

Clinical potential of brodalumab in the management of psoriasis: the evidence to date

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Abstract: Brodalumab is an anti-IL-17 receptor monoclonal antibody currently in development for the treatment of moderate-to-severe plaque psoriasis. With many systemic psoriasis therapies to choose from, and several newer agents in development, physicians need up to date evidence for the use of these drugs. A PubMed search was conducted through August 1, 2014 to identify randomized controlled trials and systematic reviews of brodalumab for the treatment of psoriasis. Results of Phase I and II trials, as well as a few smaller studies, have provided promising data on efficacy, safety, health-related quality of life, pharmacokinetics, and changes in lesional skin. Early Phase III data continue to support the use of brodalumab as a potentially valuable option for the treatment of psoriasis.

Keywords: anti-interleukin-17, psoriasis, biologic agents, efficacy, safety, systemic therapy

Introduction

Psoriasis is a chronic skin disease affecting nearly 3% of the population, characterized by red, scaly, itchy, plaques on the skin. Advances in the treatment of psoriasis have led to the availability of several newer systemic treatments including oral and biological agents. Traditional oral systemic therapies such as methotrexate, retinoids, and cyclosporine have been used by dermatologists for years, however these treatments have limited efficacy and are associated with safety issues.¹ The development of new biological therapies provides more effective and safer alternatives to older oral psoriasis treatment options. Biologics have allowed for long-term use of treatment without the need to incorporate practices such as rotational or intermittent therapy to avoid and decrease toxicities.¹ Current psoriasis treatment guidelines recommend that systemic agents, including biologics, are appropriate treatments when topical agents fail to adequately control disease.²

Emphasis on newer psoriasis therapies has largely been on biological agents. Early biologic treatments were categorized into two general classes, TNF- α and T-cell inhibitors, according to their mechanism of action. Currently there are three approved TNF- α inhibitors approved for the treatment of psoriasis including infliximab, adalimumab, and etanercept, and while all three block TNF- α , they differ in structure and exact mechanism of action. Ultimately, their blockage of TNF- α results in reversal of the epidermal hyperplasia and cutaneous inflammation characteristic of psoriatic plaques through the reduction in dendritic cell-mediated T cell activation, and cytokine, growth factor, and chemokine production by multiple cell types including lymphocytes, neutrophils, dendritic cells, and keratinocytes.³ Later, ustekinumab, a human IL 12/23 monoclonal antibody was approved for the treatment of psoriasis.

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Ustekinumab specifically binds the p40 subunit of IL-12/23, inhibiting IL-12 and IL-23 and the Th1 (IL-12) and Th17 (IL-23) inflammatory pathways.⁴

While currently approved biologics provide advantages in efficacy and safety compared to traditional systemic agents, newer agents in development strive to improve efficacy even further with, ideally, a lower risk profile. One potential approach is targeting a cytokine further downstream (though the feedback loops inherent in the pathogenesis may make the concept of “downstream” cytokines an oversimplification). While psoriasis was once thought to be a Th1-mediated disease, which is the target of TNF- α agents, a subtype of helper T cells known as Th17 T cells, which secrete IL-17, is now proposed to play a key role in the pathogenesis of psoriasis. It is currently thought that an unknown antigen or environmental trigger activates natural killer T-cells, plasmacytoid, dendritic cells, and macrophages to secrete TNF- α , IL-1 β , and IFN- α in individuals who are genetically susceptible.^{5,6} These mediators then activate myeloid dendritic cells to secrete IL-23, which acts as the key cytokine in Th17 cell differentiation and stabilization.^{5,7} Once differentiated, Th17 cells migrate back to the epidermis where they produce IL-22 and six IL-17 cytokines (IL-17A-F), which induces release of chemokines.^{6,8–11} The final result of upregulation of these pro-inflammatory mediators is a reduction in keratinocyte maturation and an increase in keratinocyte and vascular proliferation, characteristic of psoriasis.

