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ORIGINAL ARTICLE

Effects of brodalumab on psoriasis and depressive symptoms in patients with insufficient response to TNF-α inhibitors

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Abstract

The objective of this study was to evaluate emotions of depression and anxiety in psoriatic patients that due to insufficient response to tumor necrosis factor-alpha inhibition (TNF-α), underwent a treatment switch from TNF-α to interleukin 17 inhibition using brodalumab. The Self-rated Montgomery-Asberg Depression Rating Scale and the Hospital Anxiety and Depression Scale were used to assess depression and anxiety. A total of 20 patients with psoriasis were enrolled in the study. They were monitored for a period of 3 months following the transition to brodalumab treatment. The results showed a significant improvement in both the Psoriasis Area and Severity Index as well as symptoms of depression; anxiety symptoms showed a reduction, though not statistically significant. Perhaps of more interest, the positive effects on depression and anxiety seem to be independent of the reduction in skin related psoriatic lesions. These findings highlight the importance of addressing depressive and anxiety symptoms, together with psoriasis severity and quality of life, when managing patients with psoriasis.

KEYWORDS
anxiety, brodalumab, depression, IL-17 inhibitor, psoriasis

1 | INTRODUCTION

An effective psoriasis treatment will reduce the severity of skin lesions as well as the mental burden and risk of depression in psoriasis patients. Today, there are several treatment options for psoriasis, which makes it possible to change therapy when one treatment begins to lose effect. The present study showed improvement in psoriasis and mental well-being after a 12-week treatment of brodalumab, an interleukin-1 7 inhibitor. Furthermore, the improvement in mental disorder symptoms seemed to be independent of the degree of improvement in psoriasis. Even though we know that mental well-being is important for coping with life's various difficulties, consideration of the psychological burden in the treatment regimen for psoriatic patients is often overlooked.

Psoriasis is a chronic, relapsing inflammatory disorder characterized by raised areas of inflamed skin covered with a silvery-white scale.[1] It is associated with multiple comorbidities such as psoriatic arthritis, increased cardiovascular and metabolic disorders as well as depression.[2]

Good mental health is crucial to coping with everyday life. In patients with psoriasis, psoriatic lesions can cause feelings of embarrassment and unattractiveness, which may lead to reduced self-esteem and depression.[3] Several studies have assessed the rate of depression and depressive symptoms among psoriatic patients

and concluded that there is a significantly higher prevalence of depressive symptoms in patients with psoriasis compared to healthy controls.[4–8] Patients with psoriasis are vulnerable to comments and remarks about their disease, which have a negative effect on their self-esteem.[9] It is, therefore, reasonable to assume that an effective treatment for psoriasis should reduce the risk of social withdrawal and the development of depression.

Treatments for patients with moderate to severe psoriasis range from conventional systemic therapy, such as retinoids, methotrexate, and cyclosporine that impact the entire immune system, to specialized drugs such as biologics that block the action of certain cells and proteins of the immune system. The most common biologics used for psoriasis are the tumor necrosis factor-alpha (TNF-α) inhibitors and the interleukin (IL) 12, 23, and 17 inhibitors.[10]

In Sweden, TNF-α inhibitors constitute the first line of biological options for patients not responding to conventional systemic therapy.[11] According to the Swedish guidelines, treatment efficacy is assessed by Psoriasis Area and Severity Index (PASI)[12] and the Dermatology Life Quality Index (DLQI).[13] It is not unusual for the effect of TNF-α inhibitors to decrease over time, which in some patients is due to the development of neutralizing antibodies.[14] Patients qualify for treatment adjustment due to insufficient response estimated as (PASI > 7 or 3 ≤ PASI ≤ 7 and DLQI > 5).[11] Treatment adjustment can be done by either increasing the amount or frequency of doses, adding or adjusting a concomitant systemic treatment, or adding or adjusting a topical treatment. Another adjustment is to switch to another biological class, where the group of IL-17 inhibitors, including brodalumab, is recommended.[11]

Brodalumab is a fully human monoclonal antibody with a unique mechanism of action. It binds with high affinity to the IL-17 receptor subunit A (IL-17 RA), thereby inhibiting downstream signaling of multiple IL-17 family cytokines (IL-17A, IL-17F, IL-17C, IL-17E) involved in the pathogenesis of psoriasis.[15] This mechanism is unlike other anti-IL-17 biologics, such as secukinumab and ixekizumab, which specifically target IL-17A.[16,17]

The cause–effect relationship between psoriasis, psoriasis treatment, and mental health is complex and not fully established. We know that monoamine dysfunction plays a part in the pathophysiology of depression.[18,19] It is now also established that there is an interaction between the immune system, by cytokine-(such as TNF-α, IL-12/23) mediated communication, and the central nervous system in depression.[20,21] According to a meta-analysis conducted in 2010, TNF-α levels are significantly elevated in non-psoriatic patients with depression compared with controls without depression.[22] Another meta-analysis by Fleming et al., showed that TNF-α inhibitors and IL-12/23 significantly reduced depressive symptoms after 12–24 weeks of use in patients with moderate to severe psoriasis.[23] It has also become apparent that patients suffering from depression have elevated levels of IL-17 in their serum.[24–26] However, the relationship between inhibition of IL-17 and its impact on the physiopathology of anxiety and depression in patients with psoriasis must be elucidated.

