Introduction

Brodalumab is a recombinant, fully human monoclonal antibody (IgG2) which binds with high affinity to the interleukin (IL) 17 receptor A (IL17R). Brodalumab is now licensed and approved for the treatment of moderate-to-severe chronic plaque psoriasis in North America and Europe. As the third to market in this class of agents targeting IL-17, we review its place in the expanding armamentarium of cytokine-directed therapies for patients with severe psoriasis. We suggest that brodalumab is likely to be considered in those patients requiring rapid control of disease, where there is no known history of depression or suicidal ideation.

Keywords: immune-mediated inflammatory disease, psoriasis, psoriatic arthritis.

Citation

Foulkes AC, Warren RB. Brodalumab in psoriasis: evidence to date and clinical potential. Drugs in Context 2019; 8: 212570. DOI: 10.7573/dic.212570

Abstract

Brodalumab is a recombinant, fully human monoclonal antibody (IgG2) which binds with high affinity to the interleukin (IL) 17 receptor A (IL17R). Brodalumab is now licensed and approved for the treatment of moderate-to-severe chronic plaque psoriasis in North America and Europe. As the third to market in this class of agents targeting IL-17, we review its place in the expanding armamentarium of cytokine-directed therapies for patients with severe psoriasis. Brodalumab is a highly efficacious therapy for psoriasis, whose mechanism of action is separate from other treatments targeting IL-17. Its use is associated with rapid control of the disease. We suggest that brodalumab is likely to be considered in those patients requiring rapid control of disease, where there is no known history of depression or suicidal ideation.
variety of organs. The role of IL-17A has been extensively investigated in immune-mediated inflammatory diseases, and the central role of IL-17A in the pathogenesis of psoriasis and across immune-mediated inflammatory disease has been reviewed extensively with a clear overview provided by Brembilla and colleagues.

**IL-17C**

IL-17C is a member of the IL-17 family, differing from IL-17A and IL-17F in that it is predominantly produced by non-immune epithelial cells, including keratinocytes. IL-17C demonstrates commonalities with IL-17A and IL-17F in that it is proinflammatory; it is overexpressed in lesional psoriatic skin and neutralisation of IL-17C inhibited cutaneous inflammation in a psoriasis-like mouse skin inflammation model.

**IL-17F**

IL-17F has the highest homology with IL-17A and is expressed by the same immune cell types as IL-17A, including Th17 cells. It is overexpressed in psoriatic lesional skin. IL-17F is considered to act in a similar manner to IL-17A but with its effects less potent. A drug that inhibits IL17A and F is in development with promising results shown.

**IL-17 receptor**

IL-17 signals via the IL-17 receptor family members. There are five IL-17 receptor subunits (IL-17RA-RE). IL-17 cytokines signal via receptors composed of combinations of these subunits. IL-17A and IL-17F bind to the same complex of IL-17RA and IL-17RC. IL-17RA is widely expressed but other IL-17R family receptors are expressed by more restricted cell types. Upon ligand binding, IL-17 receptors uniquely engage and utilise a cytoplasmic protein, ACT1, to the receptor complex to enact downstream signalling pathways.

**Brodalumab**

Brodalumab was developed by Amgen and AstraZeneca. In May 2015, Amgen discontinued development due to suicidality seen during the clinical trial programme (see later), leaving further development to AstraZeneca. 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 the Europe (Europe trade name Kyntheum).

**Brodalumab clinical efficacy data**

**AMAGINE-1**

AMAGINE-1 was a phase III, double-blind, placebo-controlled study of adult patients with chronic plaque psoriasis designed to evaluate the efficacy of brodalumab. Patients with stable plaque psoriasis for a duration of six months or more, with a Psoriasis Area and Severity Index (PASI) of 12 or more, a static physician’s global assessment (sPGA) score of 3 or higher (scores range from 0 [clear skin] to 5 [severe disease]), and involvement of 10% or more of the body-surface area who met inclusion criteria were recruited between 2012 and 2014 in the United States, Canada and Europe. The study design is summarised in Figure 1. Patients were randomised to brodalumab (210 or 140 mg) or placebo at week 1, 2, 4, 6, 8 and 10. Co-primary end points were the percentage of patients with ≥75% improvement in PASI score from that of baseline (PASI 75) and sPGA response of 0 or 1 at week 12. At week 12, patients
who received brodalumab and responded (sPGA of 0 or 1) were rerandomised to receive brodalumab or placebo; patients who did not respond (sPGA≥2) received brodalumab 210 mg every two weeks.

