The effect of adalimumab on reducing depression symptoms in patients with moderate to severe psoriasis: A randomized clinical trial

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Background: Psoriasis is associated with health-related quality-of-life impairment and depression.

Objective: We sought to determine the effect of adalimumab on depression symptoms in patients with psoriasis.

Methods: Patients with moderate to severe psoriasis in a randomized, placebo-controlled, double-blind clinical trial were assessed for depression symptoms at baseline and week 12 or early termination (ET) using the Zung Self-rating Depression Scale (ZDS). The effects of adalimumab (40 mg every other week) versus placebo on ZDS score at week 12/ET were assessed using analysis of covariance. Relationships between ZDS and the Psoriasis Area and Severity Index (PASI), the Dermatology Life Quality Index, and the Short Form 36 Health Survey were assessed using Pearson correlations. Changes in ZDS score were compared for patients with and without a 75% or greater reduction in baseline PASI score.

Results: Compared with the placebo group (n = 52), the adalimumab group (n = 44) experienced an additional 6-point reduction in ZDS score (95% confidence interval: 2.5–9.5; \( P < .001 \)) by week 12/ET. Depression improvement was correlated with improvement in PASI (\( r = 0.5; \ P < .0001 \)) and Dermatology Life Quality Index (\( r = 0.5; \ P < .0001 \)). Greater ZDS score improvement was observed at week 12/ET in responders with a 75% or greater reduction in baseline PASI score than in nonresponders (10.6 [SD = 9.4] vs 1.4 [SD = 9.6]; \( P < .001 \)).

Limitations: This analysis cannot distinguish whether adalimumab has a direct or indirect effect on depression.


Key words: adalimumab; depression; psoriasis; tumor necrosis factor.
1 cm to several centimeters in diameter, is the most common form. Physical symptoms of the disorder include itching and pain, with repeated flareups.

In addition to physical manifestations, psoriasis is associated with broad and substantial health-related quality-of-life (HRQOL) impairment, affecting physical, psychologic, social, sexual, and occupational functioning. The impairment of physical and mental functioning in patients with psoriasis is comparable with that of patients with cancer, arthritis, hypertension, heart disease, diabetes, or depression. Psoriasis is also associated with elevated rates of psychologic and emotional disorders, including low self-esteem, anxiety, depression, and suicidal ideation. Depression in particular affects 32% to 60% of patients with psoriasis and is associated with reduced HRQOL. In severe cases, depression in patients with psoriasis is also associated with increased suicidal ideation. In a study of patients with dermatologic disorders, 10% of all patients with psoriasis expressed a wish for death and the highest rates of suicidal ideation (7.2%) were reported in severely affected inpatients with psoriasis.

Tumor necrosis factor (TNF), a proinflammatory cytokine, has been implicated in the pathogenesis of both psoriasis and depression. Patients with psoriasis have elevated concentrations of TNF in skin and serum samples, and a direct correlation exists between TNF concentrations and psoriasis symptoms as measured by Psoriasis Area and Severity Index (PASI) scores. Proinflammatory cytokines such as TNF have also been implicated in the origin of depression. Significantly elevated concentrations of TNF have been observed in the plasma of inpatients with acute depression and in patients with major depression who are resistant to therapy for inpatients with acute depression and in patients with major depression who are resistant to therapy for psoriasis. Adalimumab is a fully human monoclonal IgG1 antibody against TNF that has demonstrated efficacy and safety in the treatment of moderate to severe psoriasis. In addition to reducing the physical symptoms of psoriasis, adalimumab has been shown to improve dermatology-specific and general mental and physical HRQOL to levels comparable with that of the general population. Another anti-TNF fusion protein, etanercept, has been shown to reduce fatigue and depression symptoms in patients with moderate to severe psoriasis in addition to improving psoriasis symptoms and HRQOL. It is reasonable to hypothesize that adalimumab also reduces depression symptoms in patients with psoriasis.

The objective of this analysis was to assess the effect of adalimumab treatment for psoriasis on depression symptoms as measured by the Zung Self-Rating Depression Scale (ZDS). The secondary aim was to describe cross-sectional and longitudinal associations between depression symptoms and physical symptoms of psoriasis and HRQOL.

**METHODS**

**Data sources and study population**

Data were obtained from a phase II randomized, placebo-controlled, double-blind clinical trial (M02-528) of adalimumab for the treatment of moderate to severe psoriasis. A total of 147 anti-TNF-naive patients with moderate to severe psoriasis (body surface area ≥ 5%) that could not be controlled by topical therapy were randomized to double-blinded treatment with placebo or adalimumab 40 mg weekly or every other week starting at week 1 after an 80-mg dose at week 0. This analysis evaluated the US Food and Drug Administration–approved dosage of adalimumab (40 mg every other week) and included patients with baseline and week-12 or early termination (ET) ZDS scores.

