The safety of brodalumab for the treatment of psoriasis

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**Population**
N=4373 adults with moderate-to-severe plaque psoriasis included in one phase II and three RCT Phase III (AMAGINE-1, 2 and 3 trials)

**Aim**
To provide a detailed overview on safety and efficacy of brodalumab for the treatment of psoriasis based on data from key phase II, III as well as reviews and meta-analysis.

**Methodology used**
Pubmed search was performed using both the terms "psoriasis" and "brodalumab".

**Conclusions drawn**
- Brodalumab, a human monoclonal IgG2 antibody that targets IL-17 receptor A (IL-17RA), is one of the most efficacious agents approved for treatment of moderate to severe psoriasis, with a very rapid onset of effect, high rates of complete clearance and long term sustainability of response.
- The unique mechanism of action of brodalumab entails a broader blockade of IL-17 isoforms binding IL-17RA, which may confer a potential advantage over the more targeted approach of other IL-17A inhibitors.
- The safety profile of brodalumab in clinical trials is not affected by age and weight, is comparable with that of ustekinumab in headto-head clinical trials and is consistent with those of currently available IL-17A antagonists.
- Long-term, open-label extension studies did not identify new safety signals in patients treated with brodalumab.
The safety of brodalumab for the treatment of psoriasis

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ABSTRACT

Introduction: Brodalumab is a newly developed targeted biologic agent for the treatment of psoriasis that blocks IL-17 receptor A.

Areas covered: This review sought to provide a detailed overview on safety of brodalumab for the treatment of psoriasis. A PubMed search was conducted for relevant literature. Here we review the efficacy and safety data from key phase II, phase III and open-label extension clinical trials, as well as systematic reviews and meta-analyses.

Expert opinion: The unique mechanism of action of brodalumab offers advantages on efficacy over other targeted treatments, with a quick onset of action and long-term maintenance of treatment response. Brodalumab has a favorable safety profile, similar to other IL-17 inhibitors. Infections, especially mucocutaneous candidiasis, must be monitored. Suicidal ideation was detected in brodalumab trials, although a causal relationship has not been revealed. Brodalumab is a highly efficacious and comparably safe therapeutic choice in patients with moderate to severe psoriasis, especially when rapid control of the disease is desired.

1. Introduction
Psoriasis is a chronic and recurrent immune-mediated, multisystem disorder that manifests predominantly in the skin but entails other complications [1]. It affects negatively the quality of life and emotional well-being, creating social stigma and increasing comorbidity, mortality risk and suicidal ideation [2].

The pathogenesis of psoriasis is not fully understood and probably involves a combination of genetic, environmental and immunologic factors. The interleukin-23/T helper 17 (IL-23/Th17) pathway with its primary effector interleukin-17A (IL-17A) has been identified as a critical axis in psoriasis pathophysiology [3]. Targeted biologic therapies have been developed for the treatment of psoriasis focusing on this pathway, including secukinumab (Cosentyx®, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA), ixekizumab (Taltz®, Eli Lilly and Company, Indianapolis, IN, USA) and more recently brodalumab (Kyntheum®, LEO Pharma Inc, Thornhill, Ontario, Canada; Siliq® Ortho Dermatologics, Bridgewater, NJ, USA).

This safety review focuses on brodalumab. Brodalumab was initially developed by Amgen and AstraZeneca but in May 2015 its development was discontinued due to suicidality seen during the clinical trial program. Later, AstraZeneca partnered with Valeant Pharmaceuticals, who took over the development of brodalumab (US trade name Siliq®). In July 2016, LEO Pharma acquired the rights to develop brodalumab in Europe (European trade name Kyntheum®).

2. Methods
A search of PubMed was performed with the search terms ‘psoriasis’ AND ‘brodalumab’ on 10 November 2019 from the start of records.

3. Mechanism of action and pharmacokinetics (PK)
Biologic agents target various cytokine mediators along the molecular pathway of inflammation in psoriasis; they include TNF-alpha inhibitors, IL-12/23 inhibitors, IL-23 inhibitors, IL-17A inhibitors, and IL-17A receptor blockers.

