Impact of Ixekizumab Treatment on Depressive Symptoms and Systemic Inflammation in Patients with Moderate-to-Severe Psoriasis: An Integrated Analysis of Three Phase 3 Clinical Studies

Christopher E.M. Griffiths^a Maurizio Fava^b Andrew H. Miller^c James Russell^{d,e}
Susan G. Ball^e Wen Xu^e Nayan Acharya^e Mark Hyman Rapaport^c

^aDermatology Centre, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK;

^bDepartment of Psychiatry, Massachusetts General Hospital, Boston, MA, ^cDepartment of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, ^dDepartment of Psychiatry, Oregon Health Sciences University, Portland, OR, and ^eEli Lilly and Company, Indianapolis, IN, USA

Keywords

Ixekizumab · Psoriasis · Depressive symptoms · High-sensitivity C-reactive protein · Comorbid depression · UNCOVER

Abstract

Background: Depression is a common comorbidity in psoriasis, and both conditions are associated with systemic inflammation. The efficacy of ixekizumab, a high-affinity monoclonal antibody that selectively targets interleukin (IL)-17A, was evaluated in patients with moderate-to-severe plaque psoriasis (psoriasis) and depressive symptoms that were at least moderately severe. **Methods:** Data were integrated from 3 randomized, double-blind, controlled phase 3 trials. At baseline and week 12, depressive symptoms and inflammation were assessed by the 16-item Quick Inventory of Depressive Symptomology – Self-Report (QIDS-SR₁₆) and by a high-sensitivity assay of serum C-reactive protein (hsCRP), respectively. A subgroup of patients with at least moderately severe depressive symptoms at baseline (QIDS-SR₁₆ total score ≥ 11) was analyzed. Improvement in psoriasis

was assessed by the Psoriasis Area and Severity Index (PASI).

Results: Approximately 10% of the overall psoriasis population had at least moderately severe depressive symptoms at baseline. At week 12, comorbid patients treated with ixekizumab had significantly greater improvements in their QIDS-SR₁₆ total score (ixekizumab 80 mg every 2 weeks [Q2W], -7.1 ; ixekizumab 80 mg every 4 weeks [Q4W], -6.1) vs. placebo (-3.4) ($p < 0.001$, both comparisons) and higher rates of remission of depressive symptoms (ixekizumab Q2W, 45.2%; ixekizumab Q4W, 33.6%) vs. placebo (17.8%) ($p \leq 0.01$, both comparisons). Patients treated with ixekizumab also had significant reductions in hsCRP and PASI compared to placebo. Etanercept treatment was not associated with significant improvements in depressive symptoms compared to placebo. **Conclusions:** In this comorbid population, 12 weeks of ixekizumab therapy resulted in remission of depression for approximately 40% of patients and improved systemic inflammation as indicated by hsCRP.

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Introduction

Depression is a common comorbidity in patients with plaque psoriasis. The prevalence rate of comorbid depression varies across studies, with a recent US population survey finding comorbid depressive illness in 16.5% of patients with psoriasis [1]. Within a general medical database, Kurd et al. [2] found that patients with psoriasis had a significantly greater risk of depression, anxiety, or suicidality (thoughts or behaviors) compared to matched controls, and the risk was associated with the severity of psoriasis. A meta-analysis found an overall prevalence of 12% for depressive illness and 28% for depressive symptoms among patients with psoriasis [3].

While the psychological burden of psoriasis may be a stressor that contributes to the development of depression [4], the increased risk of depression may also be due to shared physiological mechanisms [5]. Psoriasis is recognized as an immune-mediated disorder consisting of dysregulated cytokine networks that lead to chronic inflammation [6, 7]. Similarly, some studies have suggested an association between depression and increased levels of proinflammatory cytokines, such as tumor necrosis factor- α and interleukin (IL)-6 in the blood [8]. As one marker of systemic inflammation, high-sensitivity C-reactive protein (hsCRP) has been shown to be elevated in some patients with depression [9] and in patients with psoriasis [10].

