

# Potential role of ixekizumab in the treatment of moderate-to-severe plaque psoriasis

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**Background:** Psoriasis is a debilitating autoimmune skin disease that affects 2%–3% of the world's population. Patients with moderate-to-severe plaque psoriasis suffer from a decreased quality of life as well as comorbidities. Newer biological agents have been shown to be more effective than traditional therapies. In this article, we assess the potential role of ixekizumab, an anti-interleukin (IL)-17 antibody, in treating moderate-to-severe plaque psoriasis.

**Method:** We reviewed PubMed for articles regarding ixekizumab and the epidemiology and management of plaque psoriasis.

**Results:** In a Phase I clinical trial, treatment with ixekizumab resulted in both clinical and histopathologic improvement of psoriasis, which suggests that IL-17 may be a key driver in the pathogenesis of psoriasis. In a Phase II clinical trial, treatment with ixekizumab resulted in rapid clinical improvement of psoriasis, which lends further support to its role as an effective treatment for patients with chronic moderate-to-severe plaque psoriasis. Reductions in Psoriasis Area and Severity Index (PASI) score are comparable to those associated with currently marketed biologics.

**Conclusion:** Literature concerning the effects of ixekizumab on chronic moderate-to-severe plaque psoriasis is currently limited to two clinical trials. Results suggest that ixekizumab shows great therapeutic promise. However, more large-scale and long-term trials are needed to establish safety and efficacy.

**Keywords:** IL-17, PASI, adalimumab, etanercept, infliximab, ustekinumab, biologics

## Background

Psoriasis is a chronic, inflammatory autoimmune skin disease that affects 2%–3% of the world's population.<sup>1</sup> Most patients with psoriasis have plaque psoriasis, or psoriasis vulgaris. Patients with over 5% body surface area (BSA) involvement or psoriasis of the palms, soles, head and neck, or genitalia are considered to have moderate-to-severe psoriasis<sup>2</sup> and require treatment with phototherapy, traditional systemic agents, and/or newer biological agents.<sup>1</sup>

Although psoriasis can appear at any age, onset before age 30 is most common.<sup>3</sup> Thus, most patients unfortunately are affected during the most active and productive years of their life. Psoriasis is associated with a decreased quality of life<sup>4</sup> as well as with comorbidities, such as obesity, depression, metabolic syndrome, cardiovascular disease, and malignancies.<sup>5</sup> Together, increased health care utilization and time lost from work create an additional financial burden for patients.

Over the past decade, as knowledge of the pathogenesis of psoriasis has increased, treatments directed at specific components of the immune system have been devel-

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oped. Although biologics are more expensive than other forms of therapy by about US\$30,000 per patient per year,<sup>6</sup> they may indirectly lessen costs for some patients by reducing the need, or length of hospitalization,<sup>7</sup> and by increasing productivity and reducing work limitations.<sup>8</sup> Although greater patient satisfaction has been reported with the use of biologics<sup>9</sup>, psoriasis remains incurable and potentially debilitating in severe cases.

Development of new biologics is favored because traditional topical therapies, phototherapy, and systemic medications have been associated with patient frustration<sup>10</sup> and low compliance.<sup>11,12</sup> Furthermore, topical treatments and phototherapy do not improve joint damage that is ongoing in psoriatic arthritis, and traditional systemic agents can cause long-term organ damage, such as pulmonary fibrosis and cirrhosis in patients on methotrexate. Psoriatic patients on biologics show greater improvement than do patients on topicals, phototherapy, or conventional systemic agents, and both patients and their dermatologists express greater satisfaction with biologics.<sup>13</sup>

Ixekizumab (LY2439821), a promising new humanized IgG4 anti-IL-17 monoclonal antibody, is now undergoing Phase II testing.<sup>14</sup> The aim of this article is to review the findings of ixekizumab testing thus far and to comment on its potential role in the treatment of moderate-to-severe plaque psoriasis alongside four currently approved biological agents – adalimumab, etanercept, infliximab, and ustekinumab.