**AMAGINE-1 Results**: There were 661 patients randomised, 633 of whom completed the 12-week induction phase (212 receiving brodalumab 210 mg every two weeks, 212 brodalumab 140 mg every two weeks, 209 receiving placebo) and 558 remained until week 52.

At week 12, PASI 75/90/100 response rates for brodalumab at 210 mg dose, 140 mg dose and placebo were 83%/70%/42%, 60%/43%/23% and 3%/1%/1%, respectively (see Figure 2). The corresponding percentages for sPGA 0 or 1 were 76, 54 and 1% for the brodalumab arms and placebo.

At week 52, PASI 90/100 outcomes in those who received 210 and 140 mg in the induction and withdrawal phases were 78%/68% and 67%/44%, respectively. The corresponding percentages for sPGA 0 or 1 were 83 and 70% for those who received 210 and 140 mg doses in the induction phase compared to 0 and 5% of those who were re-randomised to placebo, respectively.

At week 12, patients who were withdrawn from treatment and rerandomised to placebo then qualified for retreatment with their induction dose of brodalumab if they had return of disease (sPGA≥3) after week 16. Amongst these patients, 97% receiving 210 mg and 84% receiving 140 mg recaptured sPGA 0 or 1 after 12 weeks of retreatment.

**AMAGINE-2 and AMAGINE-3**

AMAGINE-2 and AMAGINE-3 were two large multicentre, randomised, double-blind, placebo-controlled, phase III trials, designed to compare the efficacy of brodalumab therapy with ustekinumab.11 Recruited between 2012 and 2014 across 142 worldwide sites, adults with stable chronic plaque psoriasis (using the same severity inclusion criteria as AMAGINE-1) were recruited to the study, whose design was complex. As in AMAGINE-1, there was a 12-week induction phase and a 40-week maintenance phase. During the induction phase, patients were randomly assigned to receive either brodalumab (140 or 210 mg on day 1 and weeks 1, 2, 4, 6, 8 and 10) ustekinumab (as per label), or placebo (as double-blind, double-dummy injections).

At week 12, patients who were originally assigned to receive brodalumab underwent re-randomisation to different doses of brodalumab and patients who received placebo were switched to brodalumab 210 mg every two weeks. Patients who were originally randomly assigned to receive ustekinumab continued to receive ustekinumab every 12 weeks until week 52, when they could enter a long-term extension of brodalumab 210 mg every 2 weeks. Blinding was maintained through week 52.

From week 16, those rerandomised to receive brodalumab and those who received ustekinumab who did not respond (sPGA≥2) received rescue treatment (brodalumab 210 mg every two weeks). If the response to rescue therapy was not achieved (patients who had persistent sPGA scores ≥3 over at least a 4-week period whilst receiving continuous rescue treatment for at least 12 weeks), treatment with study drug was discontinued.

The co-primary endpoints were PASI 75 response and sPGA score 0 or 1 at week 12 comparing brodalumab with placebo and PASI 100 response at week 12 comparing brodalumab with ustekinumab.

**AMAGINE-2 and AMAGINE-3 results**: The demographic and clinical characteristics of the patients at baseline were balanced across the treatment groups. In AMAGINE-2, 1601 (87%) patients completed week 52 and in AMAGINE-3, 1656 (88%) completed week 52 of the study.

At week 12, PASI 75 response for brodalumab at 210 mg dose were 86 and 85% (AMAGINE-2, n=528 (612), AMAGINE-3, n=531 (624)), 140 mg dose 67 and 69% and for placebo 8 and 6%, see Figure 3. PASI 100 response rates at week 12 were 44 versus 22% for AMAGINE-2 and 37 versus 19% for AMAGINE-3 for brodalumab and ustekinumab, respectively. Efficacy of brodalumab was comparable across subgroups defined by race or ethnicity.12

The percentages for sPGA 0 or 1 for AMAGINE-2 were 79 and 58% for brodalumab 210 and 140 mg doses, 61% for ustekinumab and 4% for placebo, and for AMAGINE-3 80 and 60% for brodalumab 210 and 140 mg doses, 57% for ustekinumab and 4% for placebo.