Ixekizumab is a high-affinity monoclonal antibody that selectively targets the proinflammatory cytokine IL-17A and has demonstrated efficacy for the treatment of moderate-to-severe plaque psoriasis (psoriasis) [11]. The objective of this analysis was to examine the effects of ixekizumab therapy on depressive symptoms and systemic inflammation in patients with psoriasis and comorbid depressive symptoms. This report focuses on the subgroup of patients who had at least moderately severe depressive symptoms in the pivotal phase 3 ixekizumab psoriasis trials.

Methods

Study Design

Data were integrated from the 12-week induction period of 3 pivotal, phase 3, double-blind, randomized, placebo-controlled trials of ixekizumab (UNCOVER-1, UNCOVER-2, and UNCOVER-3) for the treatment of patients with psoriasis. Patients were randomized to receiving either ixekizumab 80 mg every 4 weeks (Q4W; $n = 1,165$), ixekizumab 80 mg every 2 weeks (Q2W; $n = 1,169$), or placebo ($n = 792$). For the ixekizumab treatment groups,

patients received an initial dose of ixekizumab 160 mg. The induction periods of UNCOVER-2 and UNCOVER-3 also had the active comparator group of etanercept 50 mg twice weekly ($n = 739$). Etanercept comparisons were made using integrated data from these 2 studies.

Participants

The patient subset for this report was derived from the intent-to-treat (ITT) population of the trials. The comorbid depressive symptom population was defined as patients who had a 16-item Quick Inventory for Depressive Symptomatology – Self-Report (QIDS-SR₁₆) total score ≥ 11 at baseline (at least moderately severe depression). Patients were adult (age ≥ 18 years) outpatients who had been diagnosed with psoriasis for at least 6 months who met the following severity criteria: body surface area percentage coverage score $\geq 10\%$, Psoriasis Area and Severity Index (PASI) score ≥ 12 , and static Physician Global Assessment score ≥ 3 (at least moderate severity). Key exclusion criteria included: other forms of psoriasis, recent use of biological therapy within specific washout periods, an unstable serious medical disease, a recent serious infection, presence of a significant uncontrolled neuropsychiatric disorder, a history of suicide attempt or current suicide ideation (as determined by a score of 3 [frequent thoughts of suicide, a plan, or an attempt] on QIDS-SR₁₆ item 12 for thoughts of death/suicide or by investigator opinion), a history of malignant disease, and laboratory values outside of specific ranges. All patients gave written informed consent prior to study procedures. The studies were approved by institutional review boards and regulatory authorities and registered as UNCOVER-1, UNCOVER-2, and UNCOVER-3 with ClinicalTrials.gov (NCT01474512, NCT01597245, and NCT-01646177, respectively).

Measures

Depressive symptoms were measured using the QIDS-SR₁₆, a reliable and well-validated 16-item self-report questionnaire that assesses 9 domains (sad mood, concentration, self-criticism, suicidal ideation, interest, energy/fatigue, sleep disturbance [insomnia or hypersomnia], appetite/weight disturbance [decrease or increase], and psychomotor agitation or retardation) [12–14]. The total score ranges from 0 to 27; individual scores are interpreted as 0–5 (none), 6–10 (mild severity), 11–15 (moderate severity), 16–20 (severe), and 21–27 (very severe) [13]. The QIDS-SR₁₆ was administered at baseline and week 12.

Serum hsCRP was assessed at baseline through week 12 by immunonephelometry using a Siemens BNTM II nephelometer. Investigative sites were blinded to the results.

Psoriasis disease severity was measured by the PASI, which is a physician-rated instrument that combines assessment of the extent of body surface involvement in 4 anatomical regions (head, trunk, arms, and legs) and the severity of desquamation (scaling), erythema, and plaque induration/infiltration (thickness). PASI assessments yield an overall score of 0 (no psoriasis) to 72 (most severe disease) [15]. Improvements in the severity of psoriasis are reported as a percentage of the improvement in PASI compared to the baseline value; for example, a PASI of 75 indicates that the patient's postbaseline score is at least a 75% improvement compared to their baseline score. Complete resolution of psoriasis is defined as a 100% improvement in PASI score from baseline (PASI 100). The PASI assessment was administered at baseline and through week 12.

