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Original

Reduction in pain scores and improvement in depressive symptoms in patients with hidradenitis suppurativa treated with adalimumab in a phase 2, randomized, placebo-controlled trial

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Abstract

Background: Hidradenitis suppurativa (HS) is a chronic, recurrent, inflammatory skin disease with frequent comorbidities of pain and depression. Adalimumab treatment for 16 weeks improved HS lesions significantly versus placebo (NCT00918255).

Objective: The relationship between pain and depressive symptoms and the effects of adalimumab on each was examined in this post hoc analysis.

Methods: Patients with moderate to severe HS (N=154) were randomized 1:1:1 to adalimumab 40 mg weekly (ew), adalimumab 40 mg every other week (eow), or placebo. Skin pain was assessed using a visual analog scale (VAS; 0–100 mm). Depressive symptoms were assessed using the 9-item Patient Health Questionnaire (PHQ-9; score ≥10 indicative of depression).

Results: At baseline, overall mean±SD pain VAS was 54.3±26.5 mm and 41.8% of patients had PHQ-9 scores ≥10. At baseline, VAS pain scores (mean±SD) were significantly higher (P<0.001) for patients with PHQ-9 scores ≥10 (63.9±23.3) versus <10 (47.4±26.7). At Week 16, clinically relevant pain reduction was observed for ew-treated patients with baseline PHQ-9 score ≥10 (ew, 45.8%; eow, 29.4%; placebo, 23.8%) and <10 (ew, 50.0%; eow, 37.9%; placebo, 29.6%), but did not reach statistical significance. In patients with high baseline pain (≥median VAS score), adalimumab ew significantly decreased depressive symptoms versus placebo (PHQ-9 scores, –34.03% vs +2.26%; P<0.01).

Conclusion: Patients with moderate to severe HS had a high degree of pain and depressive symptoms at baseline. Adalimumab therapy was associated with decreased pain and depressive symptoms compared to baseline.

Key words: hidradenitis suppurativa, pain, depression, adalimumab, tumor necrosis factor α, quality of life

Abbreviations:
ADA, adalimumab
ANOVA, analysis of variance
DLQI, Dermatology Life Quality Index
eow, every other week
ew, every week
HS, hidradenitis suppurativa
PHQ-9, 9-item Patient Health Questionnaire
TNF-α, tumor necrosis factor α
VAS, visual analog scale

Introduction

Hidradenitis suppurativa (HS) is a chronic, recurrent, inflammatory disease that commonly involves the inguen and axilla [1, 2]; it is sometimes referred to as acne inversa [3]. Manifestations are varied and include inflamed and non-inflamed nodules, sinuses, tombstone comedones, and subsequent scarring [4]. Hidradenitis suppurativa has an estimated prevalence of approximately 1% to 4% in the general population, though its true incidence has not been fully defined [5], and is more common among women, smokers, and overweight individuals [6, 7, 8]. Comorbidities such as metabolic syndrome and depression are common in patients with HS [9, 10, 11, 12], further contributing to an already substantial burden of disease.

The psychosocial impact of HS on patients may not always be fully appreciated and has received limited research attention [13]. Compared with patients with other dermatologic conditions, such as acne and psoriasis, patients with HS have worse scores on the Dermatology Life Quality Index (DLQI), indicating worse average morbidity [14, 15]. Pain, soreness, stinging, and itching are aspects of the disease that are believed to contribute most to impairment of dermatology-specific quality of life [14]. DLQI score has been found to be positively correlated with the number of lesions per month [14] and with greater HS severity according to Hurley stage [15, 16]. Furthermore, approximately 40% to 50% of patients with HS have been diagnosed with depression at some time [9, 17], although point estimates based on questionnaire responses generally yield lower depression prevalence rates of 21% to 42% [9, 15, 16, 18]. The average severity of depressive symptoms in patients with HS appears to exceed the severity of depressive symptoms in patients with other dermatologic diseases [16, 18]. As with DLQI scores, the magnitude of depressive symptoms is related to the severity or burden of HS disease [9, 15, 16, 18]. Depressive symptoms may include feelings of hopelessness and low self-worth [19], which correspond to feelings of powerlessness over a condition like HS, which may flare at random intervals [13].

Management of HS has been described as challenging for patients and their physicians [20]. Although no medical treatment is approved, numerous strategies are used to treat HS and its symptoms. Initially, lifestyle modifications (eg, avoidance of tobacco and reduction of body weight) and supportive measures (eg, covering lesions to avoid friction) may be suggested [21, 22]. Mild disease may be also treated with topical therapies (clindamycin, dapsone, and resorcinol); however, disease progression may require the use of systemic treatments, including oral antibiotics (rifampicin, clindamycin, tetracyclines, and dapsone), retinoids (acitretin), and immunosuppressive agents (cyclosporine) [3, 21, 22].