IL-17 receptors are found in the surface of keratinocytes and bind IL-17 cytokines to promote signaling within numerous targets including keratinocytes, endothelial cells, chondrocytes, fibroblasts, monocytes and neutrophils [3–5]. The IL-17 family of cytokines (IL-17A to F) have been shown to be elevated in psoriatic skin and implicated in the pathogenesis of psoriasis. IL-17A can exist as a homodimer of two IL-17A chains or as a heterodimer with IL-17 F. Its central role in the pathogenesis of psoriasis has been reviewed extensively [3]. IL-17 F has the highest homology with IL-17A and is expressed by the same immune cell types as IL-17A. It is considered to act similarly to IL-17A but with less potent effects. Bimekizumab, a biologic drug under development that inhibits both IL-17A and IL-17 F, shows promising results [6]. IL-17 C is predominantly produced by nonimmune epithelial cells, including keratinocytes. It is the most abundant IL-17 cytokine in psoriatic lesional skin and has been characterized as critical in the development of psoriasis [7].
receptors, they are composed of 5 subunits (IL-17 RA-RE) in different dimeric combinations. IL-17A and IL-17 F bind to the same complex of IL-17RA and IL-17RC. IL-17RA is widely expressed, while the cell type expression of other IL-17R family receptors is more restricted. Upon ligand binding, these receptors engage with cytoplasmic protein ACT1 to enact downstream signaling pathways [8].

Brodalumab is a fully human monoclonal IgG2 antibody that targets IL-17 receptor A (IL-17RA) and blocks signaling of not only IL17A but also IL17 F, IL17 C, IL17A/F and IL25 [9]. Following subcutaneous administration, the estimated brodalumab bioavailability is approximately 55% based on population PK modeling, and its half-life is approximately 10.9 days at steady state. Following multiple subcutaneous doses of 140 mg or 210 mg every 2 weeks (Q2W), the mean (±SD) peak serum concentrations (Cmax) at steady state were 7.2 ± 6.5 mcg/mL and 20.6 ± 14.6 mcg/mL for 140 and 210 mg, respectively, observed 3 days post-dose. The mean (±SD) AUCtau over the two-week dosing interval were 81.4 ± 77.4 mcg·day/mL and 227 ± 167 mcg·day/mL for 140 and 210 mg, respectively. Age, sex, or race did not significantly influence the PK of brodalumab, but brodalumab clearance and volume of distribution increase as body weight increases. Serum levels of IL-17A were increased after receiving 140 mg or 210 mg brodalumab treatment compared to the pretreatment levels in subjects with moderate to severe plaque psoriasis. The increase in trough serum IL-17A levels at steady state appeared to be dose-dependent [10].

Brodalumab is dispensed as pre-filled syringes containing 210 mg in 1.5 mL solution containing proline, glutamate, polysorbate 20 and water for injection. It is administered via subcutaneous injection of 210 mg on weeks 0, 1 and 2, followed by a maintenance dose of 210 mg every other week [11].

4. Brodalumab key efficacy data

The efficacy and safety of brodalumab has been established in one phase II and three randomized, placebo-controlled phase III clinical trials including a total of 4373 adult participants with moderate-to-severe plaque psoriasis: placebo-controlled AMAGINE-1 (N = 651) and active-controlled against ustekinumab AMAGINE-2 (N = 1881) and AMAGINE-3 (N = 1831) [12] (Table 1). Long-term, open-label extension studies were conducted in AMAGINE-2/-3 [12,13] and also in the phase II dose-ranging study [14,15]. For all 3 phase III studies, PASI 75 and sPGA of 0/1 for brodalumab versus placebo at week 12 were the primary endpoints. For AMAGINE-2 and AMAGINE 3, PASI 100 for brodalumab vs ustekinumab was also a primary endpoint. Secondary endpoints in all studies included PASI 100 vs placebo at week 12, sPGA 0/1 at week 52, and change in Psoriasis Symptom Inventory (PSI) at week 12. PASI 75 results at week 12 in AMAGINE –1/-2/-3 were 83, 86 and 85%, respectively. The sPGA of 0/1 was achieved by 76, 79 and 80% of subjects treated with brodalumab. PASI 100 response rates at week 12 were also higher (44 and 37% in AMAGINE 2 and 3, respectively). These results were also significant compared to placebo (p < 0.001) and ustekinumab (p < 0.007) in AMAGINE-3 but not in AMAGINE-2 (p = 0.08) [16,17]. Post-hoc analysis demonstrated that a 50% reduction in baseline PASI was achieved at approximately 1.8 weeks [95% CI 1.7–1.9] for subjects treated with brodalumab [18].