Table 1. Baseline demographics and illness characteristics of patients with moderate-to-severe plaque psoriasis and comorbid depressive symptoms

	PBO (<i>n</i> = 93)	IXE Q4W (<i>n</i> = 120)	IXE Q2W (<i>n</i> = 107)	Total (<i>n</i> = 320)
Age, years	46.8±13.1	44.2±13.3	45.5±12.4	45.4±13.0
Males	57.0	55.8	57.9	56.9
Whites	88.2	87.5	87.9	87.8
Weight, kg	86.9±22.1	92.6±27.5	88.6±24.5	89.6±25.0
Previous biological therapy	36.6	26.7	32.7	31.6
Duration of Ps, years	18.6±13.1	16.2±11.0	17.1±12.5	17.2±12.1
sPGA (severe, very severe ¹)	53.8	60.8	49.5	55.0
PASI	22.1±9.0	23.3±8.9	22.1±8.8	22.5±8.9
QIDS-SR ₁₆ score	14.0±3.1	14.2±2.6	13.8±2.6	14.0±2.8
Psoriatic arthritis ²	39.8	32.5	42.1	37.8
hsCRP, mg/L	8.6±14.3	7.6±12.1	9.7±20.5	8.6±15.9
hsCRP (>5 mg/L), <i>n</i> / <i>Nx</i> (%)	40/89 (44.9)	43/117 (36.8)	42/100 (42.0)	125/306 (40.8)

Values are presented as means ± SD or percents unless otherwise stated. hsCRP, high sensitivity C-reactive protein; IXE Q2W, ixekizumab 80 mg every 2 weeks; IXE Q4W, ixekizumab 80 mg every 4 weeks; *n*/*Nx* = number of patients who met criteria/number of patients who had a baseline or postbaseline value; PBO, placebo; PASI, Psoriasis Area Severity Index; Ps, psoriasis; QIDS-SR₁₆, 16-item Quick Inventory for Depressive Symptomatology – Self-Report; sPGA, static Physician Global Assessment. ¹ Severe baseline sPGA (score ≥4). ² Self-reported and not based on a formal medical diagnosis.

Statistical Methods

Placebo comparisons were made using integrated induction data from the 3 studies. Etanercept comparisons were made using integrated data from UNCOVER 2 and UNCOVER 3.

Unless otherwise specified, analyses were conducted on the comorbid depressive symptom population, which is a subset of the ITT population. The last observation carried forward (LOCF) method was used to account for missing data unless otherwise specified.

The LOCF mean changes from baseline to week 12 in the QIDS-SR₁₆ total score, 9 QIDS-SR₁₆ domain scores, and hsCRP were analyzed using an analysis of covariance (ANCOVA) model with treatment, study, and baseline values as covariates. Improvements in QIDS-SR₁₆ item 12 refer to postbaseline values that are less than the reference baseline value.

Categorical data frequencies were summarized by treatment group and analyzed using the Cochran-Mantel-Haenszel test stratified by study. Clinically meaningful improvement in depressive symptoms (response) was defined as ≥50% improvement in the QIDS-SR₁₆ total score from baseline to week 12. Remission of depressive symptoms was defined as a QIDS-SR₁₆ total score ≤5 at week 12. Elevations of hsCRP, defined as hsCRP >5 mg/L, were summarized at baseline, at week 12, and by the presence or absence of psoriatic arthritis (PsA) at baseline.

Improvements in psoriasis as measured by the PASI (PASI 75, PASI 90, and PASI 100) from baseline to week 12 were analyzed using the Cochran-Mantel-Haenszel test stratified by study. If missing PASI data occurred, the patient was considered a nonresponder.

Categorical assessments of QIDS-SR₁₆ total scores and QIDS-SR₁₆ item 12 scores compared maximum postbaseline scores with maximum baseline scores.

The association between changes from baseline to week 12 (LOCF) was computed using a Pearson product correlation. The

correlation of QIDS-SR₁₆ total scores and hsCRP values, and the correlation of PASI improvements (<75, 75 to <90, 90 to <100, and 100) and QIDS-SR₁₆ remission status, were summarized.