There are many tools available for assessing depression and anxiety. Unfortunately, none of these are established or used as default for dermatology purposes. Therefore, two different tools were selected for use in our study: the Self-assessment Montgomery-Asberg Depression Rating Scale (MADRS-S)[27] for depression and the Hospital Anxiety and Depression Scale (HADS)[28] covering both depression and anxiety. Both questionnaires correlate reasonably well with expert ratings.[28,29]

For transparency, it should be noted that the original aim of the study was to support the real-life implementation of the Swedish guidelines by comparing the benefits of a treatment switch to IL-17 inhibition compared to further adjustments of TNF-α inhibition. However, due to slow patient recruitment the study was prematurely terminated and the comparison between the study arms could not be achieved.

2 | METHODS

2.1 | Data collection and subjects

The study was implemented across clinics in Sweden that are proactively prescribing biologic treatments. Subjects were recruited consecutively from visits to the outpatient clinics at the Department of Dermatology and Venereology at University Hospitals in Gothenburg and Malmö and hospitals with a dermatology department in Norrköping, Jönköping, and Eskilstuna. Data were collected from 6 December 2018to 29 January 2020.

Patients were eligible if they had received TNF-α for at least 4 months and had at the time of inclusion an absolute PASI score of > 7 or a PASI score of 3–7 and DLQI of > 5. Patients had to be ≥18 years of age at the time of screening, with good command of the Swedish language, and no serious mental or cognitive disturbance. Exclusion and inclusion criteria according to the study design were fulfilled and written informed consent was provided before study initiation. The study was approved by the Regional Ethics Committee in Gothenburg (Dnr. 473-18, Dnr: 2019-03270).

2.2 | Study design and plan-description

The study was an open-label, randomized, parallel group, multicenter, phase 4 study to evaluate the efficacy of brodalumab treatment in subjects with moderate to severe plaque psoriasis who were insufficient responders to TNF-α inhibitor treatment. A screening visit was done 1 week before the initiation of the study, only subjects who met all eligibility criteria were enrolled. Patients were randomized in a 1:1 ratio to either receive brodalumab according to the summary of product characteristics (SmPC; 210 mg weeks 0, 1, 2 and then followed by 210 mg every 2 weeks) for 12 weeks (Brodalumab arm) or to continue with TNF-α for another 12 weeks before receiving brodalumab (TNF/Brodalumab arm).

For those who continued with TNF-α inhibition (TNF/Brodalumab arm), assessments were done at initiation of the study and at weeks 8 and 12. The treatment switch to brodalumab was at week 12, or earlier due to psoriasis severity. Additional clinical assessments were

performed at weeks 16, 20 and 24. In addition, two phone calls were made to the participants in this group at weeks 4 and 28.

For patients receiving brodalumab (Brodalumab arm), assessments were done at the initiation of the study when receiving brodalumab, then at weeks 4, 8 and 12 with a follow-up phone call in week 16.

Due to the low number of recruited patients mentioned above, both arms were pooled for the data analysis with brodalumab start as baseline. Figure 1 gives an overview of the study design.

2.3 | Assessment tools

2.3.1 | Established tools for monitoring psoriasis severity

PASI

The extent and severity of psoriasis was assessed using PASI.[12]

Static Physician's Global Assessment form

The static Physician's Global Assessment form (sPGA) was used by the clinician to assess the severity of psoriasis using five categories: "clear", "almost clear", "mild", "moderate" and "severe".[12]

The Patient Global Assessment form

The Patient Global Assessment form (PaGA) was used by the patient to report the disease severity, using the same five categories as in the sPGA.[30]

Pruritus Visual Analogue Scale

Pruritus (itch) was rated on a Visual Analogue Scale (VAS). The scale is a 0–100 mm straight line without numbers or sections. The left end indicates "no pruritus", and the right end "severe" pruritus.

DLQI

The impact of the disease on the subject's daily life was assessed using the DLQI.[13]

2.3.2 | Additional tools for depression and anxiety

The Montgomery-Asberg Depression Rating Scale–Self

The self-assessment version of the Montgomery-Asberg Depression Rating Scale– (MADRS-S) questionnaire was used to assess depression.[27] It is the self-rating version of the original clinician rated MADRS,[31] which is less comprehensive for the patients to answer and sensitive to changes in different psychiatric treatments. According to studies, MADRS-S is a valid instrument with good sensitivity for screening and assessing major depressive disorders.[29,32] It contains nine questions related to emotions, each on a scale from 0 to 6. Thus, the overall score ranges from 0 to 54 and a score between 0 and 12 indicates none to minimal depression, 13–19 mild depression, and 20 and above moderate to severe depression.[29]

The HADS was used to assess depression and anxiety.[28] It is an acceptable and relatively easy questionnaire and is one of the most frequently used self-assessment tools used to screen depression in cancer patients.[33] HADS is useful for initial diagnosis and tracking the progression or resolution of psychological symptoms.[28] The questionnaire contains 14 questions about emotions on a scale of 0 to 3. Seven questions relate to anxiety (HADS-A) and the other seven to depression (HADS-D). Scores for each scale (anxiety and depression) range from 0 to 21 with scores categorized as follows: 0–7 normal, 8–10 borderline-abnormal, and 11–21 abnormal.[34]

2.3.3 | Statistical analysis

All data were analyzed using R version 3.5.3 (The R Foundation for Statistical Computing).