## Methods

Relevant articles were selected from the PubMed database using individual or combinations of search terms such as: ixekizumab, LY2439821, IL-17, plaque psoriasis, psoriasis vulgaris, comorbidity, quality of life, epidemiology, cost, biologic, adalimumab, etanercept, infliximab, ustekinumab, brodalumab, adverse effect, and efficacy. Additional publications were gathered from the reference lists of identified articles and from related citations in PubMed. As of January 2013, two clinical trials have been identified. In addition, 37 other articles were reviewed and referenced.

## Results

### Ixekizumab: mechanism of action

Recent progress in the understanding of the immune factors that drive pathogenic inflammation in psoriasis has directed our attention to type 17 helper T (Th17) cells and IL-17 as targets for therapy.<sup>15,16</sup> Th17 cells secrete proinflammatory cytokines, including IL-17A (IL-17), and have been

found in the dermis of psoriatic skin lesions.<sup>17</sup> In addition, higher levels of IL-17 have been associated with lesional (as opposed to perilesional) skin samples of patients with severe plaque psoriasis.<sup>18</sup> Cell-culture experiments suggest that IL-17 can directly activate over 40 genes in keratinocytes and that synergistic interaction with TNF-alpha can result in an even larger pool of inflammatory products.<sup>19</sup> A clinical trial evaluating the efficacy of a single dose of AIN457, an anti-IL-17 antibody, showed a 58% reduction in the Psoriasis Area and Severity Index (PASI) score relative to baseline,<sup>20</sup> further illustrating the potential role of IL-17 antagonists in the treatment of psoriasis.

Ixekizumab (LY2439821), a humanized IgG4 monoclonal antibody, selectively binds and neutralizes IL-17,<sup>14,21</sup> thus blocking keratinocyte production of cytokines, beta-defensins, antimicrobial peptides (AMPs), and chemokines – molecules that are found to be increased in psoriatic skin lesions.<sup>22</sup>

### Ixekizumab: phase I study

In a 20-week-long randomized, double-blind, placebo-controlled Phase I trial<sup>21</sup> evaluating the effects of neutralization of IL-17 on chronic moderate-to-severe plaque psoriasis, 40 subjects received 5, 15, 50, or 150 mg of subcutaneous ixekizumab or placebo at 0, 2, and 4 weeks. For each patient, punch biopsies were obtained from the same lesion at baseline, 2 weeks, and 6 weeks. Attenuation of the IL-17 pathway and improvements in disease biomarkers and clinical presentation were measured.

At 2 weeks, patients treated with ixekizumab had reduced keratinocyte proliferation, epidermal hyperplasia, dermal infiltration of T cells and dendritic cells, and keratinocyte expression of IL-17-regulated products (eg, cathelicidin, beta-defensin 2). In addition, there was a dose-dependent reduction in cytokine transcripts associated with activated Th1, Th17, and Th22 T cells as well as a reduction in IL-23. At 6 weeks, there was near normalization of skin in patients treated with 50- and 150-mg of ixekizumab but not in patients receiving placebo.

Clinical efficacy of ixekizumab was assessed using PASI 75. At 6 weeks, the proportion of patients who achieved a reduction in PASI score by at least 75% was significantly greater in the 15-mg, 50-mg, and 150-mg ixekizumab groups than in the placebo or 5-mg groups (Table 1). Significant differences were sustained through the 20 week trial. Ixekizumab was well tolerated, and there were no deaths or treatment-related adverse events during the study period.

In addition to rapid blockade of the IL-17 pathway, ixekizumab significantly suppressed 765 disease-related

**Table 1** Clinical efficacy of ixekizumab in Phase II trial, week 6

	PASI 75
150 mg	100% <sup>a</sup>
50 mg	71% <sup>a</sup>
15 mg	25% <sup>a</sup>
5 mg	0%
Placebo	0%

**Notes:** <sup>a</sup>The proportion of patients who achieved PASI 75 was significantly greater in the 150-, 50-, and 15-mg ixekizumab groups than in the 5-mg ixekizumab or placebo groups.