**Study measures and outcomes**

The ZDS is a 20-item self-assessment questionnaire with 4 response options per item. Raw scores (range 25-100) were divided by 0.8 to obtain the final ZDS scores; scores of 50 or greater indicate depression. ZDS score was considered missing for questionnaires with 10 or more unanswered items. For questionnaires with less than 10 unanswered items, the ZDS score was the average of the nonmissing items. ZDS score was assessed at baseline and week 12/ET.

Other measures included the Dermatology Life Quality Index (DLQI) (range 0-30; greater scores indicating worse impairment) and the norm-based Mental Component Summary (MCS) and Physical Component Summary (PCS) scores of the Short Form 36 Health Survey (version 1) (greater scores...
indicating better HRQOL; a score of 50 corresponds with the US general population mean). Physical symptoms were measured using the PASI (range 0-72; greater scores indicating greater symptom severity); a 75% or greater reduction in PASI score (PASI 75) from baseline to week 12/ET response was noted.

**Statistical analysis**

Baseline characteristics were compared between treatment groups by using $\chi^2$ tests for categorical variables and Student t tests for continuous variables. The percentages of ZDS scores of 50 or greater and of patients with a reported history of depression were compared between treatment groups by using $\chi^2$ tests. Changes in ZDS scores from baseline to week 12/ET within the adalimumab and placebo arms were tested using paired Student t tests. The effect of adalimumab versus placebo on the change in ZDS scores was assessed using analysis of covariance, with baseline ZDS score as a covariate. Pearson correlation coefficients were used to quantify associations between baseline ZDS scores and other baseline measures (DLQI, MCS, PCS, PASI) and between changes in ZDS score and concurrent changes in DLQI, MCS, PCS, and PASI scores. Mean changes in ZDS scores for PASI 75 responders versus nonresponders were compared using a 2-sample Student t test. No adjustment was made for multiple statistical tests.

**RESULTS**

A total of 96 patients with both baseline and postbaseline ZDS assessments were included in the analysis (44 adalimumab- and 52 placebo-treated patients). Baseline characteristics reported previously were well balanced between the treatment groups $^{19,20}$ (Table I). Adalimumab- and placebo-treated patients did not differ significantly in baseline mean ZDS scores (42.9 vs 45.8; $P = .30$), the percentages with ZDS score of 50 or greater (32% vs 37%; $P = .61$), or the percentages reporting a history of depression (16% vs 21%; $P = .51$).

<table>
<thead>
<tr>
<th>Table I. Baseline characteristics</th>
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<tr>
<td>Treatment arm</td>
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<tr>
<td>Baseline characteristic</td>
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<tr>
<td>N$^1$</td>
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<tr>
<td>Age, y, mean (SD)</td>
</tr>
<tr>
<td>Male, n (%)</td>
</tr>
<tr>
<td>White, n (%)</td>
</tr>
<tr>
<td>Psoriatic arthritis, n (%)</td>
</tr>
<tr>
<td>Psoriasis duration, y, mean (SD)</td>
</tr>
<tr>
<td>PASI, mean (SD)</td>
</tr>
<tr>
<td>History of depression, n (%)</td>
</tr>
<tr>
<td>ZDS score, mean (SD)</td>
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<tr>
<td>ZDS score $\geq$ 50, n (%)</td>
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</table>

*For treatment group differences from Student t tests for continuous variables and $\chi^2$ tests for categorical variables.

Adalimumab-treated patients experienced significant reductions in depression symptoms, with the mean ZDS score decreasing by 6.7 U (95% confidence interval: 3.3-10.1) from 42.9 (SD = 12.4) at baseline to 36.2 (SD = 11.5) at week 12/ET ($P = .003$) (Table II). Placebo-treated patients did not experience significant change in mean ZDS score, which decreased by 1.5 U (95% confidence interval: $-4.0$ to 1.0) from 45.8 (SD = 14.0) at baseline to 44.2 (SD = 14.2) at week 12/ET. In an analysis of covariance model adjusting for baseline ZDS score, adalimumab treatment reduced the mean ZDS score by 6 points more than placebo (95% confidence interval: 2.5-9.5; $P < .001$) (Fig 1).