Role of the Funding Source

The studies were designed by Eli Lilly and Company (Lilly) while consulting with external experts. Data were collected by the investigators (the complete dataset was kept at the central processing database held by Lilly). The analyses were developed by the academic investigators who had access to the data. The academic investigators made decisions about submission for publication in collaboration with Lilly, but all authors, including those employed by Lilly, had to approve the document prior to submission for publication.

Results

Within the placebo-controlled integrated dataset across the 3 studies (*n* = 3,126), approximately 10% of the patients met the criterion of a baseline QIDS-SR₁₆ total score ≥11 (placebo, *n* = 93; ixekizumab 80 mg every 4 weeks [Q4W], *n* = 120; and ixekizumab 80 mg every 2 weeks [Q2W], *n* = 107; Table 1). The demographics and baseline illness characteristics of the comorbid depressive symptom population were similar to those of the overall ITT population, with the exception of the percent of patients who had comorbid PsA (~40% in the comorbid depressive population vs. 24% in the overall ITT population). Within the analysis set that includes etanercept

Fig. 1. Least squares mean change in QIDS-SR₁₆ total score from baseline at week 12 (last observation carried forward) by treatment group. Values are presented as least squares means $\pm$ standard error. IXE Q2W, ixekizumab 80 mg every 2 weeks; IXE Q4W, ixekizumab 80 mg every 4 weeks; QIDS-SR₁₆, 16-item Quick Inventory for Depressive Symptomatology – Self-Report.

Fig. 2. Proportion of patients who met remission criteria for depressive symptoms (QIDS-SR₁₆ total score ≤ 5 at week 12 [last observation carried forward]) by treatment group. IXE Q2W, ixekizumab 80 mg every 2 weeks; IXE Q4W, ixekizumab 80 mg every 4 weeks; QIDS-SR₁₆, 16-item Quick Inventory for Depressive Symptomatology – Self-Report.

($n = 2,562$), approximately 10% of patients had a baseline QIDS-SR₁₆ total score ≥ 11 (placebo, $n = 47$; etanercept, $n = 66$; ixekizumab Q4W, $n = 74$; and ixekizumab Q2W, $n = 68$).

Effect of Treatment on Depressive Symptoms

After 12 weeks, patients with comorbid depressive symptoms who were treated with ixekizumab Q4W or Q2W had significantly greater mean reductions in their QIDS-SR₁₆ total score compared to patients who received placebo (ixekizumab Q4W, -6.1 ± 0.41 ; ixekizumab Q2W, -7.1 ± 0.44 ; and placebo, -3.4 ± 0.48 ; $p < 0.001$, both comparisons; Fig. 1). The proportion of patients who met the criteria for clinical response in depressive symptoms was also significantly greater in patients treated with ixekizumab Q4W (46.6%, $p < 0.01$) and ixekizumab Q2W (61.5%, $p < 0.001$) compared to placebo (25.6%) at week 12. Similarly, a significantly greater proportion of patients in both ixekizumab treatment groups (Q4W, 33.6%, $p = 0.01$; Q2W, 45.2%, $p < 0.001$) met criteria for remission of depressive symptoms at week 12 compared to patients who received placebo (17.8%; Fig. 2). Within the 2 studies that included etanercept, patients treated with etanercept had numerically higher values but did not differ significantly from patients treated with placebo in terms of their mean change from baseline

for QIDS-SR₁₆ total score (-4.1 ± 0.57 vs. -3.7 ± 0.68 , respectively) and the rate of clinical response for depression (30.2 vs. 26.7%, respectively) or in remission of depression (22.2 vs. 13.3%, respectively).

There were significant improvements at week 12 in patients treated with either dose of ixekizumab compared to placebo in the following QIDS-SR₁₆ domains: sad mood, self-criticism, suicidal ideation (with the exception of the ixekizumab Q2W group), interest, energy/fatigue, and agitation/retardation. Of particular clinical importance, a numerically higher proportion of patients from the combined ixekizumab treatment groups showed improvement from baseline on item 12 (thoughts of death or suicide) compared to patients treated with placebo (22.2 vs. 15.6%), whereas a numerically higher proportion of placebo-treated patients had a worsening from baseline on this item compared to patients from the pooled ixekizumab group (6.7 vs. 3.6%).