Adalimumab, a fully human, immunoglobulin G1 monoclonal antibody specifically targeted against tumor necrosis factor α (TNF-α), is approved for treatment of moderate to severe HS [23]. The efficacy and safety of adalimumab was first demonstrated in a randomized, double-blind, placebo-controlled, parallel-group, phase 2 study in patients with moderate to severe HS [24]. Treatment with adalimumab once every week (ew) resulted in a significantly greater proportion of patients achieving clinical response compared with placebo at Week 16, based on an HS Physician's Global Assessment (17.6% vs 3.9%, respectively; P=0.025), with similar incidences of adverse events in the active treatment and placebo groups. In the same trial, significant improvements to skin pain measured with a visual analog scale (VAS), and depressive symptoms measured with the 9-item Patient Health Questionnaire (PHQ-9) [19] were observed by Week 16 with weekly adalimumab compared with placebo (P=0.037 and P=0.025, respectively) [24].

Despite the wide array of possible therapeutic approaches to HS, there is limited published research on the management of pain and depression in patients with this disease [2, 25]. In clinical practice, analgesic and antidepressant drugs may be used to address

these components of the disease [2, 22, 25]. Combinations of topical/oral analgesics with anticonvulsants (gabapentin, pregabalin) and combined serotonin and norepinephrine reuptake inhibitors (duloxetine, venlafaxine) have been suggested by Scheinfeld [25].

In a general patient population, pain and depression were frequently shown to coexist and each to impair improvement of either symptom [26]. In patients with HS, a treatment that alleviates pain caused by HS might also reduce depressive symptoms, and vice versa. This report describes a post hoc analysis of the relationship between pain and depressive symptoms in patients with moderate to severe HS during the double blind period of a phase 2 study of adalimumab [24].

Methods

Study Design

The current article describes an exploratory analysis from a previously reported randomized, multicenter, 2-period study (clinicaltrials.gov entry NCT00918255) [24]. In the first period, patients were randomized 1:1:1 with stratification by Hurley stage (I/II vs III) to receive double-blind adalimumab 40 mg ew (Weeks 4–Week 15, after initial doses of 160 mg at Week 0 and 80 mg at Week 2), adalimumab 40 mg every other week (eow; Weeks 1–15, after an initial dose of 80 mg at Week 0), or matching placebo. In the second period, all patients received 36 weeks of open-label treatment with adalimumab 40 mg eow, with or without dose escalation to 40 mg ew. The study protocol was reviewed and approved by an independent ethics committee at each investigative site. Results presented here are solely from the first, randomized, double-blind period because, in the second period, all patients received the suboptimal eow dosing regimen.

Patients

Patients enrolled in this trial were at least 18 years of age and had moderate to severe HS (diagnosed at least 6 months before baseline) in at least 2 distinct anatomical areas, but were unresponsive to or intolerant of oral antibiotics. Patients were excluded for any previous treatment with a TNF-α antagonist or treatment with any systemic nonbiologic therapy, other than antibiotics, within the previous 4 weeks. Symptoms of pain and depression were not part of the entry criteria; analgesics and antidepressants were not prohibited, but concomitant use of these medications was monitored during the study. Detailed inclusion and exclusion criteria are available in the original publication [24]. All patients provided written informed consent to participate in the study.

Assessments

Table 1. Nine-Symptom Checklist of the Patient Health Questionnaire (PHQ-9) Depression Severity Measure [19]

Over the last 2 weeks, how often have you been bothered by any of the following problems?
1. Little interest or pleasure in doing things
2. Feeling down, depressed, or hopeless
3. Trouble falling or staying asleep, or sleeping too much
4. Feeling tired or having little energy
5. Poor appetite or overeating
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down
7. Trouble concentrating on things, such as reading the newspaper or watching television
8. Moving or speaking so slowly that other people could have noticed? Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual
9. Thought that you would be better off dead or of hurting yourself in some way

For each item, score 0, not at all; 1, several days; 2, more than half the days; 3, nearly every day.

Hidradenitis suppurativa–related skin pain over the past week was self-assessed at Weeks 0, 2, 4, 8, 12, and 16 using the Patient Global Assessment of skin pain on a VAS from 0 to 100 mm, with higher scores representing worse pain. Depressive symptoms over the past 2 weeks were assessed by patients at Weeks 0 and 16 using the PHQ-9 [19]. The PHQ-9 symptom checklist is shown in Table 1; the total score ranges from 0 to 27 (minimal depression, 0–4; mild depression, 5–9; moderate depression, 10–14; moderately severe depression, 15–19; and severe depression, 20–27).

Statistical Analysis

A clinically relevant reduction in pain was defined as ≥30% reduction in pain score [27] accompanied by a 10-mm absolute decrease relative to baseline score; pain reduction was analyzed only among patients with a baseline pain score ≥10 mm. Non-responder imputation was used to impute missing pain scores (ie, patients without pain scores at a study visit were imputed to have failed to achieve a 30% reduction in pain). The proportions of patients achieving a clinically relevant reduction in pain scores were analyzed using the Cochran–Mantel–Haenszel test, adjusted for the stratification factor (Hurley stage I/II vs III). Pairwise comparison was performed between each active treatment group and placebo.

A PHQ-9 score ≥10 was considered to represent evidence of at least moderate depressive symptoms [19]. Patients with a baseline PHQ-9 score were included in the analysis at Week 16. Missing PHQ-9 scores at Week 16 were imputed using the last observation carried forward method. Changes from baseline in PHQ-9 scores were analyzed using an analysis of covariance, with the stratification factor (Hurley stage I/II vs III) as a covariate. A pairwise comparison was performed between each active treatment group and placebo.