Wilcoxon's signed rank test was used for paired tests. Spearman's correlation test was used to test for correlations. Holm's method was used to adjust for multiple hypothesis tests. Wilcoxon's rank sum test was used for two-sample tests. A multiple linear regression was made with change in PASI between the start of brodalumab and after 12 weeks of treatment (ΔPASI) as the dependent variable and ΔHADS-A, ΔHADS-D,

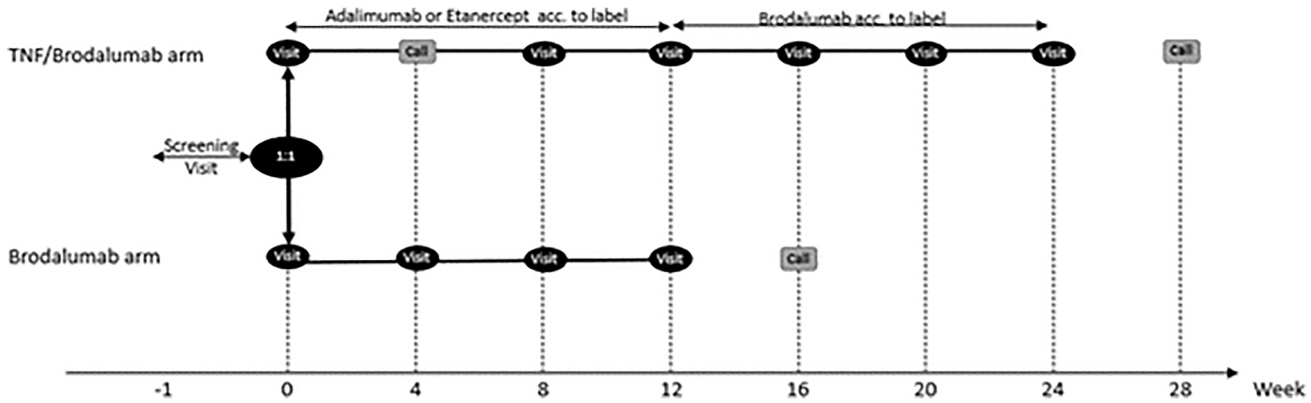


FIGURE 1 The two-arm study design. The TNF/Brodalumab arm started with brodalumab after a further 12 weeks of TNF treatment after inclusion according to label. The Brodalumab arm started with brodalumab at inclusion.

ΔDLQI and ΔMADRS-S as the predictors. All tests were two-sided and $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Participants

During the screening period, a total of 22 patients were asked to participate. Two did not meet the inclusion criteria with a PASI score of > 7 or 3 ≤ PASI ≤ 7 and DLQI > 5 and BSA > 3. The final number of participants was 20 patients, 14 men (70%) and six women (30%). Patients' characteristics at inclusion are shown in Table 1. Three did not complete the study for different reasons: joint pain ($n = 1$), traveling constraints ($n = 1$), and unspecific stomach problems during the TNF-α treatment ($n = 1$).

In summary, 20 patients contributed to the data at brodalumab start and 17 completed the study (12 men and five women). When examining the data, we used brodalumab start as baseline for all patients.

3.2 | Summary of outcomes

There were significant improvements in the mean values of PASI, sPGA, PaGA, DLQI, Pruritus VAS, and MADRS-S after 12 weeks of treatment with brodalumab. HADS-D and HADS-A also improved, but not significantly. The results are summarized in Figure 2.

3.3 | PASI

The PASI mean value for the patients ($n = 20$) was 8.8 before switching to brodalumab. For the 17 patients that attended all visits there was a significant change in PASI mean value from 8.7 to 2.5 after 12 weeks of treatment with brodalumab ($p < 0.0001$; Figure 2). The number of patients with a PASI of < 3 were reported as 1 (baseline), 12 (+4 weeks), 12 (+12 weeks; Figure 3).

After 12 weeks of treatment with brodalumab three of the 17 patients who completed the study had not responded to the treatment according to the Swedish guidelines. Two with a PASI > 7 and one with 3 ≤ PASI ≤ 7 (6.4) and DLQI > 5 (22).

3.4 | DLQI

The DLQI mean value for the patients ($n = 20$) was 10.8 before switching to brodalumab. For the 17 patients that attended all visits there was a significant change in DLQI mean value from 10.1 to 4.1 after 12 weeks of treatment with brodalumab ($p = 0.004$; Figure 2). Patient scoring per visit is shown in Figure 3.

TABLE 1 Basic sample characteristics at the patients' inclusion in the study.