As for long-term efficacy, brodalumab has demonstrated sustained efficacy at 2 years, based on pooled data from the open-label extension studies of AMAGINE –2/-3 (N = 676). PASI 75, PASI 90 and PASI 100 at 54 weeks were 93, 86 and 67%, respectively. For all the patients who had achieved sPGA 0/1, PASI 75, PASI 90 and PASI 100 by week 12, 80, 91, 80 and 62% of them sustained those results at week 108, respectively [12]. In the open-label extension of AMAGINE-2, patients receiving brodalumab 210 mg every 2 weeks (Q2 W) following ustekinumab experienced increased sPGA score 0/1, PASI 90 and PASI 100 responses and maintained them through week 120. Patients who received continuous brodalumab 210 mg Q2 W had a more rapid onset of skin clearance response compared with

### Table 1. Summary of primary endpoint results from key brodalumab clinical trials comparing them with extension study (brodalumab 210 mg Q2 W during the maintenance and long-term extension phases).

<table>
<thead>
<tr>
<th>Week</th>
<th>Study</th>
<th>Treatment</th>
<th>PASI 75 (%)</th>
<th>sPGA 0/1 (%)</th>
<th>PASI 90 (%)</th>
<th>PASI 100 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>AMAGINE-1</td>
<td>Brodalumab 210 mg</td>
<td>60.3</td>
<td>53.9</td>
<td>42.5</td>
<td>23.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Brodalumab 140 mg</td>
<td>83.3</td>
<td>75.7</td>
<td>70.3</td>
<td>41.9</td>
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<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>2.7</td>
<td>1.4</td>
<td>0.9</td>
<td>0.5</td>
</tr>
<tr>
<td>12</td>
<td>AMAGINE-2</td>
<td>Brodalumab 210 mg</td>
<td>66.6</td>
<td>58.0</td>
<td>N/A</td>
<td>25.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Brodalumab 140 mg</td>
<td>86.3</td>
<td>79.0</td>
<td>N/A</td>
<td>44.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>8.1</td>
<td>4.1</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>AMAGINE-3</td>
<td>Ustekinumab 210 mg</td>
<td>70.0</td>
<td>61.0</td>
<td>N/A</td>
<td>21.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>8.1</td>
<td>4.1</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>AMAGINE-2/3</td>
<td>Brodalumab 210 mg</td>
<td>85.1</td>
<td>80.0</td>
<td>N/A</td>
<td>36.7</td>
</tr>
<tr>
<td>108</td>
<td>AMAGINE-2/3</td>
<td>Ustekinumab 210 mg</td>
<td>69.3</td>
<td>57.0</td>
<td>N/A</td>
<td>18.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>6.0</td>
<td>4.0</td>
<td>N/A</td>
<td>0.3</td>
</tr>
</tbody>
</table>

N/A: not available.

Data from Menter A et al [13], Papp K et al [14] and Lebwohl M et al [17].
patients who received ustekinumab, with a mean decrease in baseline PASI score of 57.1% vs 29.4% respectively [12]. The efficacy, safety and patient-reported outcome findings over 5 years of brodalumab treatment have been reported recently in 181 patients who completed the phase II dose-ranging study, with a median duration of brodalumab exposure of 264 weeks [15]. For the patients who had obtained an sPGA score of ≤ 1, PASI 75 and PASI 100 by week 12, 77.3%, >60%, and ≥ 50% maintained this level of response by week 240, respectively. DLQI 0/1 was reported by more than two-thirds of patients throughout the long-term extensions. Patients with higher PASI response levels (PASI 90 to <100 or PASI 100) were more likely to have DLQI 0/1 compared with patients achieving PASI 75 to <90 [15].

Brodalumab has been found significantly more efficacious than secukinumab, ustekinumab and etanercept with regards to sustained PASI response and complete clearance at week 52 [19].