Results

Patients

Table 2. Baseline Characteristics

Characteristic	Placebo (n=51)	ADA eow (n=52)	ADA ew (n=51)
Mean age (SD), y	37.8 (12.1)	36.1 (12.5)	35.1 (10.7)
Female, n (%)	36 (70.6)	38 (73.1)	36 (70.6)
Mean body weight (SD), kg	96.5 (24.8)	99.8 (26.8)	95.4 (22.9)
Nicotine users, n (%)	29 (56.9)	26 (50.0)	30 (58.8)
Prior opioid use, n (%)	7 (13.7)	7 (13.5)	7 (13.7)
Mean VAS-measured skin pain (SD), mm	57.8 (28.5)	53.0 (26.4)	52.0 (24.5)
Mean PHQ-9 score*	9.1 (6.8)	8.1 (6.1)	11.1 (7.0)
PHQ-9 score <10, n (%)*	30 (58.5)	34 (66.7)	25 (49.0)

ADA=adalimumab; ew=every week; eow=every other week; PHQ=Patient Health Questionnaire; VAS, visual analog scale.

*Based on available data for 51 patients in each arm.

As previously described [24], baseline characteristics were generally similar among treatment groups **(Table 2)** and consistent with characteristics expected for the moderate to severe HS population [7]. A total of 14% of patients reported prior opioid use which was balanced across treatment groups [24]. Other prior medications commonly used by the study population included ibuprofen (12%), minocycline (9%), clindamycin (8%), doxycycline (7%), drospirenone with ethinylestradiol (6%) and paracetamol (acetaminophen) (6%). A medical history of depression was reported by 18% of patients. The mean age of enrolled patients (N=154) was 35 to 38 years across the treatment arms; 71% of patients were female and 71% were white. The largest proportion of patients was at Hurley stage II (55%); smaller proportions were at Hurley stage III (29%) or I (16%). The mean

duration of HS was 11 to 13 years. Approximately half of the patients (55%) were current tobacco smokers and most (84%) were either overweight or obese, which were defined as a body mass index of ≥25 to <30.0 kg/m^2 or ≥30.0 kg/m^2, respectively.

Baseline Pain Scores and Depressive Symptoms

In the overall study population, all patients had baseline VAS pain score data and 153 patients had baseline PHQ-9 data.

The mean (SD) baseline VAS skin pain score in the overall study population was 54.3 (26.5) mm, approximately in the middle region between the extremes of no pain and maximum pain. Baseline pain scores were similar (*P*=0.491; 1-way analysis of variance [ANOVA]) among the treatment groups: mean (SD) skin pain VAS scores were 57.8 (28.51) mm in the adalimumab 40 mg ew group, 53.0 (26.35) mm in the adalimumab 40 mg eow group, and 52.0 (24.51) mm in the placebo group.

The mean (SD) PHQ-9 score in the overall study population at baseline was 9.5 (6.7) and was similar (*P*=0.078; 1-way ANOVA) among the 3 treatment arms. Baseline PHQ-9 scores in the individual treatment groups bracketed the cutoff between mild and moderate depression and were similar across treatment groups; mean (SD) PHQ-9 scores were 11.1 (7.0) in the adalimumab 40 mg ew group, 8.1 (6.1) in the adalimumab 40 mg eow group, and 9.1 (6.8) in the placebo group. In the same respective treatment groups, 51.0% (n=26), 33.3% (n=17), and 41.2% (n=21) of the patients had a PHQ-9 score ≥10 (indicative of at least moderate depressive symptoms), and 49.0% (n=25), 66.7% (n=34) and 58.8% (n=30) had a PHQ-9 score <10.