	Total ($n = 20$)
Age, years	
Mean (SD)	49.6 (11.3)
Median	50.5
Min, Max	30, 70
Sex *n* (%)	
Female	6 (30)
Male	14 (70)
Ethnicity *n* (%)	
Hispanic or Latino	1 (5.0)
Not Hispanic or Latino	19 (95)
BMI, mean (SD)	30 (4.3)
Tobacco (*n*)	
Smokers	3
Age at first diagnosis of psoriasis, years	
Mean (SD)	21.8 (10.1)
Median	17.5
Min, Max	11, 44
Involvement of scalp [*n* (%)]	
Yes	13 (65)
No	7 (35)
Involvement of nails *n* (%)	
Yes	8 (40)
No	12 (60)
Diagnosis of psoriatic arthritis *n* (%)	
Yes	3 (15)
No	17 (85)
Diagnosis of depression *n* (%)	
Depressed	2 (10)
Diagnosis of anxiety *n* (%)	
Anxiety	1 (5.0)
PASI, mean (SD)	9.3 (3.5)
sPGA, mean (SD)	3.0 (0.51)
PaGA, mean (SD)	3.2 (0.63)
DLQI, mean (SD)	10.3 (7.2)
VAS pruritus, mean (SD)	51 (28)
HADS anxiety, mean (SD)	3.8 (3.0)
HADS depression, mean (SD)	4.3 (2.9)
MADRS, mean (SD)	7.3 (6.0)

Abbreviations: BMI, body mass index; DLQI, Dermatology Life Quality Index; HADS, Hospital Anxiety and Depression scale; MADRS-S, Montgomery-Asberg Depression Rating Scale-self assessment; PaGA, Patient Global Assessment form; PASI, Psoriasis Area and Severity Index; sPGA, static Physician's Global Assessment form; VAS, visual analogue scale.

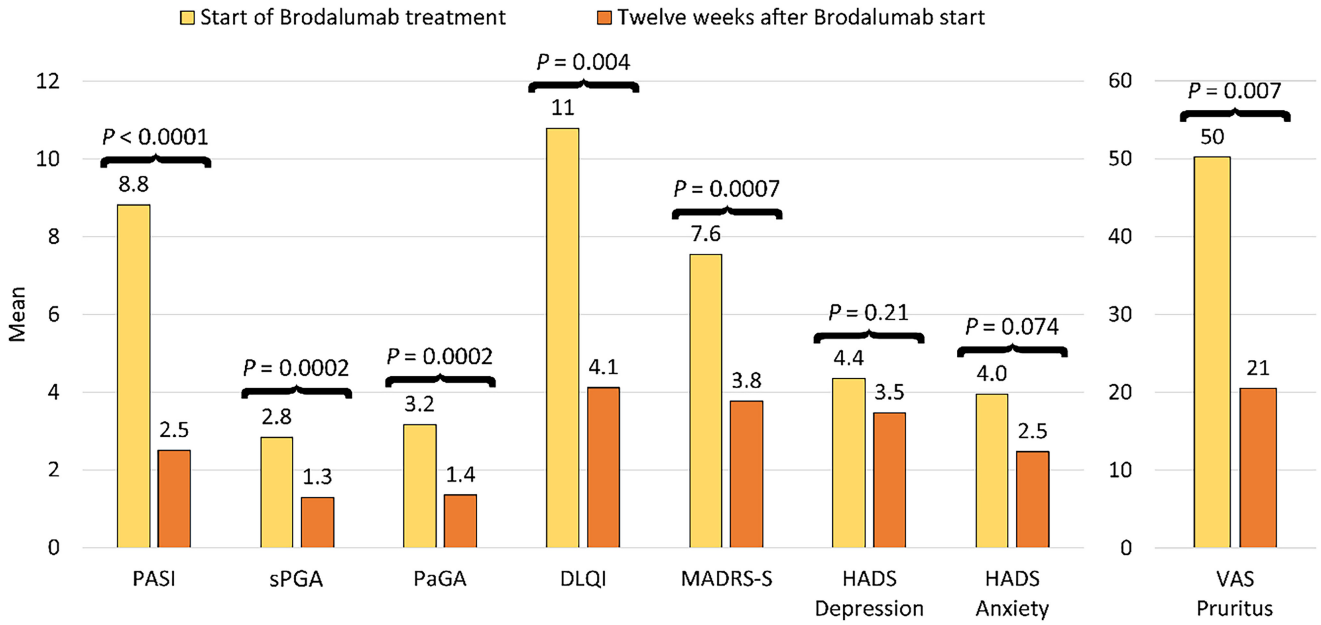


FIGURE 2 Mean values of pooled data from both arms at brodalumab start ($n=20$) and after 12 weeks of treatment with brodalumab ($n=17$) for Psoriasis Area and Severity Index (PASI), Static Physician's Global Assessment (sPGA), Patient Global Assessment (PaGA), Dermatology Life Quality Index (DLQI), Montgomery-Asberg Depression Rating Scale self-assessment (MADRS-S), Hospital Anxiety and Depression Scale for Depression(HADS-D), HADS for Anxiety (HADS-A) and the Pruritis Visual Analog Scale (VAS-Pruritus). The *p*-values were produced by Wilcoxon's signed rank test (paired test).

3.5 | Pruritus VAS

The Pruritus VAS mean value for the patients ($n=20$) was 50 before switching to brodalumab. For the 17 patients that attended all visits, there was a significant change in Pruritus VAS mean value from 47 to 21 after 12 weeks of treatment with brodalumab ($p=0.007$; Figure 2).