Currently there are three biological agents, secukinumab, ixekizumab, and brodalumab, under development that target IL-17 produced by Th17 cells. Secukinumab, is a fully human immunoglobulin G (IgG)-1k monoclonal anti-IL-17A antibody that selectively binds to and counteracts IL-17A, a chief pro-inflammatory cytokine.¹² Ixekizumab, is a humanized IgG4 monoclonal anti-IL-17A that suppresses keratinocyte production of cytokines, beta-defensins, antimicrobial peptides, and chemokines, which are increased in psoriatic skin lesions.¹³ Finally, brodalumab is an anti-IL-17 receptor monoclonal antibody that blocks the activity of IL-17A, IL-17F, IL-17A/F, and IL-17E.¹⁴

With the development of an increasing number of treatment options for psoriasis aimed at improving efficacy and patient safety, it is important that physicians have access to up to date, evidence based literature on each of these proposed therapies. The goal of this study is to review literature and provide evidence for the use of the anti-IL-17 agent brodalumab for the treatment of psoriasis.

Methods

We conducted a systematic review of the literature through August 1, 2014 to identify all randomized controlled trials and systematic reviews of brodalumab for the treatment of psoriasis. PubMed was searched for the terms “psoriasis + brodalumab or AMG 827”. Identified publications were reviewed for content and those in a language other than English were excluded. Publications that met inclusion criteria were then grouped and discussed in terms of efficacy, safety, health-related quality of life (HRQoL), pharmacokinetics (PK), and molecular and cellular changes in lesional skin.

Results

Efficacy

In a Phase I, randomized, placebo-controlled trial of brodalumab (AMG 827), a single dose of 350 mg subcutaneously (SC) or 700 mg intravenously (IV) led to a rapid, dose-dependent improvement in Psoriasis Area Severity Index (PASI) scores (Table 1).¹⁵ Twenty-five psoriasis patients with a baseline average PASI score of 14.1 were administered a single dose of brodalumab at either 140 mg SC, 350 mg SC, 700 mg IV, or placebo. Improvement in PASI scores was seen within 2 weeks of administration of brodalumab 350 mg SC or 700 mg IV. All eight subjects who received 700 mg IV reached a PASI score of 50 by day 29, seven subjects reached a PASI score of 75, and three subjects achieved a PASI score of 90 by day 43. In the 350 mg SC cohort, six out of eight and three out of eight reached a PASI score of 50 and 75, respectively. Two of the four subjects who received brodalumab 140 mg SC achieved a PASI score of 50. No subjects who were given placebo showed improvement in PASI scores.

In a Phase II randomized, double-blind, placebo-controlled trial by Papp et al, the main objective was to establish a dose-response profile for brodalumab and to assess its short-term efficacy and safety in patients with moderate-to-severe plaque psoriasis.¹⁴ A total of 198 subjects were randomized to receive either 70 mg, 140 mg, or 210 mg at day 1 and weeks 1, 2, 4, 6, 8, and 10, or 280 mg monthly, or placebo. Patients receiving the various doses of brodalumab had significant improvement in efficacy measures as compared with patients in the placebo group, with the efficacy results better for patients in the higher-dose groups than for those in the 70 mg group, suggesting that there is a dose-response effect. At week 12, 77% of the patients in the 140 mg brodalumab group and 82% of the patients in the 210 mg group reached a PASI score of 75, while 72% and 75% of the 140 mg and 210 mg groups, respectively, reached a PASI score of 90, compared

Table 1 Efficacy data for brodalumab in the treatment of psoriasis

Publications	No of patients	Average age	Dose	Duration	Baseline PASI	% achieving PASI-75	Change in DLQI	Adverse effects
Papp et al ¹⁵	4	43	140 mg SC	85 days	14.1	0	NR	There were no serious AEs. AEs during treatment were mild and moderate in severity among both brodalumab and placebo subjects. Anti-AMG 827 antibodies (non-neutralizing) were detected in two of 20 subjects who received 350 mg SC and 700 mg IV, respectively.
	8		350 mg SC			38		
	8		700 mg SC			88		
	5		Placebo			0		
Papp et al, ¹⁴ Gordon et al ²¹	39	42.1	70 mg SC	12 weeks	18.8	33	6.2	Three serious AEs were reported, including one in the placebo group. Two cases of grade 3 asymptomatic neutropenia were reported from patients receiving the 210 mg dose. Commonly reported AEs were nasopharyngitis, upper respiratory tract infection, arthralgia, and erythema at the injection site. Discontinuation occurred due to urticaria in one patient administered 280 mg. Anti-brodalumab antibodies (non-neutralizing) detected in 5%–9.8% of subjects.
	39	44	140 mg SC		19.4	77	9.1	
	40	42.1	210 mg SC		20.6	82	9.6	
	42	42.3	280 mg SC		17.9	67	7.1	
	38	41.8	Placebo		18.9	0	3.1	
Osamu et al ¹⁶	6	21–69	140 mg SC	64 days	>10	50	NR	Well tolerated in all groups at all doses. No serious AEs. AEs were mild or moderate in severity with injection site erythema most common in all groups. No anti-brodalumab antibodies were detected.
	7		350 mg SC			85.7		