At week 52, 63% of those who received 210 mg dose and 43% of those who received 140 mg of brodalumab maintained sPGA 0 or 1 in AMAGINE-2 and 61% of those who received 210 mg dose and 45% of those who received 140 mg dose of brodalumab maintained sPGA 0 or 1 in AMAGINE-3. At week 52, 94% of patients who switched from placebo to brodalumab 210 mg dose and 91% of those who switched from ustekinumab to brodalumab 210 mg dose reached PASI 75 in AMAGINE-2; 93 and 82% of corresponding patients reached PASI 75 in AMAGINE-3.

**Quality of life**

The *Psoriasis Symptom Inventory* (PSI) is a validated, eight-item, psoriasis-specific questionnaire administered daily that rates the severity of signs and symptoms in the last 24 hours from 0 to 4, for a total score from 0 (best) to 32 (worst). This patient-reported outcome measure was monitored in AMAGINE-1, AMAGINE-2 and AMAGINE-3, with response categorised as a reduction of ≤8 points from baseline score, with each item rated as 0 (not at all) or 1 (mild).

In AMAGINE-1, a total of 61% of patients randomised to 210 mg and 53% of patients randomised to 140 mg brodalumab
Figure 2. AMAGINE-1 Psoriasis Area and Severity Index (PASI) responses through week 12. Percentages of patients with (a) ≥ 75% improvement in PASI (PASI 75), (b) PASI 90 and (c) PASI 100 responses over time in patients randomized to brodalumab (140 or 210 mg) or placebo every 2 weeks (Q2W) for 12 weeks. Reproduced with permission.¹⁰
achieved a PSI response in comparison to 4% who received placebo at 12 weeks. In AMAGINE-2 and AMAGINE-3, 68 and 61% of patients receiving brodalumab 210 mg dosing achieved a PSI response in comparison to 55 and 52% of those receiving ustekinumab and 6 and 7% of those receiving placebo at week 12. The Dermatology Life Quality Index (DLQI) was not reported.

In AMAGINE-2/-3, the proportions of patients treated with brodalumab achieving a total DLQI score of 0 or 1 at week 12 were 60.4% in biologic-naïve (versus 44.7% in patients treated with ustekinumab) and 58.4% in biologic-experienced patients (versus 42.1% in ustekinumab patients).

When reporting the PSI, patients rate the itch during the previous 24 hours from 0 (not at all) to 4 (very severe). Gottlieb and colleagues\textsuperscript{13} analysed PSI itch scores from across AMAGINE-1/-2/-3 and reported that this improved with brodalumab 140 and 210 mg doses, starting at week 2 and sustained through week 12. The PSI itch response associated with brodalumab 210 mg was greater than that of ustekinumab through to week 12, and at week 52 for patients who remained on constant treatment with either therapy after re-randomisation.\textsuperscript{13}

### Rapidity of onset

In AMAGINE-1, the median time median times to both PASI 75 and sPGA 0/1 were 4 and 6 weeks in patients randomised to brodalumab 210 and 140 mg, respectively.\textsuperscript{10} Blauvelt and colleagues reported the rapidity of onset of efficacy with brodalumab, analysing data from AMAGINE-2 and AMAGINE-3\textsuperscript{14} with an estimated time for 25% of patients to achieve PASI 75 as 2.1 weeks for brodalumab, compared to 4.8 weeks for ustekinumab.\textsuperscript{15}
Use in biologic naïve versus biologic experienced patients