3.6 | MADRS-S

The mean value for MADRS-S ($n=20$) was 7.6 before switching to brodalumab. For the 17 patients that attended all visits there was a significant ($p=0.0007$) change in MADRS-S mean value from 7.1 to 3.8 (Figure 2 and Table 2).

The scoring for each MADRS-S emotion, nine in total, showed varying degrees of change. Seven emotions improved and two emotions worsened, however, without significance. The MADRS-S score for each patient during the study and the individual emotions in MADRS-S questionnaire are summarized in Table 2 and Figure 4.

At brodalumab start ($n=20$) four patients scored as depressed according to MADR-S. One of them had a diagnosis of anxiety at inclusion in the study. This patient remained with a score close to depression after the treatment (MADR-S: 14 → 12) and did not respond to brodalumab with (PASI: 8.8 → 6.4 and DLQI: 19 → 22). One of the four with a score of 13 at the start of the study, did not complete the study. The remaining two scored 23 and 19 respectively and were not scored as depressed after 12 weeks of treatment (Figure 4).

After 12 weeks of treatment ($n=17$) with brodalumab only one of patients scored as depressed (Figure 4).

For clarification, two participants already had a diagnosis of depression at inclusion in the study but did not score as depressed according to MADR-S at the start or after 12 weeks of treatment with brodalumab.

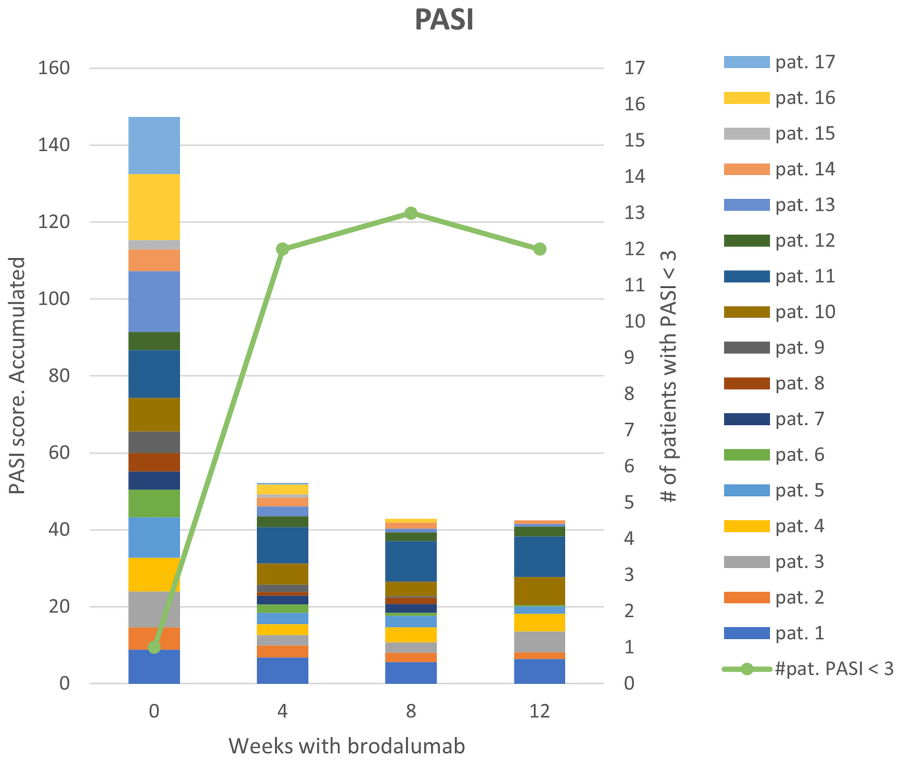
3.7 | HADS-D

The mean value for HADS-D ($n=20$) was 4.4 before switching to brodalumab. For the 17 patients that attended all visits there was a non-significant ($p=0.21$) change in HADS-D mean value from 4.4 to 3.5 (Figure 2 and Table 2).

The scoring for each HADS-D emotion, seven in total, showed varying degrees of change. Four emotions improved, two emotions did not change, and one emotion worsened, however, all without significance. The HADS-D score for each patient during the study and the individual emotions in HADS-D questionnaire are summarized in Table 2 and Figure 5.

At brodalumab start ($n=20$), four patients scored as depressed according to the HADS-D. One of them, who did not complete the study, scored 8 at the start. The others scored 11, 10, and 8 respectively. None of them scored as depressed after 12 weeks of treatment (Figure 5).