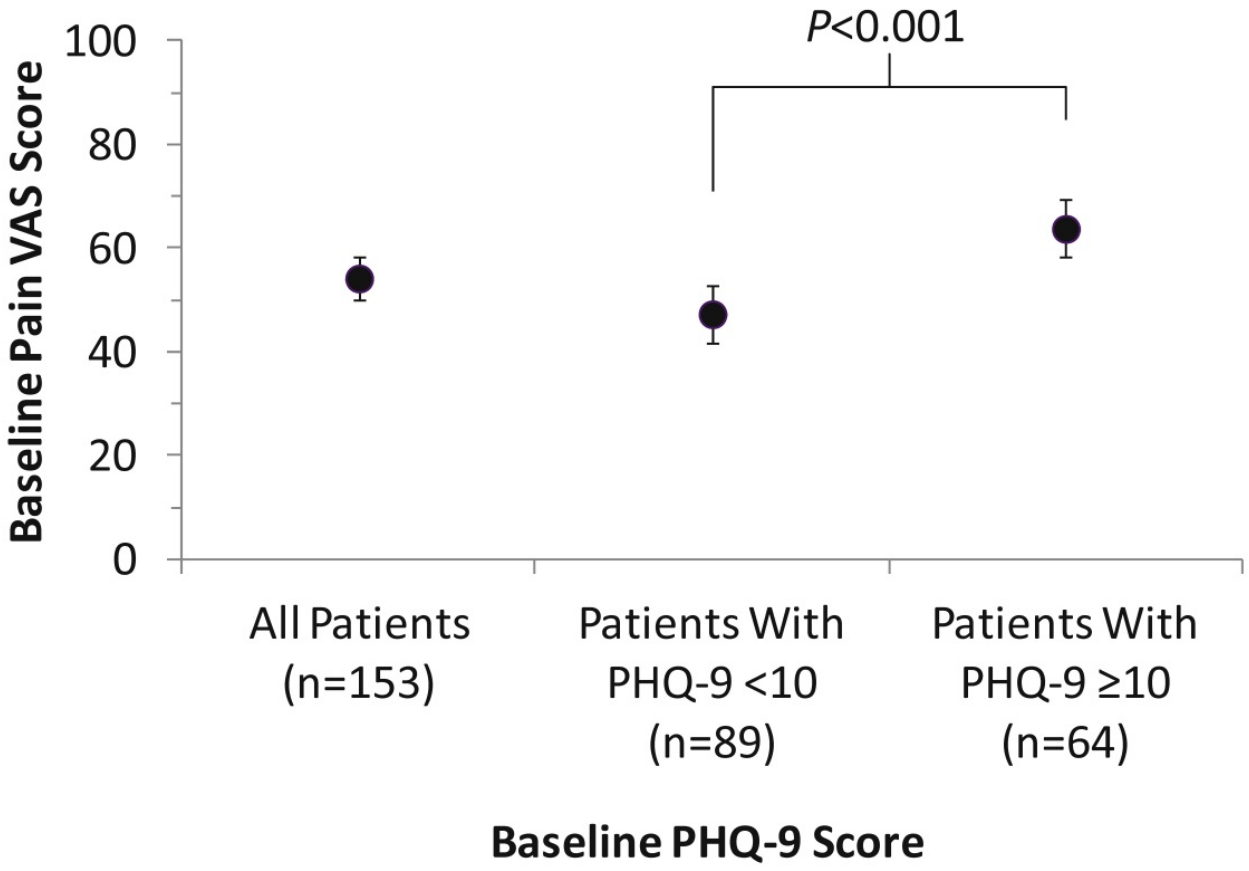
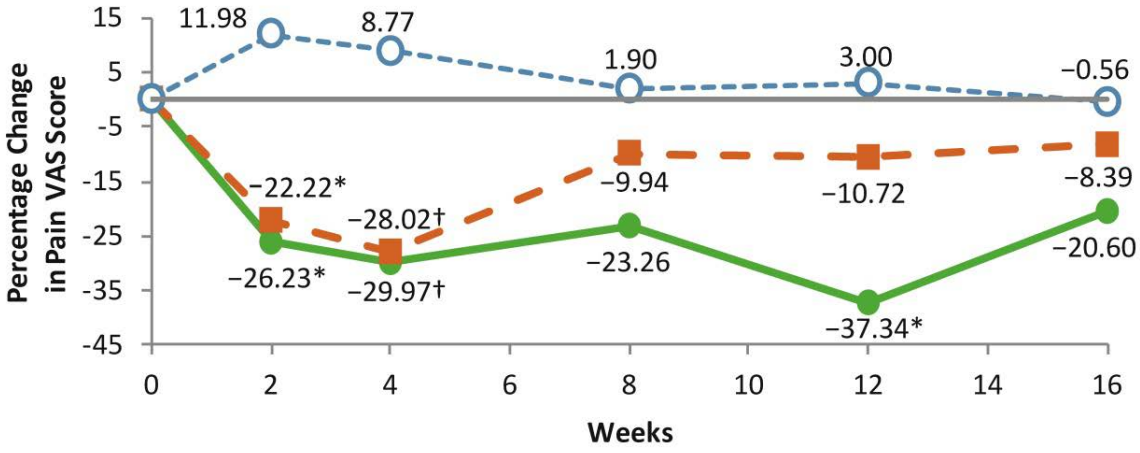


Figure 1. Mean Patient Global Assessment of pain at baseline using a visual analog scale according to the presence of depressive symptoms based on PHQ-9 scores. PHQ-9=9-item Patient Health Questionnaire. Error bars denote the 95% CI. *P* values were derived from 1-way analysis of variance.

