalgia, influenza, diarrhea, oropharyngeal pain, nausea, injection-site reactions, fatigue, neutropenia, and *Tinea* infections.[1] Among the 45 cases of headache (0.99 events/100 PYs), 29 (64%) occurred among women, and the 2 cases reported during the fourth year had other potential contributing causes. Since the 3-year pharmacovigilance report, 3 new cases of myalgia were reported (0.68 events/100 PYs), with 2 patients continuing treatment. Of 1 new case of influenza, brodalumab was discontinued as the patient also reported COVID-19 and strep pharyngitis; it is unknown if therapy was resumed. One new case of diarrhea was reported in year 4 (0.72 events/100 PYs). Of 1 new case of oropharyngeal pain (0.46 events/100 PYs), which was described as pain in the back of the throat, dosage was maintained. Of 29 cases of nausea (0.64 events/100 PYs), most occurred among patients aged between 40 and 69 years and 17 (59%) occurred among women. In year 4, there were no new reports of injection-site reactions, fatigue, or neutropenia; no *Tinea* infections were reported throughout the 4 years.

Clinical Events of Special Interest

Clinical events such as serious infections, fungal infections, inflammatory bowel disease, malignancies, depression, and suicide have been deemed of special interest by the reporter or company (Figure 1).

Infections

All cases of infection, including duplicate diagnoses, such as COVID-19 and pneumonia on the same report, were counted separately. Overall, there were 102 serious infections reported, 3 of which were determined to be related to brodalumab (as previously reported[4]). The rate of serious infections (2.24 events/100 PYs) decreased compared with previously reported data (3.0 events/100 PYs).[4] Although no serious fungal infections were reported, 1 new fungal infection, onychomycosis, led to the patient discontinuing brodalumab. There were no new reports of oral candidiasis.

There were 24 cases of confirmed COVID-19 and 2 cases of suspected COVID-19. For most of these cases (21/26; 81%), patients had underlying comorbid conditions, and 12 (46%) cases were deemed serious by the company. There were 3 deaths due to COVID-19 (1 of which occurred before vaccine availability, 1 of which the patient was not vaccinated, and 1 with unknown vaccination status). All 3 COVID-19–related deaths were in patients aged ≥65 years with comorbid conditions.

One case of tuberculosis (TB) was reported. The patient began treatment with brodalumab in November 2019. After a positive test for TB on an unknown date in 2020, the patient discontinued brodalumab while receiving TB treatment and then tested negative for TB in July 2020. History of travel exposure, prior therapies, or concomitant therapies was not reported.

Inflammatory Bowel Disease

No new cases of Crohn's disease were reported since the 3-year pharmacovigilance report. One case of Crohn's disease was previously reported in a patient who had symptomatic history before brodalumab initiation, which led to discontinuation.[5]

One new case of ulcerative colitis was reported in a patient who started brodalumab in July 2018 after failing to respond to tumor necrosis factor α and interleukin-17A inhibitors. In October 2020, the patient was officially diagnosed with ulcerative colitis, which was not suspected to be related to brodalumab, and brodalumab therapy was not discontinued.

The event rate for inflammatory bowel disease in this analysis (0.04 events/100 PYs) is similar to the previously reported rate in the 3-year analysis.[4]

Malignancies

Malignancy rates from a long-term clinical trial and 1-, 2-, and 3-year US pharmacovigilance studies were 0.9, 1.0, 0.8, and 1.1 events/100 PYs, respectively.[4] In this 4-year analysis, 37 malignancies were reported in 32 cases (0.81 events/100 PYs), reducing the event rate previously reported in the 3-year analysis (1.1 events/100 PYs).[4] Types of reported malignancies included hepatic, lung, ovarian, endometrial, prostate, renal, and gallbladder cancers; 1 case of plasma cell myeloma; 3 other neoplasms (neck tumor, carcinoma removed from the leg, and malignancy removed from the arm); and other unspecified neoplasms. Dermatologic malignancies included 1 keratoacanthoma-type squamous cell carcinoma, 8 other squamous cell carcinomas, 7 basal cell carcinomas, and 1 malignant melanoma. None of the reported malignancies were deemed related to brodalumab. Of the 32 cases with malignancies, 10 continued and 18 discontinued brodalumab. Treatment status was unknown for the remaining 4 cases.