After 12 weeks of treatment ($n=17$) with brodalumab one patient scored as depressed (HADS-D: 6 → 9; Figure 5). This is the same patient mentioned in the result section for MADR-S



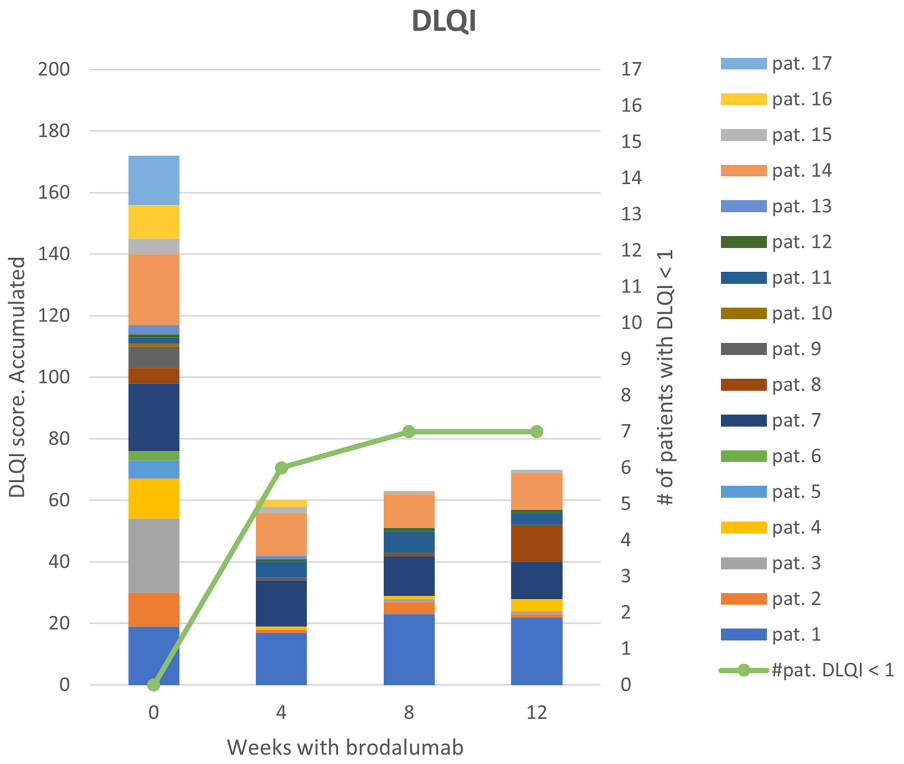


FIGURE 3 Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI) scores for the 17 patients that attended all visits. Showing the number of patients with PASI score of < 3 and DLQI score of < 1.

who already had a diagnosis of anxiety at inclusion in the study and did not respond to brodalumab (PASI: 8.8 → 6.4 and DLQI: 19 → 22).

For clarification, two participants already had a diagnosis of depression at brodalumab start but did not score as depressed according to HADS-D at the start or after 12 weeks of treatment.

3.8 | HADS-A

The mean value for HADS-A ($n = 20$) was 4.0 before switching to brodalumab. For the 17 patients that attended all visits there was a non-significant ($p = 0.074$) change in HADS-A mean value from 3.8 to 2.5 (Figure 2 and Table 2).

TABLE 2 Mean score of each question in Montgomery-Asberg Depression Rating Scale self-assessment (MADRS-S), Hospital Anxiety and Depression Scale for Depression (HADS-D), Hospital Anxiety and Depression Scale for Anxiety (HADS-A) at start and after 12 weeks treatment with brodalumab.

Questions about emotions	Mean score at Brodalumab start ($n = 17$)	Mean score 12 weeks after Brodalumab start ($n = 17$)	p-value	Adjusted p-value	Relative change, %
MADRS-S					
1. Mood	0.59	0.24	0.56	1	−60
2. Feelings of unease	1.06	0.47	0.047	1	−56
3. Sleep	1.47	0.88	0.13	1	−40
4. Appetite	0.41	0.18	0.25	1	−57
5. Ability to concentrate	1.41	0.47	0.012	0.28	−67
6. Initiative	0.94	0.29	0.13	1	−69
7. Emotional involvement	0.71	0.59	0.91	1	−17
8. Pessimism	0.47	0.53	1	1	12
9. Zest of life	0.06	0.12	1	1	100
Total of MADRS-S	**7.12**	**3.76**	**0.0007**	**0.018**	**−47**
HADS depression					
2. I still enjoy things I used to enjoy	1.06	0.82	0.22	0.20	−22
4. I can laugh and see the funny side of things	0.88	0.47	0.15	1	−47
6. I feel cheerful	0.47	0.41	1	1	−13
8. I feel as I am slowed down	1.12	0.71	0.031	1	−37
10. I have lost interest in my appearance	0.29	0.53	0.31	1	80
12. look forward with enjoyment to things	0.29	0.29	1	1	0
14. I can enjoy a good book or radio or TV program	0.24	0.24	1	1	0
Total of HADS Depression	**4.35**	**3.47**	**0.21**	**0.72**	**−20**
HADS anxiety					
1. I fell tense or wound up	0.88	0.35	0.008	0.20	−60
3. I get a sort of frightened feeling as if something awful is about to happen	0.29	0.41	0.75	1	40
5. Worrying thoughts go through my mind	0.41	0.35	0.69	1	−14
7. I can sit at ease and feel relaxed	0.29	0.24	1	1	−20
9. I get a sort of frightened feeling like “butterflies in the stomach”	1.06	0.53	0.008	1	−50
11. I feel restless as I have bon on the move	0.12	0.18	1	1	50
13. I get sudden feelings of panic	0.71	0.41	0.19	1	−42
Total of HADS Anxiety	**3.76**	**2.47**	**0.074**	**1**	**−34**
Total of HADS	**8.12**	**5.94**	**0.059**	**1**	**−27**

Note: Wilcoxon's signed rank test was used to compute p-values. Holm's method was used to compute adjusted p-values (adjusting for multiple tests). The bold values are to highlight the totals of MADRS-S, HADS Depression, HADS Anxiety, and HADS.