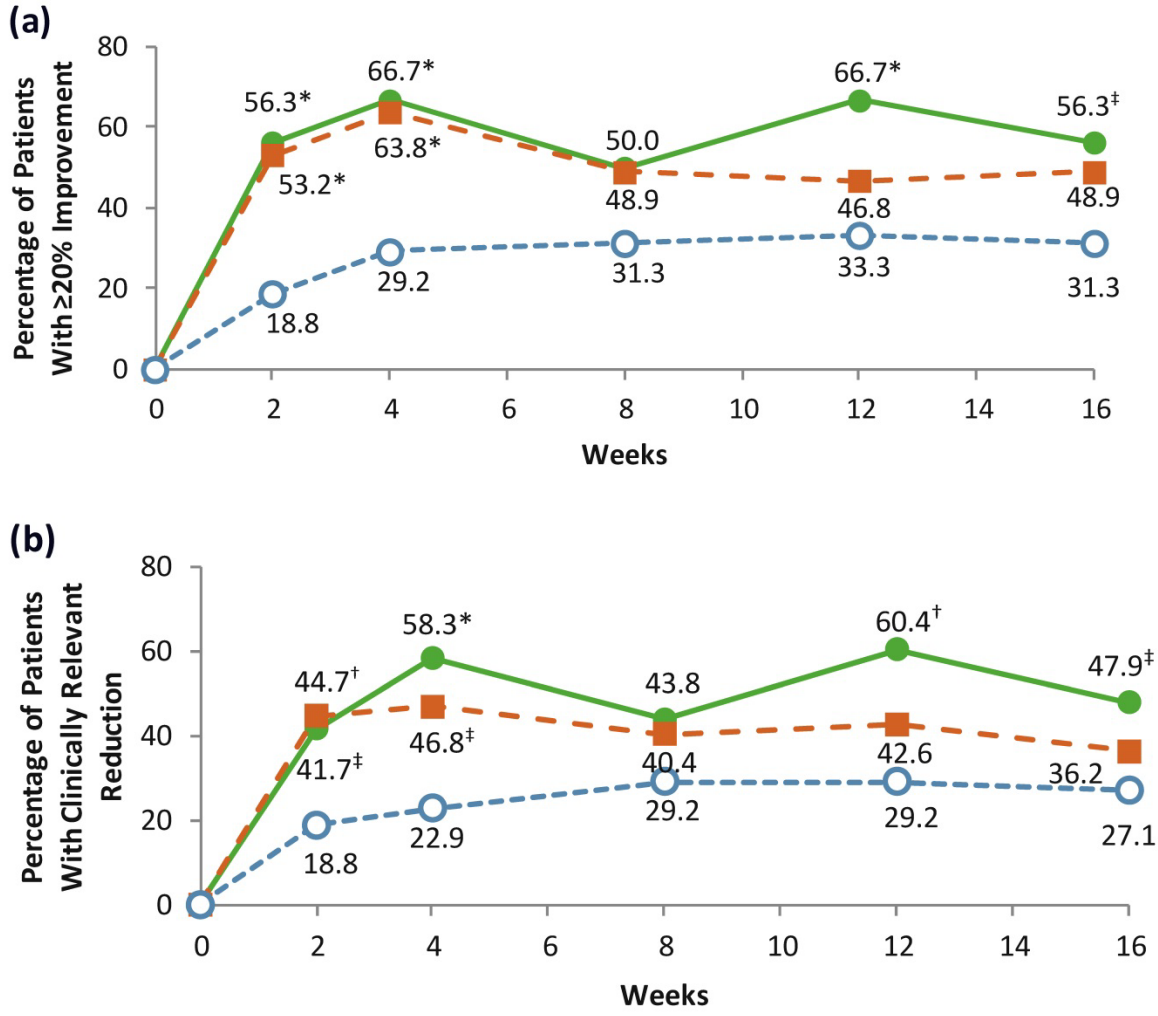
In the overall study population, the mean VAS pain score at baseline was significantly higher (*P*<0.001; 1-way ANOVA) in patients with at least moderate depressive symptoms (PHQ-9 score ≥10; mean VAS pain score, 63.9 mm) than in patients without evidence of depressive symptoms (PHQ-9 score <10; mean VAS pain score, 47.4 mm; **Figure 1**).

Overall Changes in Pain Scores



N					
ADA 40 mg ew	47	47	47	47	47
ADA 40 mg eow	46	47	47	47	47
Placebo	47	47	47	47	47

Figure 2. Mean percentage change in VAS pain score in patients with baseline VAS pain scores ≥10. ADA=adalimumab; eow=every other week; ew=every week; VAS=visual analog scale. **P*<0.001; †*P*<0.01 compared with placebo. *P* values were derived from an analysis of covariance with baseline Hurley stage strata (I/II vs III) as a covariate within each stratum. Least-squares mean was presented.