As shown in Table III, greater baseline ZDS scores were significantly correlated with impaired HRQOL as measured by DLQI, MCS, or PCS scores ($P < .0001$ for each comparison); the correlation with MCS score was particularly strong ($r = -0.8$) (Table III). ZDS and PASI scores were not significantly correlated at baseline. However, reductions in ZDS scores from baseline to week 12/ET were significantly correlated with reductions in PASI and improvement in HRQOL as measured by DLQI, MCS, and PCS scores ($P < .0001$ for each comparison) (Table III). As shown in Fig 2, week-12/ET PASI 75 responders (n = 26) experienced an average reduction in ZDS score of 10.6 (SD = 9.4), whereas nonresponders (n = 70) experienced a significantly smaller reduction of only 1.4 (SD = 9.6) ($P < .001$).
DISCUSSION

The results of this randomized, placebo-controlled trial indicate that adalimumab treatment substantially reduced symptoms of depression in patients with moderate to severe psoriasis. At baseline, depression symptoms were associated with lesser HRQOL, but not with psoriasis severity. During the 12-week treatment period, however, reductions in depression symptoms were significantly correlated with both improvements in HRQOL and reductions in psoriasis severity. PASI 75 responders experienced a significantly greater improvement in depression symptoms than nonresponders.

The finding that adalimumab treatment is associated with reduction in the symptoms of depression is consistent with a study of etanercept, another TNF antagonist, suggesting that anti-TNF therapies as a class can reduce depression in patients with psoriasis. Compared with the current study, a smaller percentage of patients in the etanercept study had significant depression at baseline, potentially owing to selection bias. In contrast, the baseline rate of depression observed in the current study, which included patients with body surface area of 5% or greater, is slightly greater than published estimates for patients with all grades of psoriasis. Therefore, the results presented here may better represent the prevalence of depression symptoms in patients with moderate to severe psoriasis and the potential for improving depression symptoms in this population. Furthermore, previous studies have found that depression symptoms are often unrecognized or untreated in patients with psoriasis. The high prevalence of baseline depression symptoms observed in patients with psoriasis in the current study compared with the lesser rate of reported previous diagnosis underscores the importance of depression screening in patients with psoriasis.

The improvements in ZDS scores observed after adalimumab treatment in this study are comparable with those observed in studies of other diseases and treatments. For example, a placebo-controlled study of fluoxetine as a prophylactic for migraine found a 7.5-point improvement in ZDS scores in the fluoxetine arm, and a study of the effects of darbepoetin in patients with anemia with chronic heart failure found a 10-point ZDS score improvement in the

Table II. Change in Zung Self-rating Depression Scale score from baseline to week 12/early termination by treatment group

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>ZDS score, mean (SD)</th>
<th>Change in ZDS score*</th>
<th>Difference in change†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Wk 12/ET</td>
<td>Mean 95% CI P value**</td>
<td>Mean 95% CI P value**</td>
</tr>
<tr>
<td>Adalimumab 40 mg eow</td>
<td>42.9 (12.4) 36.2 (11.5)</td>
<td>−6.7 −10.1 to −3.3 .0003</td>
<td>−6.0 −9.5 to −2.5 .001</td>
</tr>
<tr>
<td>Placebo</td>
<td>45.8 (14.0) 44.2 (14.2)</td>
<td>−1.5 −4.0 to 1.0 .23</td>
<td></td>
</tr>
</tbody>
</table>

CI, Confidence interval; eow, every other wk; ET, early termination; ZDS, Zung Self-rating Depression Scale.
*Change calculated as wk 12/ET value minus baseline value.
†Estimated using analysis of covariance model adjusting for baseline ZDS score.
‡From paired Student t test.

Table III. Correlation of depression symptom severity, psoriasis symptom severity, and health-related quality of life with baseline Zung Self-rating Depression Scale scores and score changes

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Baseline scores</th>
<th>Score changes from baseline to wk 12/ET</th>
<th>Pearson correlations with ZDS score</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>r P value*</td>
<td>r P value*</td>
<td></td>
</tr>
<tr>
<td>PASI</td>
<td>0.1 .21</td>
<td>0.5 &lt;.0001</td>
<td></td>
</tr>
<tr>
<td>DLQI</td>
<td>0.5 &lt;.0001</td>
<td>0.5 &lt;.0001</td>
<td></td>
</tr>
<tr>
<td>SF-36 MCS</td>
<td>−0.8 &lt;.0001</td>
<td>−0.6 &lt;.0001</td>
<td></td>
</tr>
<tr>
<td>SF-36 PCS</td>
<td>−0.4 &lt;.0001</td>
<td>−0.4 &lt;.0001</td>
<td></td>
</tr>
</tbody>
</table>