Depression and Reported Case of Suicide Attempt

There were 52 reported cases of depression (1.14 events/100 PYs), with 4 cases previously determined to be related to brodalumab. There were 4 new cases of depression, with no causality assessments provided by the reporter. As previously described, a physician reported a case involving a suicide attempt, with no indicated causal relationship between brodalumab and the reported adverse events (depressed mood and attempted self-harm).[4] No new suicide attempts were reported in year 4, and no completed suicides were reported throughout the 4 years.

DISCUSSION

This pharmacovigilance report summarizes 4 years of the most common AEs from the brodalumab package insert and additional AEs of special interest reported from August 15, 2017, through August 14, 2021, in the United States. Consistent with clinical trials and previous pharmacovigilance reports, arthralgia was the most frequently reported AE (115 events). No new cases of suicide attempts were reported since the 3-year report, and no completed suicides were reported. Depression was documented in 52 cases, with 4 cases previously reported to be related to brodalumab.[4] Serious infections, none of which were fungal, were reported in 102 cases, and 3 cases were previously reported to be related to brodalumab.[4] There were 26 COVID-19 cases, with 3 COVID-19–related deaths occurring during year 4 (all in patients aged ≥65 years with comorbid conditions). No trends were established from reported infections.

Brodalumab has demonstrated a consistent safety profile during long-term clinical trials and throughout 4 years of pharmacovigilance monitoring. There were no new reports of injection-site reactions, fatigue, or neutropenia since the 3-year report; overall, no *Tinea* infections have been reported. Although 1 case of suicide attempt was previously reported, no causal relationship with brodalumab was established.[4]

Several limitations of this 4-year report should be considered. There are no groups included for comparison (eg, patients not receiving brodalumab), and only AEs reported to Ortho Dermatologics were documented. Additionally, exact brodalumab administration dates were not available, resulting in the use of patient-exposure estimates based on prescription-dispensing authorization dates. Lastly, contextual information is absent in pharmacovigilance reporting, limiting the interpretation of the relationship between the drug and AEs.

DISCLOSURES

ML is an employee of Mount Sinai; receives research funds from AbbVie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Cara Therapeutics, Dermavant Sciences, Eli Lilly, Incyte, Janssen Research & Development, LLC, Ortho Dermatologics, Regeneron, and UCB, Inc.; and is a consultant for Aditum Bio, Almirall, AltruBi Inc., AnaptysBio, Arcutis, Inc., Arena Pharmaceuticals, Aristea Therapeutics, Arrive Technologies, Avotres Therapeutics, BiomX, Brickell Biotech, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Castle Biosciences, Corevitas, Dermavant Sciences, Dr. Reddy's Laboratories, Evelo Biosciences, Evommune, Inc., Facilitation of International Dermatology Education, Forte Biosciences, Foundation for Research and Education in Dermatology, Helsinn Therapeutics, Hexima Ltd., LEO Pharma, Meiji Seika Pharma, Mindera, Pfizer, Seanergy, and Verric. JK has been a consultant or speaker for AbbVie, Amgen, Eli Lilly, EPI, Janssen, LEO Pharma, Novartis, Ortho Dermatologics (a division of Bausch Health US, LLC), Pfizer, Regeneron Pharmaceuticals, Sanofi, and Sun Pharmaceutical. CL has been a consultant, investigator, or speaker for AbbVie, Actavis, Allergan, Amgen, Boehringer Ingelheim, Celgene, Cellceutix, Coherus, Corrona, Dermira, Eli Lilly, Galderma, Glenmark, Janssen, LEO Pharma, Merck, Novartis, Novella, Pfizer, Sandoz, Sienna, Stiefel, Sun Pharmaceutical, UCB, Vitae, and Wyeth. AA has served as a research investigator for and/or scientific advisor to AbbVie, BMS, Dermavant, Dermira, Incyte, Janssen, LEO Pharma, Lilly, Modmed, Novartis, Ortho Dermatologics (a division of Bausch Health US, LLC), Pfizer, Regeneron Pharmaceuticals, Sanofi, Sun Pharmaceutical, and UCB. NR and AJ are employees of Ortho Dermatologics (a division of Bausch Health US, LLC). EG is an employee of Bausch Health.

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AUTHOR CORRESPONDENCE

Mark Lebwohl MD
E-mail:..... lebwohl@aol.com