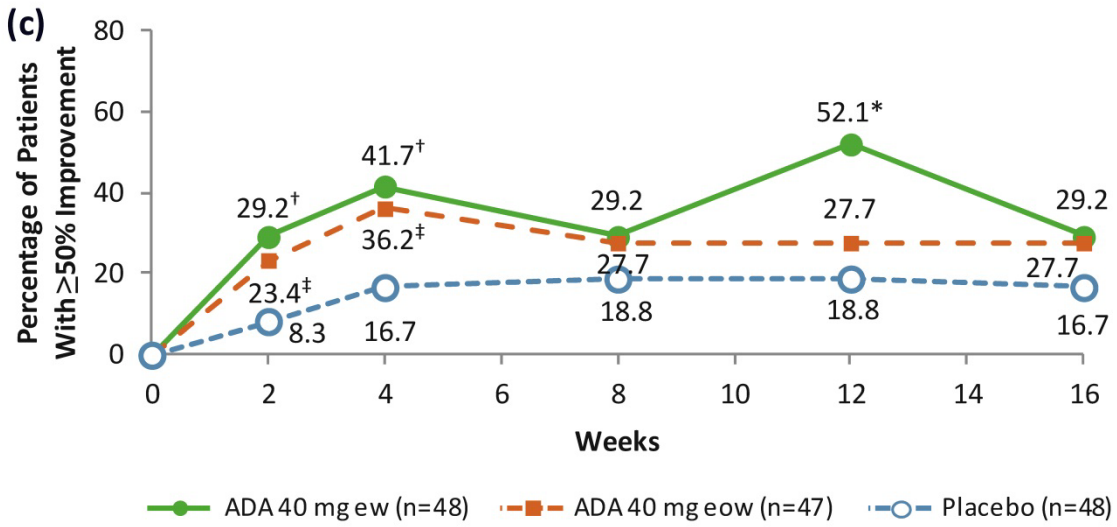


Figure 3. Percentage of patients with improvements from baseline in VAS pain score of (A) ≥20%, (B) clinically relevant reduction, and (C) ≥50%. ADA=adalimumab; eow=every other week; ew=every week; VAS=visual analog scale. **P*<0.001; †*P*<0.01; ‡*P*<0.05 compared with placebo. *P* values were derived from a Cochran–Mantel–Haenszel test adjusted for Hurley stage strata (I/II vs III).

In patients with a baseline VAS score ≥10 mm (n=143), skin pain consistently decreased more in patients treated with either dose of adalimumab compared with placebo at every assessment over the 16-week study period, reaching statistical significance at several time points **(Figure 2)**. Across all visits, average pain scores in patients on placebo worsened or remained at approximately the baseline level. The proportions of patients who responded with an improvement in pain score of at least 20% **(Figure 3A)**, at least 30% **(Figure 3B)**, or at least 50% **(Figure 3C)** were greater with adalimumab than placebo over time, reaching statistical significance at several time points.

Changes in Pain Scores by Baseline Depressive Symptoms

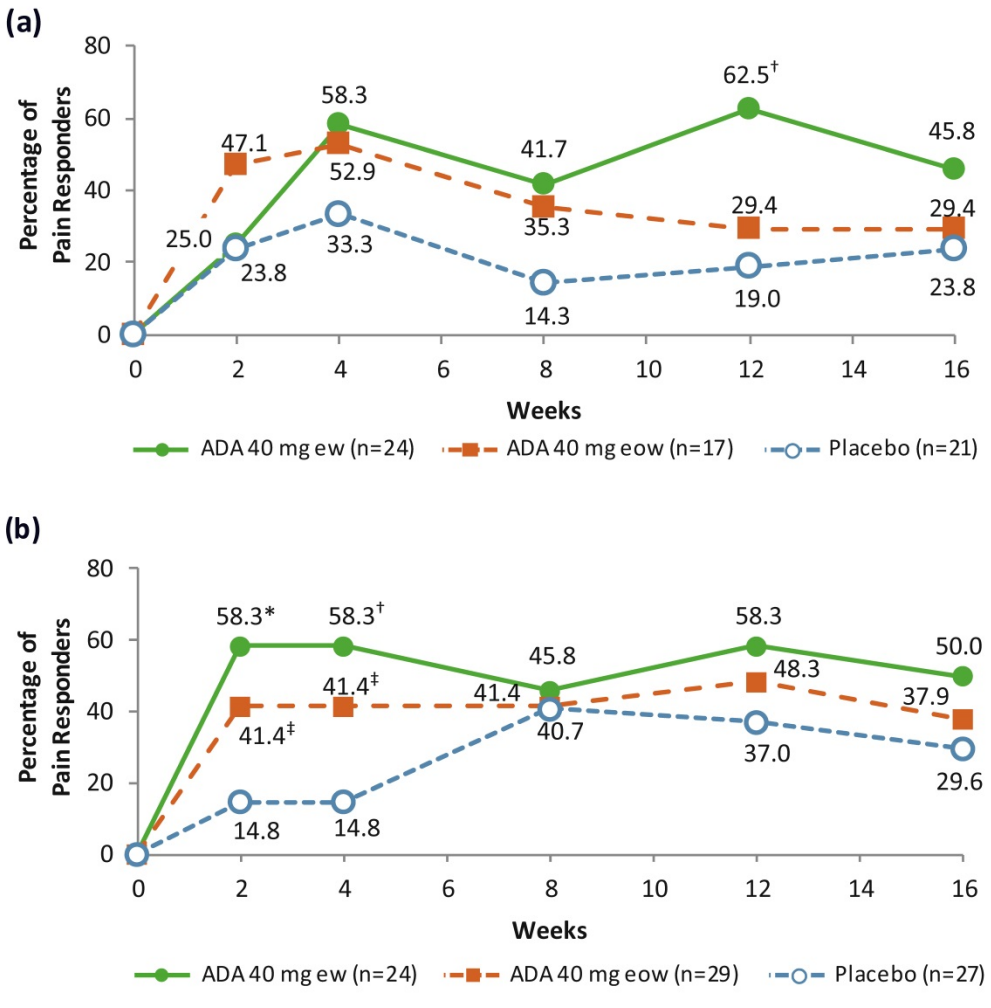


Figure 4. Percentage of pain responders (ie, with a clinically relevant reduction) in patients with baseline PHQ-9 scores (A) ≥10 and (B) <10. ADA=adalimumab; eow=every other week; ew=every week; PHQ-9=9-item Patient Health Questionnaire; VAS=visual analog scale. **P*<0.001; †*P*<0.01; ‡*P*<0.05 compared with placebo. *P* values were derived from a Cochran–Mantel–Haenszel test adjusted for Hurley stage strata (I/II vs III).