Brodalumab is also effective in bio-failure patients. Post-hoc analysis of AMAGINE-2 and AMAGINE-3 demonstrated that prior biologic use did not impact the efficacy of brodalumab, being similar in patients with or without previous exposure to biologics at week 12. PASI 100 was met by 40.9% and 39.5% of bio-naïve and bio-experienced patients at week 12, compared with 21.1% and 17% with ustekinumab (p < 0.001) [20]. In a subgroup analysis of AMAGINE-2/-3 of patients rescued with brodalumab at week 16 after experiencing inadequate response to ustekinumab, higher skin clearance rates were observed at week 52 (PASI 75, 90, 100 of 72.6, 58.1 and 36.3% vs 61.7, 25.5 and 5.4% for the patients who continued on ustekinumab, respectively) [21]. Rescue with brodalumab in ustekinumab-treated patients was effective in both those with and without prior biologic use, although higher response rates were observed in those without prior biologic use [21]. A study evaluated the efficacy of brodalumab in the treatment of moderate-to-severe psoriasis in patients who have failed anti–IL17A therapies. Of the 39 patients previously treated with secukinumab and ixekizumab, sPGA 0/1 was achieved in 71% and PASI75, 90 and 100 responses were met in 69, 44 and 28% of them, respectively [22]. A multicenter, multinational retrospective study analyzed intra-class switching among IL-17 antagonists: 7 patients were switched from secukinumab to brodalumab and 3 from ixekizumab to brodalumab, reaching PASI 75 in 66 and 57% of cases, respectively [23]. These results support brodalumab as a good treatment for bio-failure patients, including those having failed anti-IL-17A agents.

Brodalumab is also effective in erythrodermic, nail, scalp and generalized pustular psoriasis, as evidenced in a Japanese open-label, multicenter, long-term phase III study in patients with generalized pustular psoriasis and psoriatic erythroderma [24]. Besides, a case of palmoplantar pustular psoriasis successfully treated with brodalumab who had failed to adalimumab and secukinumab has been published recently [25]. IL-17 plays important roles in pustular forms of psoriasis and positivity of IL-17A, IL-17C and IL-17F has been detected in palmoplantar pustular lesions. These findings support brodalumab as a potent therapeutic option for rare and severe types of psoriasis.

As for recapture of efficacy upon retreatment, among patients in AMAGINE-1 who experienced return of the disease (sPGA ≥ 3) and were retreated with induction, 100% achieved PASI 75 response, with 96.2% and 83.5% of patients achieving PASI 90 and PASI 100 responses, respectively. Mean times to recapture PASI 75, PASI 90 and PASI 100 responses after withdrawal and retreatment with brodalumab were 29.7, 44.7 and 55.3 days, respectively [9].

The efficacy of brodalumab in psoriatic arthritis has been assessed in a phase II randomized double-blind placebo-controlled 12-week trial, followed by an open-label extension trial of up to 5 years [26]. Adults with active psoriatic arthritis were randomized to receive brodalumab at doses 140 or 280 mg or placebo. The primary endpoint was 20% improvement in American College of Rheumatology response criteria (ACR 20) at week 12. At week 12, the brodalumab 140 mg and 280 mg groups had significantly higher rates of ACR 20 than the placebo group (37 and 39% respectively vs 18%); they also had higher rates of ACR 50 (14 and 14% vs 4%). However, no significant efficacy was demonstrated for dactylitis [26]. Currently, brodalumab is not approved for treatment of psoriatic arthritis. Clinical trials for assessing its efficacy in psoriatic arthritis are ongoing (AMVISION-1 and AMVISION-2) [27].

5. Safety evaluation

5.1. Adverse events (AE)

In brodalumab clinical trials, the most commonly reported AE in the first 12 weeks were arthralgia, headache, fatigue, diarrhea, oropharyngeal pain, nausea, myalgia, injection site reactions, influenza, neutropenia and tinea infections [16,17]. Long-term, open-label extension studies did not identify new safety signals in patients treated with brodalumab. The most common AE included nasopharyngitis, upper respiratory tract infection and arthralgia (29, 24 and 20%, respectively) [12–15,28]. The exposure-adjusted rate of all AE was highest in the first year of treatment and decreased in subsequent years [12]. These results are consistent with most common AE reported in clinical trials of IL-17 antagonists (nasopharyngitis, upper respiratory tract infections, neutropenia, injection site reactions and mucocutaneous candidiasis) [29,30].

Regarding special populations, brodalumab has not been associated with higher rates of AE in the elderly [31], and no appreciable differences in overall safety have been observed between nonobese and obese patients [32].