Abbreviations: AE, adverse events; IV, intravenously; NR, not reported; SC, subcutaneously; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area Severity Index.

with 0% in the placebo group ($P<0.001$). The percentage of patients with a static physician's global assessment of clear or minimal disease was 26%, 85%, 80%, and 69% with the 70 mg, 140 mg, 210 mg, and 280 mg doses, respectively, compared with 3% with placebo ($P<0.01$).

In a randomized, dose escalated, placebo controlled trial assessing the pharmacology of brodalumab in normal, healthy Japanese subjects and subjects with moderate to severe psoriasis, clinical response was also measured.¹⁶ Six subjects received a single administration of brodalumab 140 mg SC and seven subjects received 350 mg SC. Fifty percent and 85.7% of patients who received 140 mg and 350 mg, respectively, reached a PASI-75 score or greater, showing a dose-dependent improvement. The time at which these patients achieved this improvement was not reported. In the group of healthy, normal participants, eight subjects were randomized in a 2:6 ratio to either receive a single dose of placebo or brodalumab at 70, 140, 210, or 420 mg SC, or 210 mg IV. Brodalumab was well tolerated in all groups at all doses.

Brodalumab was among the agents reviewed in a systematic review of 55 publications on biologic agents including anti-IL-12, IL-17, and IL-23 agents for the treatment of moderate-to-severe psoriasis.¹⁷ Overall, data from clinical trials support the use of these agents as safe and effective, although long-term data for these drugs are lacking. Phase II data for the anti-IL-17 agents specifically, including brodalumab, were also reviewed by Nwe et al. The review concluded that the clinical data are very encouraging, with improved efficacy and faster response than current psoriasis treatment options. However, the Phase III trials for the anti-IL-17 agents are heavily influenced by risk factors of the anti-TNF and the anti-IL-12/23 agents, with exclusion criteria that will likely result in inclusion of subjects who are healthier than the general psoriasis population and may underestimate the risks of IL-17 blockade.^{6,18}

A review by Brown et al compared Phase II data for the anti-IL-17 psoriasis agents secukinumab, ixekizumab, and brodalumab. The efficacy was comparable among the most effective dosages between the different drugs, with 82% of secukinumab, 83% of ixekizumab, and 82% brodalumab patients reaching PASI-75 score ($P<0.001$ compared to placebo for all agents).¹⁹ Overall, the anti-IL-17 agents result in significant clinical improvement rapidly, providing further support that the IL-17 pathway is a key target in the treatment of psoriasis.

Safety

In both the Phase I study and the study by Osamu et al, where patients only received a single dose of brodalumab, there

were no serious adverse events or dose-limiting toxicities.^{15,16} Adverse events during treatment were mild and moderate in severity among both brodalumab, placebo subjects, and healthy subjects. Headache, gastroenteritis, and development of Koebner phenomena at the biopsy site were the most commonly reported adverse effects in patients who received brodalumab in the Phase I study. Injection site reaction was most commonly reported in all groups including placebo in Osamu et al's pharmacology study.

Three serious adverse events were reported in the Phase II study, including one in the placebo group.¹⁴ At week 2, two cases of grade 3 asymptomatic neutropenia were reported from patients receiving the 210 mg dose, both of which normalized after drug was withheld. Among the commonly reported adverse events were nasopharyngitis, upper respiratory tract infection, arthralgia, and erythema at the injection site. Discontinuation of the drug occurred in one patient who was being administered 280 mg, reporting mild urticaria on day 26.

The development of non-neutralizing brodalumab binding antibodies was reported in the Phase I and II studies.^{14,15} Two subjects who received 350 mg SC and 700 mg IV developed anti-AMG 827 antibodies by day 85 in the Phase I study. In the Phase II study, antibodies were detected in 5% to 9.8% of subjects, with the cumulative incidence similar among all the brodalumab groups.