The scoring for each HADS-A emotion, seven in total, showed varying degrees of change (five emotions improved and two emotions worsened), however, all without significance. The HADS-A score for each patient during the study and the individual emotions in HADS-A questionnaire are summarized in Figure 6 and Table 2).

At brodalumab start ($n = 20$) three patients scored as having anxiety, according to the HADS-A. One patient, who had a score of 9 at start, did not complete the study. One had a score of 12 at the start and still scored for anxiety after 12 weeks with a score of 8. This patient scored PASI: 4.8 → 0.1, DLQI: 22 → 12 MADR-S: 12 → 14, HADS-D: 8 → 6, but did not have a diagnosis of anxiety or depression at inclusion in the study. One patient scored 8 at the start and ended the study with a score of 0 (Figure 6).

After 12 weeks of treatment ($n = 17$), two patients scored as having anxiety including the one mentioned above who ended with a score of 8. The other scored HADS-A: 7 → 9, PASI: 4.8 → 0, DLQI: 5 → 12, MADR-S: 19 → 9, HADS-D: 11 → 7 (Figure 6).The patient developed severe facial seborrheic dermatitis during the treatment.

For clarification, one participant already had a diagnosis of anxiety at inclusion in the study but did not score for anxiety according to the HADS-A at the start or after 12 weeks of treatment.

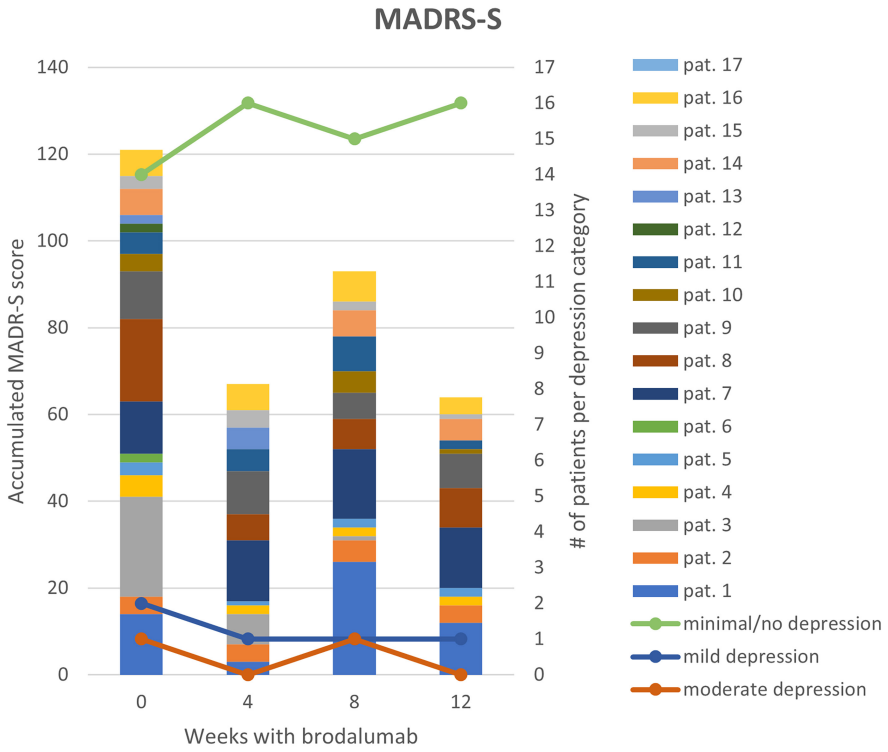
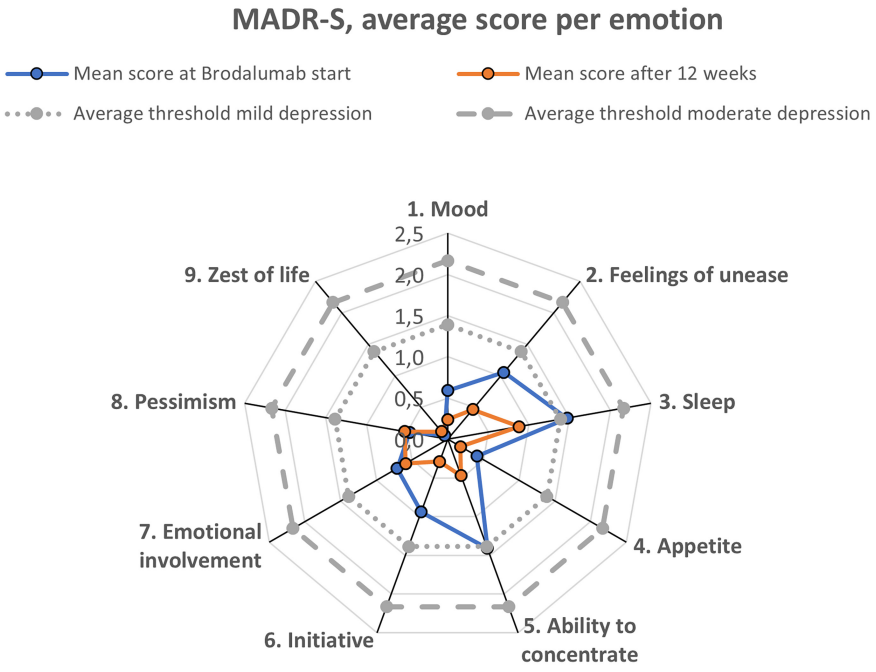