5.1.1. Infections

Th17 cells and IL-17 play a critical role in immunity against extracellular pathogens and for the protection of skin and mucous membranes, so inhibition of IL-17A can result in an increased risk of infections, specifically mucocutaneous candidiasis [29]. In mice, IL-17A and IL-17F recruit granulocytes and induce the secretion of antimicrobial peptides from epithelial cells [33]. A systematic review of 8 studies with 4431 psoriasis or psoriatic arthritis brodalumab-treated patients showed that 177 (4%) developed Candida infections, with rates ranging from 0% to 6.7% [33]. In AMAGINE-1, Candida infections were reported in 1 patient in the 140 mg brodalumab group and 5 in the 210 mg group [16]. In AMAGINE-2 and –3 Candida infections occurred more frequently in patients receiving brodalumab compared with either placebo or ustekinumab [17]. All infections were mild to moderate in severity, did not interrupt treatment, and resolved with appropriate therapy. In
a review of Candida infections in patients treated with IL-17 inhibitors, brodalumab was found to have the highest incidence rates (4% brodalumab, 3.3% ixekizumab, 0.3% placebo) [33]. This could be explained by the potential role of IL-17RA in IL-17F and IL-17E recognition and signaling. Patients initiating anti-IL-17 therapy should be educated on the increased risk of fungal infections and should be monitored and treated appropriately. The diagnosis should always be confirmed by culture to rule out azole resistance in non-albicans Candida species [33]. In AMAGINE-1/-2/and 3 serious infections and fungal infections were observed at a higher rate in patients treated with brodalumab compared to those treated with placebo. There was one case of cryptococcal meningitis that led to discontinuation of therapy [16,17]. All patients should be screened for latent tuberculosis before the initiation of treatment. Live vaccines should be avoided in patients treated with brodalumab. IL-17 inhibition has not been linked to an increased risk of herpes zoster infections [34].

5.1.2. Neutropenia
IL-17 promotes the differentiation and migration of neutrophils to sites of infections [35]. Therefore neutropenia is another potential side effect that has been associated with all anti–IL17 therapies in different clinical trials [29,30]. Although typically mild (absolute neutrophil count >1000/mm³), transient and self-resolving, it may increase the risk of infections so patients should be monitored for signs and symptoms of infection. Neutropenia was reported in one patient receiving brodalumab 140 mg in AMAGINE-1 [16]. Neutropenia was reported more frequently during the induction phase in patients receiving brodalumab and ustekinumab in comparison to placebo [17].

5.1.3. Inflammatory bowel disease
Anti–IL–17 therapies have not been successful in the treatment of inflammatory bowel disease. Moreover, exacerbations or de novo occurrence of Crohn’s disease and ulcerative colitis were observed in clinical trials for all monoclonal antibodies targeting IL-17, and therefore patients should be screened for a personal and family history of inflammatory bowel disease before initiating an IL–17 inhibitor or IL–17 receptor antagonist [29,36]. In a phase II placebo-controlled clinical trial of brodalumab in patients with moderate-to-severe Crohn’s disease, no evidence of clinical efficacy was seen. Moreover, worsening of Crohn’s disease was observed in 24 (18%) of 130 patients, causing early termination of the clinical trial [37]. The incidence of new-onset Crohn’s diseases in patients treated with brodalumab in clinical trials was approximately less than 1:1000. One brodalumab-treated patient was withdrawn after developing Crohn’s disease [17]. Brodalumab is contraindicated in patients with active Crohn’s disease and must be used with caution in those with known inflammatory bowel disease [38].

5.1.4. Depression and suicidal behavior
In the AMAGINE-1/-2/-3 studies, rates of psychiatric AEs were low and comparable among treatment groups. Of the 3066 patients treated with brodalumab, 3 reported serious psychiatric AEs (suicide attempt, alcohol abuse, and depression). The 3 affected patients had a history of psychiatric disorders or substance abuse [16,17,39]. Psychiatric, depressive and nervous system AE rates for brodalumab were largely unchanged from the 52-week assessment at the end of the study.

HADS assessment tool was used in AMAGINE-1 to assess the prevalence of depression. The incidence and severity of depression were similar across all treatment groups before treatment was initiated. By week 12, the baseline HADS score significantly decreased in the brodalumab-treated subjects (p < 0.001) and depression was significantly lower in the group whose psoriasis had been treated with brodalumab (13 vs 32% p < 0.001) [39].

Suicidal ideation and behavior, including a total of six completed suicides, occurred in patients treated with brodalumab during clinical trials (four in psoriasis, one in rheumatoid arthritis and one in psoriatic arthritis). There were two completed suicides in the 210 mg treatment arm of AMAGINE-2, with one during the study and one in the open-label extension, compared to none in the ustekinumab of placebo treatment arm [17]. Two suicides were also completed during long-term trials of brodalumab [16]. In open-label extension studies with extended treatment over 5 years, no suicides occurred and only one case of suicidal ideation was reported [15]. Lebwoh and colleagues’ study with psychiatric AE data from five clinical trials of brodalumab included 4464 patients with 9162 patient-years of brodalumab exposure. The investigators reported a lack of evidence of a causal relationship between brodalumab and SIB [39]. Furthermore, the FDA conducted a thorough analysis of the clinical trials and didn’t found a causal or temporal relationship of suicide with brodalumab. It determined that there was no established drug-related risk of suicide or suicidal ideation [40].