Sequencing of biologic therapies based on prior biologic exposure is an important clinical scenario where evidence is lacking. Papp et al. evaluated the impact of prior biologic therapy on the efficacy of brodalumab, analysing data from AMAGINE-2 and AMAGINE-3. They reported that prior biologic use did not impact the efficacy of brodalumab, which was similar in patients with or without previous exposure to biologics at week 12. Further analysis showed a PASI 75 for patients with prior successful biologic therapy as 86.3 versus 81.3% for those with prior treatment failure. Patients who had been rescued with brodalumab at week 16 after experiencing inadequate response to ustekinumab had higher skin clearance rates at week 52 (73, 58 and 36% achieved psoriasis area and severity index 75, 90 and 100% improvement, respectively) than patients who continued on ustekinumab (62, 26 and 5%, respectively).16

Brodalumab safety data

Amgen and AstraZeneca halted the development programme in May 2015 due to the emergence of a suicide signal. A total of six completed suicides in all brodalumab clinical trials were reported (four in psoriasis, one in rheumatoid arthritis and one in psoriatic arthritis); however, one suicide was later adjudicated as indeterminate due to the possible accidental drug overdose.

The US Food and Drug Administration mandated additional suicidal ideation and behaviour evaluations across the ongoing brodalumab psoriasis trial programme. Patients with psoriasis report a higher level of anxiety and depression, suicidal ideation and self-harm compared to the general population and patients with other dermatological diseases.17

All subjects who completed suicide in the psoriasis program were treated with brodalumab in the long-term open-label phases of treatment. In case 1, a 58-year-old male completed suicide 329 days after beginning treatment with brodalumab. There was no known psychiatric history but financial stressors were present. In case 2, a 39-year-old male completed suicide 140 days after his first dose of brodalumab. This patient had a history of depression and anxiety and had reported stress and isolation due to relocation. In case 4, a 56-year-old male completed suicide 845 days after commencing brodalumab. This patient had a history of depression and suicide was completed with a mixed overdose. On the recommendation of the US Food and Drug Administration, additional evaluations were implemented across the brodalumab programme and the Columbia Classification Algorithm for Suicide Assessment was performed to independently adjudicate suicides. Case 4 was ruled a suicide by the coroner but was considered indeterminate in the Columbia Classification Algorithm for Suicide Assessment review.

Lebwohl and colleagues collated psychiatric adverse event data from five clinical trials of brodalumab. In their analysis of 4464 patients with 9162 patient-years of brodalumab exposure, they reported a lack of evidence of a causal relationship between brodalumab and suicidal ideation and behaviour. As a precaution, brodalumab in the United States is available only through a risk evaluation and mitigation strategy (REMS) program with which prescribers and pharmacies must be certified.

Their discussion highlighted important aspects of clinical trial design, namely the inclusion and exclusion criteria in relationship to the general population, commenting that most clinical trials of systemic drugs for psoriasis have specific exclusion criteria for psychiatric disorders or substance abuse, making data hard to interpret for the population of patients in whom they will subsequently be used.

Inflammatory bowel disease

There is a significant genetic association between psoriasis and inflammatory bowel disease. Despite the successes of anti-IL-17 therapies in immune-mediated inflammatory disorders, these therapies have not been successful in the treatment of inflammatory bowel disease. Conversely, flares of existing inflammatory bowel disease and reports of new-onset disease have been reported during clinical trials of their use. For patients with Crohn’s disease, no evidence of clinical efficacy was seen with brodalumab therapy and furthermore, a disproportionate number of cases of worsening of Crohn’s disease were observed in the active treatment groups compared with placebo and thus the study was terminated early. There were no reports of inflammatory bowel disease during AMAGINE-1. One case of Crohn’s disease was reported during AMAGINE-2. Brodalumab is contraindicated in active Crohn’s disease. A review of the management of patients with psoriasis and inflammatory bowel disease concluded that brodalumab, amongst the treatments targeting the IL-17 pathway, must be used in caution in those with known inflammatory bowel disease.