Comparison of brodalumab with secukinumab and ixekizumab supports a favorable short-term safety profile in the anti-IL-17 agents.¹⁹ The agents were similar in regards to safety, with nasopharyngitis, upper respiratory infections, and injection site reactions among the most frequently reported adverse events. Low-grade neutropenia, which was predominantly transient and asymptomatic, was reported in a small number of patients.

HRQoL

In the Phase II trial, HRQoL measures were reported with the Dermatology Life Quality Index (DLQI) significantly lower in the brodalumab groups than in the placebo group at week 12, with lower scores observed as early as week 4.^{14,20} Mean improvements in DLQI were 6.2 for the 70 mg, 9.1 for the 140 mg, 9.6 for the 210 mg, and 7.1 for the 280 mg group compared to 3.1 for the placebo group.²⁰ Gordon et al also used a novel psoriasis specific patient reported outcome measure, the Psoriasis Symptom Inventory, which is an 8-item measure that assesses symptoms such as itch, redness, scaling, burning, cracking, stinging, flaking, and pain.²⁰ Significant improvement in the mean Psoriasis Symptom

Inventory total and item scores were reported as early as week 2 and maintained through week 12 for the brodalumab groups. Timing of improvement varied by item, with burning, stinging, cracking, and pain items improving earlier, with a majority of patients achieving a score of 0 by week 2. By week 12, improvement in all items in all brodalumab groups were significantly improved. A significantly greater proportion of subjects reached a total Psoriasis Symptom Inventory score of 0 (no symptoms) in the brodalumab groups than in the placebo group at week 12. At week 12, 41% of the subjects in the 140 mg and 55% of the 210 mg group achieved a total score of 0 compared to 0% in the placebo group ($P < 0.0001$).

Viswanathan et al further analyzed pooled Phase II data to determine the effects that achieving total skin clearance has on HRQoL and psoriasis symptom severity.²¹ More subjects who achieved a static physician global assessment (sPGA) of 0 (clear) reached a DLQI of 0 compared to patients with an sPGA of 1 (almost clear) at week 12, though not statistically significant (61.4% and 45.7% respectively, $P = 0.15$). Similarly, 60.7% of subjects who achieved a PASI score of 100 at week 12 had a DLQI score of 0 compared with 53.2% of subjects with a PASI score of 75 to < 100 ($P = 0.5$). Significantly more subjects, 65.5% of subjects with an sPGA 0, achieved a Psoriasis Symptom Inventory of 0 compared to 32.6% of subjects with an sPGA 1 ($P = 0.001$). In terms of PASI scores, 64.8% subjects who reached a PASI score of 100 had no psoriasis symptoms (Psoriasis Symptom Inventory = 0) compared to 45.7% of subjects with a PASI score of 75 to < 100 ($P = 0.04$). Overall, subjects with total skin clearance, according to sPGA and PASI scores, were more likely to have no impairment in HRQoL and no psoriasis symptoms than subjects who were almost clear.

PK

PK of brodalumab was studied in several papers. Endres et al developed a population PK model using Phase Ia and II data in healthy and psoriasis subjects.²² Findings were similar to studies on other monoclonal antibodies with a relatively low serum concentration of 0.223 L/day and a low volume distribution of 5.4 mg/day, suggestive that brodalumab stays largely concentrated in the serum with limited tissue penetration. The between-subject variability was also comparable to other monoclonal antibodies, estimated at 69.2, 69.6, and 25.9% for total clearance (CL), central distribution volume, and maximum elimination velocity, respectively. Total body weight and age were found to influence CL, central distribution volume, and/or maximum elimination velocity, with the

magnitude of change decreased for the median area under the curve for steady state and maximum serum concentration at steady state, as dose increased. Area under the curve was predicted to be more than two-fold higher in subjects weighing less than 75 kg for doses between 140 and 210 mg in the simulation model.

PK was reported in the Phase I trial of brodalumab (AMG 827).¹⁵ The concentration level of AMG 827 in serum versus time profiles demonstrated nonlinear PK. In subjects receiving the 700 mg IV dose, pharmacokinetic parameters and concentration-time profiles appeared similar to those seen in healthy volunteers.