5.1.5. Immunogenicity
Biologic drugs can induce immune responses in humans, with the formation of anti-drug antibodies (ADAs). ADAs may form immunocomplexes and increase the likelihood and severity of infusion reactions and alter the PK/pharmacodynamics profile [9]. Moreover, neutralizing antibodies bind to the antigen-binding site and thus prevent the attachment and effect of the monoclonal antibody, thus decreasing its efficacy. Intermittent therapy has been reported to contribute to the formation of ADA, as opposed to continuous treatment [9].

In a study evaluating the immunogenicity of brodalumab in 4461 patients -with different durations of follow-up based on treatment changes in each study design-, 2.5% of 4246 patients with a result after their first brodalumab dose tested positive for brodalumab-specific ADAs at any time after receiving brodalumab; ADAs were transient in more than half of them (1.4%). No neutralizing ADAs were detected from baseline through week 52 in 28 brodalumab-treated patients (1.8%) who developed ADAs in AMAGINE-2 and 37 brodalumab-treated patients (2.3%) in AMAGINE-3 [17]. Even though sPGA and PASI response rates were somewhat lower in patients with ADAs, there were no clear initial indications that patients with ADAs developed
tolerance to brodalumab with loss of therapeutic effect [9]. No patient had neutralizing antibodies.

5.1.6. Hypersensitivity and injection-site reactions

Data from AMAGINE-1/-2/-3 [16,17], showed no meaningful differences in hypersensitivity or injection-site reaction incidence for brodalumab versus placebo or ustekinumab. The most frequent hypersensitivity reaction was pruritus, occurring in <1% of patients receiving brodalumab and 1.6% receiving placebo. Injection-site reactions (pain, erythema and or bruising) were experienced by 1.8% of brodalumab-treated patients, 2% of ustekinumab-treated patients, and 1.3% of placebo-treated patients [9]. Of note is the lower frequency of injection-site reactions with brodalumab, administered every two weeks, compared to ustekinumab.

5.1.7. Major adverse cardiovascular events

A meta-analysis of randomized controlled trials of biologic therapies -including ixekizumab and secukinumab but not brodalumab- concluded that there was no significant impact of the use of biologic therapies on the risk of major adverse cardiovascular events in adult patients with plaque psoriasis over short term [41].

In the AMAGINE-2/3 studies, 3 deaths from cardiac arrest occurred: one in a patient who received brodalumab 210 mg continuously, one in a patient who had received 140 mg of brodalumab Q2W followed by 210 mg and another one in the ustekinumab group. After exposure, one death from cardiomyopathy occurred in a patient who had received 140 mg of brodalumab Q2W followed by 210 mg, 87 days after the last dose [17].

5.1.8. Paradoxical reactions

Three cases of paradoxical response in the form of pustulosis have been reported with brodalumab, all of them after switching from secukinumab due to loss of therapeutic effectivity [42,43]. Sadik and colleagues have hypothesized that patients losing responsiveness to the therapeutic neutralization of IL17A become prone to paradoxical activation of neutrophils under IL-17RA inhibition through brodalumab [42].

5.2. Comparison of safety with other drugs

Two meta-analysis comparing the efficacy and safety data of IL-17 and IL-23 inhibitors showed significantly higher rates of AE for IL-17 inhibitors [29,44]. This data is supported by a network meta-analysis evaluating the short-term efficacy and safety of IL-17, IL-12/23 and IL-23 inhibitors [45]. Bai and colleagues found out that IL-17 inhibitors were less tolerant than other biological agents, with ixekizumab associating a greater likelihood of causing serious AE and discontinuations [45].

In clinical trials, the AE profile of brodalumab at week 12 was similar to that of ustekinumab [16,17,20,21]. In a subgroup analysis of AMAGINE-2/-3 with patients rescued with brodalumab at week 16 after experiencing inadequate response to ustekinumab, the overall exposure-adjusted AE rate was similar between treatment groups although rates of grade ≥ 3 and serious AE were higher in patients receiving continuous ustekinumab therapy compared with rates of grade ≥ 3 and serious AE in ustekinumab-treated patients rescued with brodalumab [21]. Rates of psychiatric disorders were higher with ustekinumab than with brodalumab through week 52 (9.3% vs 7.6%, respectively). Depression and nervous system AE rates were also similar with brodalumab and ustekinumab [39].