Neutropenia

IL-17 expression results in the recruitment and sustained presence of neutrophils. Anti-IL-17 therapies have been associated with neutropenia throughout their clinical trial programmes. Neutropenia was reported in one patient receiving brodalumab 140 mg in AMAGINE-1. Neutropenia was reported more frequently during the induction phase in patients receiving brodalumab and ustekinumab in comparison to placebo in AMAGINE-2 and AMAGINE-3.
The cases of neutropenia were not associated with serious infection, and most were deemed mild (absolutely neutrophil count >1000 per mm$^3$).\textsuperscript{31}

**Candida infection**

IL-17 is critical for immunity against extracellular pathogens, including yeasts. Defects in IL-17 axis genes are associated with chronic mucocutaneous candidiasis. Candida infections were reported in nine patients (three in placebo, one in 140 mg and five in 210 mg) in AMAGINE-1.\textsuperscript{10} Candida infections occurred more frequently in patients receiving brodalumab in comparison to either ustekinumab or placebo in both the induction and maintenance phases of AMAGINE-2 and AMAGINE-3.\textsuperscript{31} All the candida infections were graded as mild or moderate, and none were systemic. A review of candida infections in patients with psoriasis and psoriatic arthritis treated with interleukin-17 inhibitors summarises that IL-17 blockade presents only a small increase in risk for the development of candidiasis when compared with infection rates in patients with controlled psoriasis and psoriatic arthritis (PsA) treated with ustekinumab, etanercept or placebo.\textsuperscript{22} The authors provide algorithms for screening and treatment of patients with potential candida infection.\textsuperscript{23}

**Serious infection**

At present, data from clinical trials are available for the evaluation of the safety of brodalumab with limited real-world use. The risk of serious infection in patients treated with biologic therapies can be difficult to ascertain due to the lack of powering of clinical trials for these outcomes.\textsuperscript{24} Prospective registry data evaluating the risk of serious infection in patients treated with biologic therapies has not yet evaluated treatments targeting IL-17 pathway.\textsuperscript{25} Through week 52, the rates of serious infectious episodes were 1.0 (AMAGINE-2) and 1.3 (AMAGINE-3) per 100 patient-years of exposure to brodalumab.

**Major adverse cardiovascular events**

Concerns have been raised regarding the incidence of major adverse cardiovascular events (MACE) in patients treated with biologic therapy for psoriasis. A meta-analysis of randomised controlled trials of biologic therapies concluded that there was no significant impact of the use of biologic therapies on the risk of MACE in adult patients with plaque psoriasis over the short term.\textsuperscript{26} This study evaluated secukinumab and ixekizumab but not brodalumab. In brodalumab-treated patients in the AMAGINE programme, one death from stroke occurred during the induction phase in AMAGINE-2, in a patient in the 210-mg brodalumab group, 20 days after the last dose, one death occurred from cardiac arrest in a patient who received 210 mg of brodalumab continuously throughout the study and in the AMAGINE-3 study, one from cardiac arrest (in a patient who had received 140 mg of brodalumab every 2 weeks followed by 210 mg).

**Brodalumab immunogenicity**

The use of biologic therapies has been associated with the development of an immunologic response, including the formation of antibodies known as antidrug antibodies. Antidrug antibodies may be neutralising, which bind to the antigen binding site, preventing the monoclonal antibody attaching and thus impacting efficacy, or non-neutralising, binding to the antibody without interfering with it attaching to its target. The mechanism of antidrug antibodies is poorly understood. Fully human antibodies are derived from human gene sequences and are the least immunogenic. A systematic review of the literature to determine if IL-17 inhibitors are prone to develop antidrug antibodies and evaluate how the efficacy of treatment is influenced reported no neutralising antibodies with the administration of brodalumab.\textsuperscript{27} Neutralising antibodies were detected in 2 of 14 papers included in the systematic review and neither of these was with the administration of brodalumab. Non-neutralising antidrug brodalumab antibodies were detected during the period from baseline through week 52 in 28 brodalumab-treated patients (1.8%) in the AMAGINE-2 study and in 37 brodalumab-treated patients (2.3%) in the AMAGINE-3 study.\textsuperscript{31} None were associated with a loss of efficacy or adverse events. No patient had neutralising antibodies.