One of the primary objectives of the study by Osamu et al of brodalumab in Japanese healthy subjects and subjects with psoriasis was to assess PK and pharmacodynamics.¹⁶ In accordance with Papp et al Phase I data, brodalumab showed nonlinear PK with the mean serum concentration-time profile and PK parameters comparable between healthy subjects and psoriasis subjects. The time to reach maximum mean serum concentration was between 1 to 7 days and the maximum mean IL-17A receptor (IL-17RA) occupancy was reached after 0.5 hours for the 210 mg IV group and 3 days for the SC administered groups. IL-17A receptor occupancy correlated with the serum concentration of brodalumab in a dose dependent manner and remained at a maximum level when serum brodalumab concentration was greater than 1 µg/mL. This serum concentration was maintained in the group receiving 140 mg SC at 2 weeks suggesting that dosing every 2 weeks would maintain optimal IL-17RA occupancy.

Molecular and cellular changes in lesional skin

The Phase I trial of brodalumab analyzed skin biopsies from lesional and non-lesional skin in psoriasis patients.^{15,23} After a single dose of brodalumab, genes expressed by keratinocytes normalized rapidly, while T-cell specific genes that encode cellular markers of the inflammatory infiltrating leukocytes declined more slowly. Significant reductions were seen in epidermal thickness, KRT16 levels, and Ki67-expressing cells from patients who received the 350 mg SC (at day 8) and 700 IV (at day 15) doses. In seven of eight patients who received 700 mg IV, KRT16 protein in suprabasal keratinocytes declined to levels seen in non-lesional skin by day 43. Messenger RNA (mRNA) from lesional skin showed significant improvement after 2 weeks in several IL-17-modulated keratinocyte-derived factors, as well as cytokines not directly related to IL-17 including IL-22 and both IL-23 subunits. At 2 weeks, IL-17A, IL-17C, and IL-F

mRNA, IL-17 ligand genes which are upregulated in lesional skin, were all downregulated in a dose-dependent manner, reaching non-lesional levels over 6 weeks.

The Phase II trial included histologic analysis of 19 biopsies taken prior to treatment and at week 12.¹⁴ All samples from the 140 mg, 210 mg, and 280 mg groups showed a reduction in keratin 16 (KRT16) staining of the upper epidermis at week 12, with eleven of these 12 samples having KRT16 staining confined to the basal keratinocytes only. Samples from the 140 mg and 210 mg brodalumab groups also displayed a significant reduction in epidermal thickness and dermal CD3 counts. Dermal CD3 counts also decreased significantly in the 70 mg brodalumab group, and epidermal thickness decreased significantly in the 280 mg group. This reduction of T-cell infiltration and loss of suprabasal expression of KRT16 suggest reversal of pathologic characteristics typical of psoriasis with brodalumab treatment.

Discussion

Treating psoriasis can be challenging for both the patient and the physician. Severity of disease, drug efficacy and safety, and patient preferences are all important factors in choosing the most appropriate treatment. Today's systemic treatment options are vast with several biologic agents to choose from, as well as the recent addition of the oral agent apremelast. Still, newer biologic agents targeting IL-17, such as brodalumab, are in development with the goal of providing even greater efficacy and safety. Clinical data thus far for brodalumab in the treatment of psoriasis are promising in terms of efficacy and potential risk factors. The Phase III study will include data on 1,800 patients with psoriasis, and while results have not yet been published, a recent news release was encouraging.²⁴ Brodalumab was more effective than ustekinumab in achieving CL of skin disease, with 27% and 36.7% of patients receiving 140 mg and 210 mg of brodalumab, respectively, and 18.5% of subjects receiving ustekinumab reaching a PASI score of 100. These early data appear to support earlier findings on efficacy. Still needed is better characterization and guidance for the management of adverse events such as neutropenia that has been reported with all three of the emerging anti-IL-17 agents. Long-term data for the current TNF-α inhibitors have lessened safety concerns and supported their use as first line agents in the treatment of psoriasis, however, concerns about serious infections and malignancies still exist.²⁵ Similar long-term data and head-to-head studies will be needed to conclusively make comparisons between existing biologic agents and the newer anti-IL-17 agents.

Brodalumab has the potential to become a valuable treatment option in the management of psoriasis. The study by Viswanathan et al provided beneficial insight on how the difference in reaching complete clearance of psoriasis compared to almost clear impacts HRQoL and psoriasis symptoms.²¹ What may seem like a small difference in disease severity may impact the patient to a greater extent. For this reason, the development of new drugs such as brodalumab, which have the potential to clear psoriasis completely in some patients, warrants continued support.

Disclosure

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