6. Conclusion

Brodalumab, a human monoclonal IgG2 antibody that targets IL-17 receptor A (IL-17RA), is one of the most efficacious agents approved for treatment of moderate to severe psoriasis, with a very rapid onset of effect, high rates of complete clearance and long term sustainability of response. The safety profile of brodalumab in clinical trials is not affected by age and weight, is comparable with that of ustekinumab in head-to-head clinical trials and is consistent with those of currently available IL-17A antagonists. Mucocutaneous Candida infections have been reported to occur in 4% of patients in clinical trials, but are mild or moderate in severity, respond to topical or oral treatment, and usually do not require discontinuation of brodalumab. Neutropenia can occur, but it is infrequent and typically mild, and does not require laboratory monitoring. ADAs have been reported to occur in approximately 2% of patients, and have not been found to be neutralizing in any case or to determine loss of therapeutic effect. Injection-site reactions occur in less than 2% of patients. Paradoxical pustular reactions have been reported on rare occasions. Brodalumab is contraindicated in patients with active Crohn’s disease and must be used with caution in those with known inflammatory bowel disease. Suicidal ideation and behavior have been reported in clinical trials of brodalumab, but there is no evidence of causality.

7. Expert opinion

When selecting an appropriate therapy for moderate-to-severe psoriasis several factors must be considered, including speed of onset and durability of response.

The unique mechanism of action of brodalumab entails a broader blockade of IL-17 isoforms binding IL-17RA, which may confer a potential advantage over the more targeted approach of other IL-17A inhibitors [29,46]. Brodalumab has the fastest onset of action to date, with a median time to achieve PASI 50 of less than 2 weeks (4 weeks for PASI 75) [46,47], and complete clearance is more likely with brodalumab than with other biologic drugs [19]. Complete (PASI 100) or almost complete (PASI 90) clearance of psoriasis is associated with greater improvements in DLQI [48], and drugs that maintain this improvement over long periods have a long-term positive effect on health-related quality of life in patients with psoriasis [49]. The increased likelihood of achieving complete skin clearance with brodalumab may allow further improvement of patient quality of life. In a network meta-analysis, brodalumab -the only FDA-approved biologic for psoriasis that has PASI 100 as a primary endpoint- ranked first in achieving PASI 100 at 12 weeks [45]. But broader blockade of not only IL-17A but other important cytokines such as IL-17 F and IL-17E entail a potential higher risk of AEs concerning Candida infections and maintenance of bowel mucosa integrity. An increased
susceptibility to Candida infections in brodalumab-treated patients and its contraindication in patients with Crohn’s disease support this concern.

Brodalumab treatment might be advantageous in patients with previous exposure or failure to other biological treatments. The mechanisms underlying loss of efficacy of biological treatments in psoriasis are multifactorial and not completely understood [50]. Registries such as PSOLAR [51] and BABDIR [52] have shown that discontinuation of previous biologic therapies may be predictive of lower drug survival with other biologics. However, brodalumab efficacy doesn’t seem to be affected by previous biologic exposure, even in patients treated with other IL-17 inhibitors [20,21,23]. Furthermore, maintenance of brodalumab efficacy has been observed through week 264 [15].

Although new psoriasis treatments specifically targeting IL-23 can achieve prolonged clinical remission upon discontinuation of treatment, recurrence of psoriasis upon withdrawal of systemic therapies is the norm. This could be explained at least in part by formation of a site-specific disease memory during active disease that is maintained during remission. Specifically, tissue resident memory T cells persisting at the site of psoriasis plaques have been implicated in recurrence of psoriasis [53]. CD8+ T cells producing IL-17 and CD4+ T cells producing IL-22 have been found in resolved psoriatic lesions [54].