**Abbreviation:** PASI, Psoriasis Area and Severity Index.

genes in week 2 biopsy specimens in the 150-mg group but not the placebo group. In contrast, the TNF-alpha antagonist etanercept was shown to modulate only 200 genes by two weeks.<sup>23</sup> Furthermore, 643 of 1200 genes usually upregulated in psoriatic lesions were found to be normalized after 2 weeks of treatment with ixekizumab compared to only 104 genes after 2 weeks of treatment with etanercept. Normalization of many of these genes was found to suppress Th1-, Th22-, and Th17-associated cytokines as well as downstream pathways active in psoriasis. Meta-analysis further showed that ixekizumab is more effective than etanercept at reducing keratin 16 and beta-defensin 4 mRNA, epidermal thickness, and keratinocyte proliferation. Ixekizumab had the greatest influence on genes regulated by IL-17 alone and was more effective than etanercept at modulating genes co-regulated by IL-17 and TNF-alpha.<sup>23</sup>

## Ixekizumab: phase II study

In a 20-week-long randomized, double-blind, placebo-controlled Phase II trial<sup>14</sup> evaluating the safety and efficacy of subcutaneous ixekizumab in patients with chronic moderate-to-severe plaque psoriasis, 142 subjects received 10, 25, 75, or 150 mg of subcutaneous ixekizumab or placebo at 0, 2, 4, 8, 12, and 16 weeks.

Selected study patients were at least 18 years old with a history of chronic moderate-to-severe plaque psoriasis of at least 6 months, psoriasis involving at least 10% BSA, a PASI score of at least 12, and a static Physician's Global Assessment (sPGA) score of at least 3. Patients with non-plaque psoriasis, a significant flare of psoriasis within 12 weeks before randomization, an active infection within 5 days before administration of ixekizumab, a recent infection necessitating hospitalization or antibiotics, receipt of conventional systemic psoriasis therapy or phototherapy within 4 weeks or topical psoriasis therapy within 2 weeks before randomization, or recent use of any biologic agent were excluded from the study. During the study, patients were allowed to use topical moisturizers, bath oils, oatmeal

baths, and topical salicylic acid preparations as needed. Use of weak topical steroids was limited to the face, axillae, or genitalia. All topical agents were discontinued 24 hours prior to PASI assessments.

The primary end point was the proportion of patients with a reduction in the PASI score by at least 75% at 12 weeks. Secondary end points included the proportion of patients who achieved a reduction in PASI score by at least 90% and 100%, the static Physician's Global Assessment (sPGA) score, the joint-pain Visual Analogue Scale (VAS), the Nail Psoriasis Severity Index (NAPSI), the Psoriasis Scalp Severity Index (PSSI), and patient-reported itch VAS and Dermatology Life Quality Index (DLQI) scores.

Results showed that at 12 weeks, the proportion of patients who achieved PASI 75 or PASI 90 was significantly greater in the 25-mg, 75-mg, and 150-mg ixekizumab groups than in the placebo group (Table 2). In addition, PASI 100 was significantly greater in the 150-mg and 75-mg ixekizumab groups than in the placebo group. Significantly more patients in the 25-mg, 75-mg, and 150-mg ixekizumab groups had a sPGA score of 0 (clear of disease) or 1 (minimal disease) than in the placebo group at week 12. Significant differences between the 150-mg group and the placebo group in PASI 75 and sPGA were identified at as early as 2 weeks and sustained through 20 weeks. About 40% of patients in the 150-mg and 75-mg groups had complete clearance of psoriasis plaques (PASI 100 or sPGA score of 0) at 12 weeks.