Effect of Treatment on Systemic Inflammation

At baseline, patients with comorbid depressive symptoms had higher mean and median serum hsCRP levels (8.57 and 4.02 mg/L, respectively) relative to patients from the overall ITT population of the phase 3 pivotal trials (5.89 and 2.95 mg/L, respectively). Approximately 41% of the patients with comorbid depressive symptoms met the

Fig. 3. Least squares mean change from baseline in hsCRP (mg/L) at week 12 (last observation carried forward) by treatment group. Values are presented as least squares means $\pm$ standard error. hsCRP, high-sensitivity C-reactive protein; IXE Q2W, ixekizumab 80 mg every 2 weeks; IXE Q4W, ixekizumab 80 mg every 4 weeks.

criteria for elevated hsCRP (>5 mg/L) at baseline. Patients with comorbid depressive symptoms who were treated with ixekizumab had significantly greater mean reductions in hsCRP at week 12 (Q4W, -4.2 ± 0.67 mg/L; Q2W, -4.4 ± 0.72 mg/L) compared to placebo (-0.8 ± 0.77 mg/L) ($p < 0.001$, both comparisons) (Fig. 3). Similarly, the median change in hsCRP was -0.73 mg/L (IQR -3.09 to 0.30) and -0.62 mg/L (IQR -3.5 to 0.15) for ixekizumab Q4W and Q2W, respectively, and it was $+0.20$ mg/L (IQR -1.8 to 1.1) for placebo. After 12 weeks, compared to the baseline frequency, the proportion of patients in the ixekizumab treatment groups with elevated hsCRP had decreased by approximately a third (35–37%) and it was significantly different from that for placebo (Fig. 4). The Pearson product correlation between mean reduction in hsCRP value and mean improvement in QIDS-SR₁₆ total score from the comorbid depressive symptom population was $r = 0.11$ ($p = 0.001$). Patients with comorbid depressive symptoms who were treated with etanercept also had a significant mean reduction in hsCRP (-3.2 ± 1.04 mg/L) compared to their placebo counterparts ($+0.12 \pm 1.2$ mg/L) after 12 weeks ($p = 0.033$). The median change was -1.34 mg/L (IQR -2.7 to 0.16) for etanercept and $+0.25$ mg/L (IQR -1.4 to 1.3) for placebo.

The reduction in hsCRP was also examined by the presence or absence of PsA at baseline in the subgroup of

Fig. 4. Percentage of patients with at least moderately severe depressive symptoms who met criteria for elevated hsCRP at baseline and at week 12 (last observation carried forward) by treatment group. hsCRP, high-sensitivity C-reactive protein; IXE Q2W, ixekizumab 80 mg every 2 weeks; IXE Q4W, ixekizumab 80 mg every 4 weeks.

patients with comorbid depressive symptoms. A greater proportion of patients with comorbid PsA met criteria for elevated hsCRP at baseline compared to patients who did not have comorbid PsA (47.0 and 37.2%, respectively). After 12 weeks, the proportion of patients with elevated hsCRP who were treated with ixekizumab decreased by a similar percentage between the subgroups of patients with or without PsA (data not shown).

Effect of Treatment on Skin Clearance

Similar to the overall ITT population [11, 16], patients with comorbid depressive symptoms who were treated with ixekizumab had significantly greater improvement in PASI scores from baseline compared to placebo ($p < 0.001$, all comparisons). The proportion of patients who achieved a PASI 75 at week 12 was 78.3% (ixekizumab Q4W), 86.0% (ixekizumab Q2W), and 1.1% (placebo). The proportion of patients who had nearly complete resolution (PASI 90) was 60.0% (ixekizumab Q4W), 68.2% (ixekizumab Q2W), and 0% (placebo). The response rates for complete resolution of psoriasis (PASI 100) were 31.7, 37.4, and 0% for ixekizumab Q4W, ixekizumab Q2W, and placebo, respectively. The Pearson correlation between PASI improvement scores and depression remission status at week 12 for the comorbid depressive population was $r = -0.25$.