**Brodalumab and clinical efficacy in related disorders**

The efficacy of brodalumab has been assessed in related immune-mediated inflammatory disorders. As discussed earlier, the phase II programme of brodalumab for Crohn's disease was terminated early due to the worsening of disease in active treatment groups compared with placebo.\textsuperscript{20} The efficacy of brodalumab in psoriatic arthritis has been assessed in a randomised double-blind placebo-controlled 12-week trial (followed by an open-label extension trial, up to 5 years).\textsuperscript{28} Adults with active psoriatic arthritis (on the basis of the Classification Criteria for Psoriatic Arthritis) were randomised to receive brodalumab at doses of 140 or 280 mg or placebo by subcutaneous injection on day 1 and at weeks 1, 2, 4, 6, 8 and 10. The primary end point was 20% improvement in American College of Rheumatology response criteria (ACR 20) at week 12. At week 12, the brodalumab 140 and 280-mg groups had significantly higher rates of ACR 20 than the placebo group (37 and 39%, respectively, versus 18%); they also had higher rates of 50% improvement (ACR 50) (14 and 14% versus 4%). Rates of 70% improvement were not significantly higher in the brodalumab groups.
Clinical use of brodalumab

Consideration of the clinical use of brodalumab requires further knowledge than the clinical trial data, and it requires an understanding of national and local approvals, cost in the context of other currently available treatments, which include recently approved agent(s) which target the p19 molecule of IL-23. Brodalumab is the third in a class of anti-IL-17 agents, following secukinumab and ixekizumab. Secukinumab is a recombinant, high-affinity, fully human IgG1κ monoclonal antibody that selectively binds to IL-17A, 29 and ixekizumab is a humanised monoclonal antibody IgG that selectively binds to IL-17A. 30 Table 1 compares brodalumab with secukinumab and ixekizumab.

Summary

Despite the licensed, approved biologic agents who have revolutionised clinicians’ treatment of patients with severe disease, complexities in treatment remain. These include the selection of first-line and subsequent appropriate sequencing of biologic agents.

Brodalumab is a highly efficacious therapy for psoriasis. Its use is associated with rapid control of disease. The mechanism of action of brodalumab is unique amongst the treatments targeting IL-17, in the blockade of IL-17R. This broader action may, in theory, confer an advantage over treatments blocking IL-17A through blockade of additional members of the IL-17 cytokine family, including IL-17C and IL-17F. However, there is also a theoretical risk that withdrawal of therapy could lead to a rebound effect, hypothesised via rapid stimulation of effector Th17 cells responsible for psoriasis recurrence. 31

Treatment selection relies heavily on national and local approvals, but patient factors including the presence of absence of comorbidities are also key. Although real-world registry data such as that of the British Association of Dermatologists’ Biologic Interventions Register (BADBIR), 32 PsoBest 33 and BIOBADADERM 34 may assist prescribing physicians in their discussion of treatment selection with patients, national guidelines such as these are not prescriptive. Thus, the use of brodalumab, amongst the licensed approval available therapies, has uncertainties.

We suggest that brodalumab is likely to be considered in those patients with severe disease, eligible for biologic therapy, in particular where rapid control is favourable. Brodalumab is licensed and approved for the first-line use. Clinical data support its consideration for subsequent line therapy, including in patients where treatments targeting IL-17A have already been used. Until more pharmacovigilance data are available, it may perhaps not compete in the first-line space. With the launch of agents targeting IL-23, brodalumab will have significant competition and additionally we have yet to see the impact of adalimumab biosimilar agents.

There are of course other factors which come into play with a wide range of biologic choices available. Brodalumab is likely to be avoided in those with known inflammatory bowel disease
and where there is a history of depression or suicidal ideation. Although brodalumab may be considered less favourably at present in those with confirmed psoriatic arthritis because there is neither a license nor a large-scale Phase III study of its use, there is evidence that it works in this important comorbidity.

Treatment selection for patients with severe psoriasis remains highly complex, even for the expert prescriber, with changes in the field including the advent of biosimilar agents and a pipeline of agents in later phases of development. Prescribing clinicians will need to keeping abreast of changes to continue to optimise treatment selection for their patients. Brodalumab adds to our highly effective available therapeutic options, with a unique place amongst licensed approved therapies, and as real-world registry data are collected, we will be able to evaluate its use in more detail over coming years.

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