The interruption of brodalumab treatment upon clinical trial discontinuation provided a unique opportunity to assess persistence of its therapeutic effect. A multicenter retrospective study evaluated the outcome of brodalumab-treated patients who had to interrupt treatment abruptly and analyzed the pattern of psoriasis recurrence and the time to relapse [55]. All 77 patients relapsed within 9 months with a median time to relapse of 6 to 7 weeks. Interestingly, 5% of patients presented with severe forms of psoriasis and 10% developed symptoms suggestive of psoriatic arthritis. Gaffen and colleagues demonstrated that IL-17A-induced signaling strength correlated with cell surface expression levels of IL-17RA, and high levels of the receptor were required for effective responses to IL-17A. In addition, IL-17RA limits signaling by receptor-mediated internalization of IL-17A, as surface expression of IL-17RA decreases after IL-17A binding [4]. This could explain the rebound effect observed upon treatment withdrawal, as accumulated IL-17A would be ready for binding to the now available IL-17RA, together with a rapid stimulation of effector Th17 cells.

A potential cause of concern for clinicians prescribing brodalumab are the confirmed suicides and suicidal ideation and behavior (SIB) in clinical trials, which led to the inclusion of a black box warning in the brodalumab U.S. label and implementation of a post-marketing risk management program, even though a critical review of trial data by the FDA found no causal association between brodalumab and SIB. Only three of the four suicides in the psoriasis development program were adjudicated by an independent board. Case 1 lost his disability income as brodalumab gave him a PASI 100 and faced serious financial problems. Case 2 was about to be incarcerated. Case 3 had a history of depression and anxiety and had reported stress and isolation due to work relocation. All three suicides occurred at one center (Mount Sinai Medical Center, New York, NY, USA) out of 390 research sites worldwide [39]. Most clinical trials of systemic drugs for moderate-to-severe psoriasis have specific exclusion criteria for psychiatric disorders or substance abuse. In the brodalumab studies, exclusion criteria were limited, allowing patients with SIB risk factors at baseline to participate. All the 18 committee members voted in favor of an FDA approval, though 14 out of the 18 also voted for implementing the additional drug labeling information and post-marketing risk management obligations for SIB [40].

Higher rates of depression, anxiety, self-harm, and suicidal ideation have been detected in patients with psoriasis compared with the general population or individuals with other dermatologic conditions [2]. Therefore, it is not surprising that SIB events occurred in the brodalumab trials and that most patients with SIB events during the brodalumab trials had a history of predisposing risk factors. Despite the history of psychiatric disorders/SIB risk factors in brodalumab psoriasis clinical studies, the serious psychiatric AE rates over long-term treatment were in a range comparable to what has been reported in trials for other psoriasis treatments [39]. Data from five clinical trials did not reveal a causal relationship between suicidality and brodalumab treatment [19].

Underlying inflammatory mediators that are upregulated in psoriasis may contribute to high rates of depression. Elevated levels of pro-inflammatory cytokines such as TNF alpha, IL-6, and IL-17A have been found in both psoriasis and psychiatric disorders including depression and post-traumatic stress disorder [39,40,56,57]. Indirect action of brodalumab on the brain is possible, but the brain-blood barrier limits cerebrospinal fluid concentrations of IgG to 1% of serum levels [57]. Whether these alterations may eventually lead to suicidal behavior in humans has not been determined. Interestingly, in mice models, IL-17RA expression in the brain has been detected in the absence of inflammation, and behavior modifications have been observed following disturbance of IL-17 signaling. Interestingly, brain Th17 cells increase with depressive-like behavior and blockade of Th17 signaling with anti–IL17A antibodies reduced depression-like behavior [56]. Furthermore, a hypothetical increase of depression and suicidality related to brodalumab would be paradoxical considering that neuroinflammation in psoriasis is known to promote depression [57].

In summary, brodalumab is a highly efficacious and comparably safe therapeutic choice in patients with moderate to severe psoriasis, especially when rapid control of the disease is desired. Infections, especially mucocutaneous candidiasis, must be monitored and adequately treated in patients receiving brodalumab, as well as any IL-17A antagonists. Brodalumab is contraindicated in patients with active Crohn’s disease and clinically important active infections, and the risk and benefit of brodalumab treatment should be weighed in patients with a history of depression or suicidal ideation.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.


• Highly relevant paper discussing IL-17 role in psoriasis.


• Open-label extension study with long-term efficacy and safety results of brodalumab.


• Key phase II brodalumab trial.


• Key phase III brodalumab trial.


• Phase III studies showing superiority of brodalumab compared to ustekinumab.


• Study analyzing efficacy of brodalumab in patients with previous biologic use.


• Systematic review and meta-analysis of brodalumab’s safety and efficacy.


• Review of Candida infections in IL-17 inhibitor-treated patients.

• Expert review discussing suicidal behavior and IL-17 inhibitors.
Original article:
Safety of brodalumab for the treatment of psoriasis

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