DLQI, Dermatology Life Quality Index; ET, early termination; MCS, Mental Component Summary; PASI, Psoriasis Area and Severity Index; PCS, Physical Component Summary; SF-36, Short Form 36 Health Survey; ZDS, Zung Self-rating Depression Scale.
*For tests of zero correlation.
By comparison, the adalimumab-treated patients in the current study had a ZDS score mean improvement of 6.7 points, and PASI 75 responders had a mean improvement of 10.6 points. Although there is no established minimum important difference for ZDS score changes, it is notable that the observed effects of adalimumab versus placebo and of PASI 75 response versus nonresponse are comparable with half the SD of baseline ZDS scores, a commonly used measure of clinical significance. These results indicate that successful management of psoriasis with adalimumab can substantially reduce depression symptoms for patients with psoriasis.

At baseline in this study, worse depression symptoms, as measured by greater ZDS scores, were significantly correlated with impaired HRQOL, as measured by DLQI, Short Form 36 Health Survey, MCS, and PCS scores. However, baseline depression symptoms were not correlated with greater psoriasis severity, as measured by PASI scores. These findings are consistent with studies showing that plaque visibility and palmoplantar location, which are not specifically measured in the PASI score, can have a greater impact on HRQOL than plaque severity. Reductions in ZDS scores over 12 weeks were correlated with improvements in physical symptoms (PASI scores) and all HRQOL measures. This latter finding is in contrast to the finding by Tyring et al, wherein reductions in depression symptoms with etanercept were not significantly correlated with improved PASI scores, despite a larger sample of more than 600 patients. The reason for this difference between studies is unclear, but it could stem from differences in patient populations, including the lesser baseline prevalence of depression in the study by Tyring et al, the use of different instruments to measure depression symptoms, or differences between adalimumab and etanercept.

Several studies have suggested that depression may be directly mediated by inflammatory cytokines. Patients with major depression exhibit increased concentrations of inflammatory cytokines, which can access areas of the brain involved in depression. Mediators of inflammation such as TNF have also been associated with the development of depression through the stimulation of neuronal hormones that are known to be elevated in major depression. Persistently elevated concentrations of TNF in patients resistant to therapy for depression suggest a possible direct link between TNF and depression origin. These findings suggest that inhibition of inflammatory cytokines in patients with depression may improve depression symptoms, but further studies are needed to address this question.

Although psoriasis is an inflammatory disease mediated by TNF, it is unclear to what degree depression in psoriasis is TNF mediated versus a consequence of other psoriasis symptoms. The results of this analysis cannot distinguish whether adalimumab has a direct or indirect effect on depression. Because the study data included ZDS assessments only at baseline and at the final visit, it was not possible to assess the degree to which depression symptoms improved before versus after psoriasis symptoms improved. Furthermore, joint symptoms were not assessed in the current study for patients with comorbid psoriatic arthritis. Substantial physical impairment is associated with psoriatic arthritis, and it is possible that improvements in depression symptoms may be associated with improvements in joint symptoms in these patients. Further studies are needed to address these questions and to address the possibility of a direct link between TNF and depression origin in psoriasis.

Patients included in this analysis were naïve to anti-TNF treatment. Depression symptoms in patients with psoriasis and a history of anti-TNF treatment may respond differently to adalimumab. It was not possible to assess whether the adalimumab and placebo arms were well balanced on key risk factors and cofactors associated with depression, such as family history and life stress, because these characteristics were not recorded. Recorded baseline characteristics such as age, sex, PASI, and DLQI were well balanced between treatment arms, as reported previously.

This study corroborates previous findings that depression is a common comorbidity of psoriasis and has a substantial negative impact on HRQOL. Furthermore, these results suggest that a comprehensive approach to psoriasis treatment, including
screening for and management of depression, could benefit patients and potentially lead to cost savings. The estimated annual per-patient cost for psoriasis in 1998 to 2005 was approximately $1500, and depression, too, is associated with substantial costs estimated at $1743 per patient in 2000. Given the high prevalence of depression in patients with moderate to severe psoriasis, further study of the benefits of detecting, treating, and reducing depression symptoms in patients with psoriasis is warranted.

CONCLUSION

Compared with placebo, adalimumab significantly reduces symptoms of depression in patients with moderate to severe psoriasis. Reductions in depression symptoms were significantly correlated with reductions in psoriasis severity and improvements in dermatologic quality of life. Attainment of a PASI 75 response was associated with a significant improvement in depression symptoms. Although screening for depression symptoms is not commonplace in dermatology practice, appropriate management of psoriasis should include depression screening, with reduction of depression symptoms a treatment goal.

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REFERENCES