Among patients with scalp psoriasis, significant reductions in the PSSI score ( $P \leq 0.01$  versus placebo) were observed at 12 weeks in the 25-mg ( $-87.1 \pm 23.6$ ), 75-mg ( $-94.8 \pm 14.5$ ), and 150-mg ( $-84.8 \pm 41.5$ ) ixekizumab groups. Similarly, among patients with nail psoriasis, significant reductions in the NAPSI score ( $P < 0.05$  versus placebo) were observed at 2 weeks in the 75-mg ( $-57.1 \pm 36.7$ ) and 150 mg ( $-49.3 \pm 35.9$ ) ixekizumab groups, and among

**Table 2** Clinical efficacy of ixekizumab in phase 2 trial, week 12

	PASI			sPGA	
	PASI 75	PASI 90	PASI 100	0 or 1	0
150 mg	82% <sup>a</sup>	71% <sup>a</sup>	39% <sup>a</sup>	71 <sup>a</sup>	46 <sup>a</sup>
75 mg	83% <sup>a</sup>	59% <sup>a</sup>	38% <sup>a</sup>	72 <sup>a</sup>	38 <sup>a</sup>
25 mg	77% <sup>a</sup>	50% <sup>a</sup>	17%	70 <sup>a</sup>	20 <sup>b</sup>
10 mg	29%	18%	0%	25	7
Placebo	8%	0%	0%	8	0

**Notes:** <sup>a</sup> $P \leq 0.001$  versus placebo; <sup>b</sup> $P < 0.05$  versus placebo.

**Abbreviations:** PASI, Psoriasis Area and Severity Index; sPGA, static Physician's Global Assessment.

patients with psoriatic arthritis, significant improvement on the joint-pain VAS ( $P < 0.05$  versus placebo) was observed at 12 weeks in the 150-mg ( $-39.0 \pm 27.5$ ) ixekizumab group. Significant differences were sustained through 20 weeks for all clinical measures. In addition, significant reductions in DLQI and itch-VAS scores were reported at 8 weeks and sustained through 16 weeks in the 25-mg, 75-mg, and 150-mg ixekizumab groups compared to the placebo group.

Adverse events (eg, nasopharyngitis, upper respiratory infection, injection-site reaction, headache) occurred equally (63%) in both the combined ixekizumab groups and the placebo group. There were no reports of serious adverse events (eg, major cardiovascular events, serious infections) or dose-related patterns in the frequency or severity of adverse events. However, four patients discontinued the study due to hypertriglyceridemia, peripheral edema, hypersensitivity, or urticaria. There were no sustained significant changes in liver enzyme levels in any ixekizumab group. Two ixekizumab patients developed grade 2 neutropenia without infection.

## Discussion

Literature concerning the effects of ixekizumab on chronic moderate-to-severe plaque psoriasis is currently limited to two randomized, double-blind, placebo-controlled Phase I and Phase II trials involving 182 patients. Results of these studies show that ixekizumab, a humanized anti-IL-17 monoclonal antibody, improves both pathologic skin features and clinical symptoms of chronic moderate-to-severe plaque psoriasis. This suggests that IL-17 is an important driver of psoriasis pathogenesis. However, in order to establish long-term safety and efficacy of ixekizumab, additional trials following a greater number of patients for a longer amount of time are needed.

One concern is that blocking IL-17-mediated chemokine production – and consequently, neutrophil trafficking – may increase susceptibility to klebsiella<sup>24</sup> and candida<sup>25</sup> infections. In addition, potential formation of neutralizing antibodies could affect both initial response to and long-term efficacy of ixekizumab.<sup>26,27</sup>

Biological agents currently used to treat moderate-to-severe plaque psoriasis are infliximab, adalimumab, etanercept, and ustekinumab. Infliximab, adalimumab, and etanercept inhibit TNF-alpha while ustekinumab inhibits IL-12 and IL-23. Based on indirect comparisons of primary endpoints, a meta-analysis of 20 short-term (10–16 weeks) trials has shown that infliximab 3–10 mg/kg has the highest predicted mean probability of response, followed by ustekinumab 90 mg every 12 weeks, ustekinumab 45–90 mg