Through Week 16, a higher proportion of patients receiving adalimumab therapy achieved a clinically relevant reduction in pain (defined as an improvement from baseline in VAS score of ≥30% and ≥10 mm) compared with patients receiving placebo, regardless of whether patients had at least moderate depressive symptoms at baseline (PHQ-9 score ≥10; **Figure 4A**) or had milder or no depressive symptoms at baseline (PHQ-9 score <10; **Figure 4B**). Statistical significance in comparisons of the adalimumab treatment groups versus the placebo group was reached at some assessments, despite the small sample sizes.

Changes in Depressive Symptoms by Baseline Pain Scores

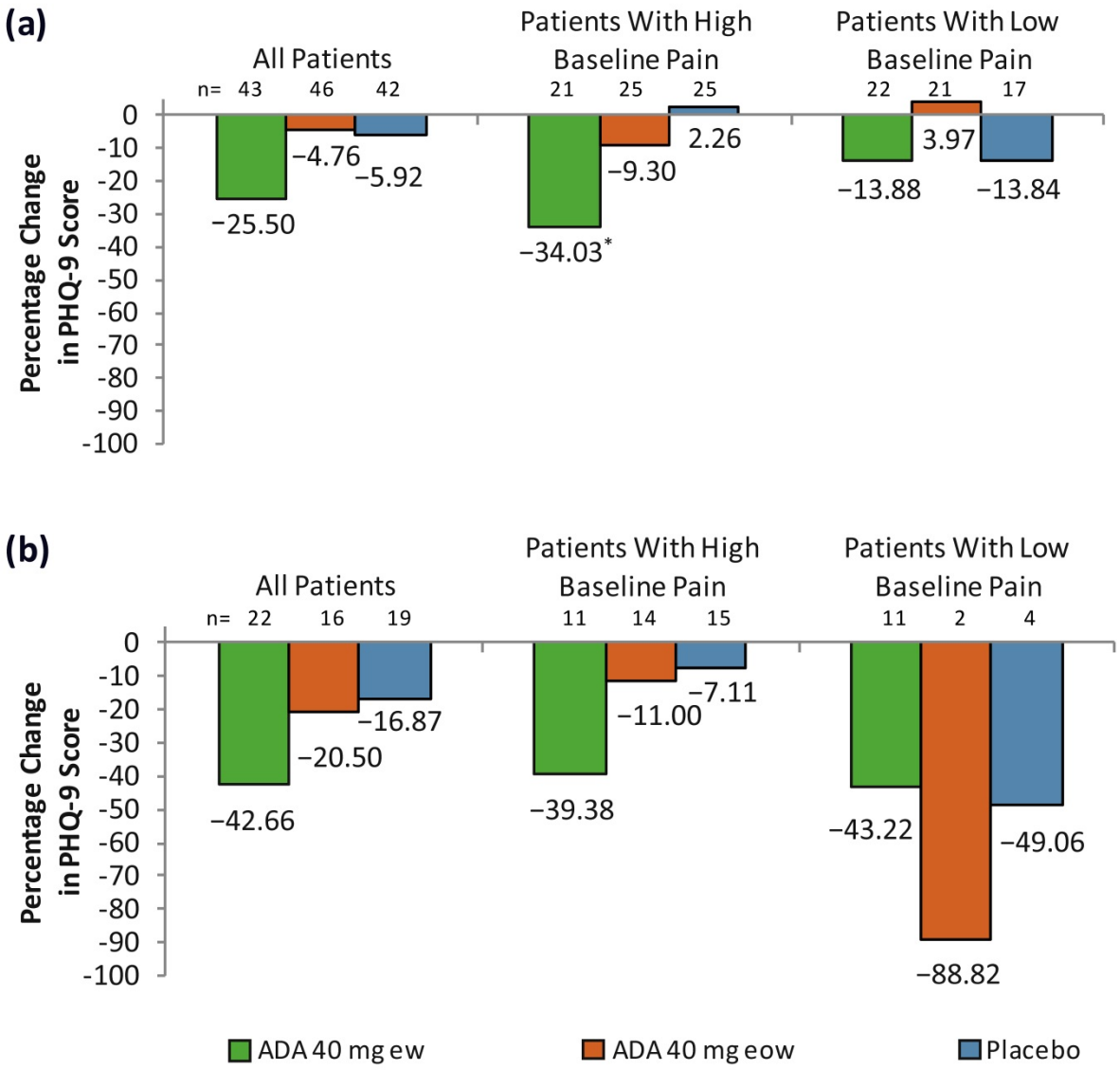


Figure 5. Mean percentage change from baseline to Week 16 in PHQ-9 scores in (A) the overall population and (B) patients with baseline PHQ-9 Scores ≥10 according to baseline pain category. **P*<0.01 compared with placebo. *P* values were derived from an analysis of covariance with baseline Hurley stage strata (I/II vs III) as a covariate within each stratum. High baseline pain was defined as a VAS score greater than or equal to the median; low baseline pain was defined as a VAS score less than the median. Least-squares mean was presented.