Discussion

From the integrated database, approximately 10% of patients with psoriasis had at least moderately severe depressive symptoms as defined by a QIDS-SR₁₆ total score ≥ 11 at baseline. Patients treated with ixekizumab therapy had significant mean reductions from baseline in depressive symptoms and systemic inflammation, as represented by circulating levels of serum hsCRP. Within this comorbid population, 45% of patients treated with the recommended dose of ixekizumab (80 mg Q2W) over the 12-week induction period achieved remission of their depressive symptoms. The proportion of patients who achieved PASI 75, PASI 90, or PASI 100 from this subgroup at week 12 was comparable to the rates observed within the individual phase 3 trials after 12 weeks [11]. The majority of patients achieved either meaningful improvement or nearly complete resolution of their psoriatic plaques.

The effect of ixekizumab on depressive symptoms is consistent with results from other biological therapies that have shown significant reductions in depressive symptoms in patients with psoriasis [17]. However, the findings from the etanercept treatment group differ from a published report in which the percentage of patients with psoriasis treated with etanercept who had a 50% improvement in depressive symptoms was significantly higher in patients treated with placebo (43 vs. 32%) [18]. In contrast, the findings from the current study showed that etanercept-treated patients did not have a significant improvement in depressive symptoms compared to placebo-treated patients. The difference in outcomes between these studies may be related to differences in the severity symptoms of the study population and the assessment tool for depression. Only 2% of the sample from Tyring et al. [18] met criteria for at least moderately severe depressive symptoms at baseline, and depressive symptoms were assessed by the Hamilton Depression Rating Scale, a clinician-rated measure [19].

The difference in outcomes between etanercept and ixekizumab relative to placebo may also be potentially related to the underlying pathophysiology given the difference in mechanisms of action of etanercept, a tumor necrosis factor- α inhibitor, and ixekizumab, an IL-17A antagonist. Although, both etanercept and ixekizumab resulted in anti-inflammatory effects as measured by hsCRP levels, the lack of an effect on depressive symptoms by etanercept in the present study suggests that tumor necrosis factor- α may not play a primary role in the cytokine dysregulation underlying the comorbidity

between psoriasis and depressive symptoms. The literature suggests that the IL-17A pathways may have potential CNS effects [20] in which the cytokine IL-6 plays a specific role in increased immune-inflammation through the regulation of Th17 cells and IL-17 production [21].

The improvement in depressive symptoms following ixekizumab therapy occurred across 7 of the 9 symptom domains associated with a major depressive disorder. Notably, given that patients with psoriasis are at an increased risk for suicide-related thoughts and behaviors [2], patients treated with ixekizumab did not experience significant changes in thoughts of death or suicide, and numerically ixekizumab therapy resulted in greater improvement on this item compared to placebo. Interpretation of this finding must consider that patients with frequent suicidal ideation (that is, a score of 3 on item 12 of the QIDS-SR₁₆) were excluded at baseline. Nonetheless, patients with comorbid depressive symptoms did not experience a significant increase in suicide-related thoughts and behaviors with ixekizumab therapy. The finding of no increased risk of worsening of depression or suicide in the comorbid psoriasis and depressive symptoms is consistent with analyses for the overall ITT patient population [22, 23].

A strength of this analysis is that the ixekizumab psoriasis program included over 3,000 patients, which allowed identification of over 300 (~10%) patients with at least moderately severe symptoms. In addition, depressive and systemic inflammatory outcomes were assessed using valid and reliable measures. Limitations of the analyses are that this study was a post hoc analysis of a subgroup from an integrated dataset; patients were not systematically diagnosed for psychiatric illness, and depressive symptoms were measured only at baseline and at week 12, which precludes time course analyses.

In summary, in patients with moderate-to-severe psoriasis and clinically relevant depressive symptoms, 12 weeks of therapy with ixekizumab was superior to placebo in improving depressive symptoms, reducing the inflammatory biomarker of hsCRP, and attaining high levels of skin clearance.

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J. Russell is a retiree of Eli Lilly and Company and owns stock. S. Ball, W. Xu, and N. Acharya are full-time employees of Eli Lilly and Company and own stock.

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