every 12 weeks, adalimumab 40 mg every 1 to 2 weeks, etanercept 50 mg twice weekly, and etanercept 25 mg twice weekly (Table 3).<sup>28</sup> Taken together, the PASI scores for established biologics are impressive, but there is still room for improvement. In addition, these results may not adequately reflect long-term effects of treatment as different drugs may achieve maximal effect and lead to side effects at different rates.<sup>29,30</sup> It is difficult to compare the efficacy of ixekizumab against these other biological agents due to there being only two small trials thus far. However, based on PASI data obtained from the existing Phase I and Phase II trials, it appears that ixekizumab 150 mg, 75 mg, 50 mg, and 25 mg may be comparable to or more effective than infliximab or ustekinumab 90 mg. A greater understanding of ixekizumab's safety profile and recommended dosage is needed before such conclusions can be drawn though. Future trials may also consider the efficacy of combining low doses of ixekizumab and other therapeutic agents such that an optimal balance between reduction in disease severity and risk of side effects is achieved.

Although they are rapid-acting and highly effective, the TNF inhibitors infliximab, adalimumab, and etanercept are all associated with serious infections, autoimmune conditions, and lymphoma.<sup>31</sup> However, a recent study found that during the first year of treatment, the rate of success with anti-TNF therapy was several orders of magnitude greater than the likelihood of serious toxicity.<sup>32</sup> In contrast to the TNF antagonists, ustekinumab has not been associated with a significant risk of malignant neoplasm or infection.<sup>33,34</sup> Furthermore, it has been shown to benefit patients who have an inadequate response or contraindications to systemic therapies and anti-TNF biologics.<sup>35,36</sup> Like ustekinumab, recent clinical trials have shown ixekizumab to be fast-acting and well-tolerated. Because it blocks a different component of the inflammatory pathway than the anti-TNF agents and ustekinumab, future studies of ixekizumab may reveal that it offers a risk-benefit ratio that is more beneficial to some patients. Although studies

**Table 3** Results of meta-analysis of 20 short-term (10–16 week) trials

	Mean PASI 75	Mean PASI 90
Infliximab	80%	54%
Ustekinumab 90 mg	74%	46%
Ustekinumab 45 mg	69%	40%
Adalimumab	58%	30%
Etanercept 50 mg	52%	24%
Etanercept 25 mg	39%	15%
Placebo	4%	1%

**Abbreviation:** PASI, Psoriasis Area and Severity Index.

have suggested that etanercept and infliximab may potentially be effective in treating pediatric patients with severe recalcitrant psoriasis, the impact of currently marketed biologics on pregnant women and fetuses is unknown and indications for use in the pediatric population is not well supported<sup>37</sup> due to an understandable avoidance of treating young patients with high-risk medications. However, researchers might consider these special populations as avenues for future research and as a potential way for ixekizumab to distinguish itself from the other biological agents.

Future evaluations of the potential role of ixekizumab in the treatment of chronic moderate-to-severe plaque psoriasis should also take into consideration its cost-effectiveness, which may vary across countries, and associated level of patient satisfaction. In a recent Spanish study evaluating the cost-efficacy of adalimumab, etanercept, infliximab, and ustekinumab for moderate-to-severe plaque psoriasis, adalimumab at a dose of 40 mg every other week beginning 1 week after a loading dose of 80 mg was found to be most efficient in terms of cost per patient achieving PASI 75 while ustekinumab at a dose of 90 mg was found to be the least efficient (€8013 versus €17,981).<sup>38</sup> In contrast, a US study of etanercept, infliximab, and adalimumab found infliximab 3 mg/kg intravenous to be most efficient in terms of cost per patient achieving PASI 75, followed by infliximab 5 mg/kg and adalimumab 40 mg SQ every other week.<sup>39</sup> Factors that affect patient satisfaction include dosing schedule and mode of administration. Etanercept, adalimumab, and ustekinumab, which are administered subcutaneously, are easier to take than infliximab, which is given intravenously. In addition, ustekinumab offers the most convenient dosing schedule (every 12 weeks following initial injections at 0 and 4 weeks). It remains to be seen how ixekizumab will compare.

## Disclosure

The authors have no conflicts of interest in this work.

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