Improvement in depressive symptoms from baseline to Week 16 was noted in the adalimumab ew group, as demonstrated by a 25.5% mean decrease in PHQ-9 score compared with a mean reduction of 5.9% in the placebo group; however, statistical significance was not reached for either dose of adalimumab compared with placebo in the overall study population **(Figure 5A)**. PHQ-9 scores improved significantly more with adalimumab 40 mg ew (34.0% reduction) compared with placebo (2.3% reduction) from baseline to Week 16 in patients with high baseline pain (ie, greater than or equal to the median pain score; *P*<0.01) but not in patients with low baseline pain (ie, less than the median pain score; **Figure 5A**).

Similar trends as in the overall patient population were observed in the subgroup of patients with at least moderate depressive symptoms at baseline (PHQ-9 score ≥10). Numerically greater but non-significant reductions in depressive symptoms from baseline to Week 16 were found with adalimumab ew compared with placebo in all patients with a PHQ-9 score ≥10 at baseline (42.66% vs 16.87%; *P*=0.060; **Figure 5B)**, as well as those patients with high baseline pain (39.38% vs 7.11%; *P*=0.056). Due to the very small sample size, no conclusion could be drawn among the patients with low pain at baseline.

Conclusions

The results from this analysis provide empirical support for the hypothesis that pain and depression form a destructive *pas de deux* in HS [25]; depression makes pain worse, and pain worsens depression [25]. In this randomized, placebo-controlled, double-blind, phase 2 trial of adalimumab in patients with HS, large proportions of participants experienced pain and depressive symptoms at baseline, and those patients with worse depressive symptoms reported significantly more pain at baseline. Adalimumab weekly therapy was associated with significant improvement in pain scores overall and in significant reduction of depressive symptoms among patients with high baseline pain scores. The improvements in pain and depression were consistent with the primary findings of the trial, which demonstrated that adalimumab 40 mg ew significantly improved HS lesions and DLQI scores compared with placebo [24]. Although written descriptions corresponding to numeric pain scores have not been established specifically for HS-related skin pain with this scale, scores in the middle region of pain scales across other diseases generally correspond to moderate pain [28, 29, 30].

These results extend prior research demonstrating that the burden of HS extends beyond physical pain and disfigurement. Patients with HS experience emotional reactions, including anger, sadness, worry, and depression, as well as the psychosocial impact of these emotions on daily life [13, 15, 16]. In a study conducted in Israel involving 3207 patients, HS was associated with depression and anxiety as well as other psychiatric disorders [31]. This observation suggests that evaluation of therapeutic improvements of HS should not only focus on objective assessments, but also on subjective patient-reported outcomes, such as pain and depression.

In the current post hoc analysis, greater mean reductions in pain with adalimumab compared with placebo occurred irrespective of the presence of depressive symptoms. In the converse situation, however, the results were different; a substantial mean reduction in depressive symptoms with adalimumab ew compared with placebo was seen to occur only in the subgroup of patients with high baseline pain (greater than the median level). Although this exploratory analysis cannot provide definitive proof, it is consistent with the hypothesis that effectively treating pain associated with HS enables concomitant lessening of depressive symptoms, which are known to be common in patients with HS [31].

Limitations of the current analysis include that it was a post hoc analysis, which was not prospectively designed to test an outcome. Patterns of use of concomitant analgesic and antidepressant drugs during the study were not analyzed. The small number of patients, particularly in certain subgroups, might explain why treatment differences between adalimumab and placebo were not consistently statistically significant (eg, at week 8). Furthermore, the limited duration of the double-blind period may not have allowed full resolution of depressive symptoms, which typically require years of maintenance treatment [32]. Dose-response patterns over time were not always clearly apparent, although the effects on pain assessed with the mean VAS score and the responder analysis appeared to be better sustained with adalimumab ew compared with adalimumab eow. Consistent with this observation, a better clinical response with the ew than eow dosing was also noted in the primary analysis [24].

In conclusion, patients with moderate to severe HS had a high degree of pain and depressive symptoms at baseline. Adalimumab therapy reduced pain to a greater extent than placebo, irrespective of the presence of depressive symptoms. However, patients with higher levels of baseline depression had higher baseline pain, and adalimumab was associated with a reduction in depressive symptoms mostly in those patients with high baseline pain. Further findings regarding adalimumab ew for the treatment of patients with HS are expected from the larger phase 3 trials, PIONEER I (NCT01468207) and PIONEER II (NCT01468233), which include Hospital Anxiety and Depression Scale assessments.

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Conflict of Interest/Disclosure Information: The authors and AbbVie scientists designed the study, and analyzed and interpreted the data. All authors contributed to the development of the content; all authors and AbbVie reviewed and approved the manuscript; the authors maintained control over the final content. N. Scheinfeld has received payments and honoraria from AbbVie and Celgene for participation as an investigator. M. Sundaram, H. Teixeira, and Y. Gu receive salaries as employees of AbbVie and may also receive AbbVie stock and stock

options. At the time of manuscript writing, M. Okun was an employee of AbbVie and held AbbVie stock; he is now affiliated with Fort HealthCare, Fort Atkinson, Wisconsin and works as a consultant for AbbVie.

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