FIGURE 4 Montgomery-Asberg Depression Rating Scale self-assessment (MADRS-S) scores for the 17 patients that attended all visits. A total score between 0 and 12 indicates none to minimal depression, 13–19 mild depression, and 20 and above moderate to severe depression The upper diagram shows individual total scoring per visit and number of patients in each category. The lower diagram shows the mean score for each emotion in the MADR-S questionnaire [0–6 points].



3.9 | Correlation studies

All correlation tests are presented in Table 3.

Two correlations were significant: DLQI at brodalumab start correlated positively with VAS pruritus at brodalumab start (p-adj = 0.0021, p = 0.79) and change in PASI from brodalumab start to 12 weeks after correlated positively with change in sPGA from brodalumab start to 12 weeks after (p-adj = 0.015, p = 0.87).

We divided the group of patients into those that had PASI-improvement <75% and ≥75% (n = 7 and n = 10). Figure 7 gives an

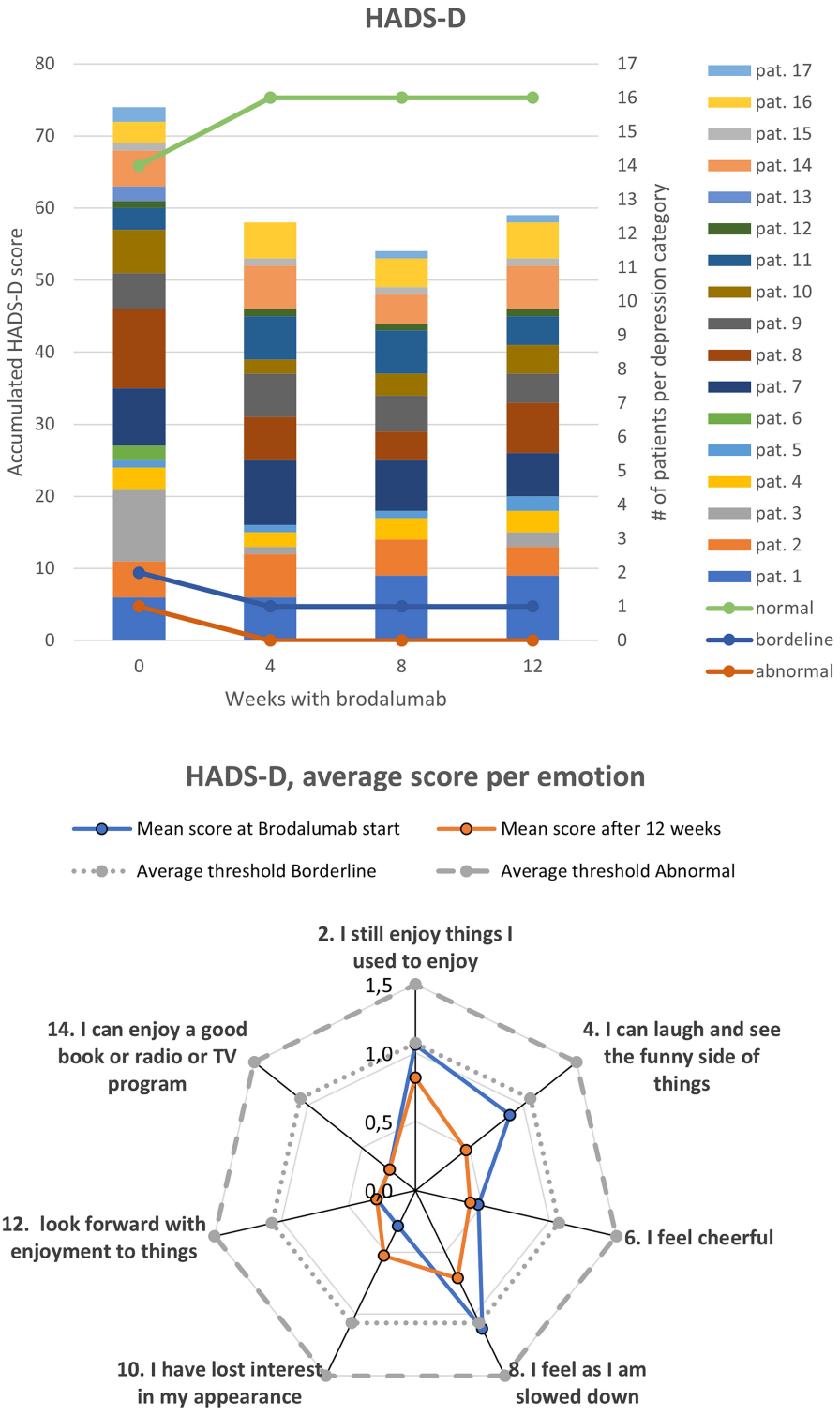


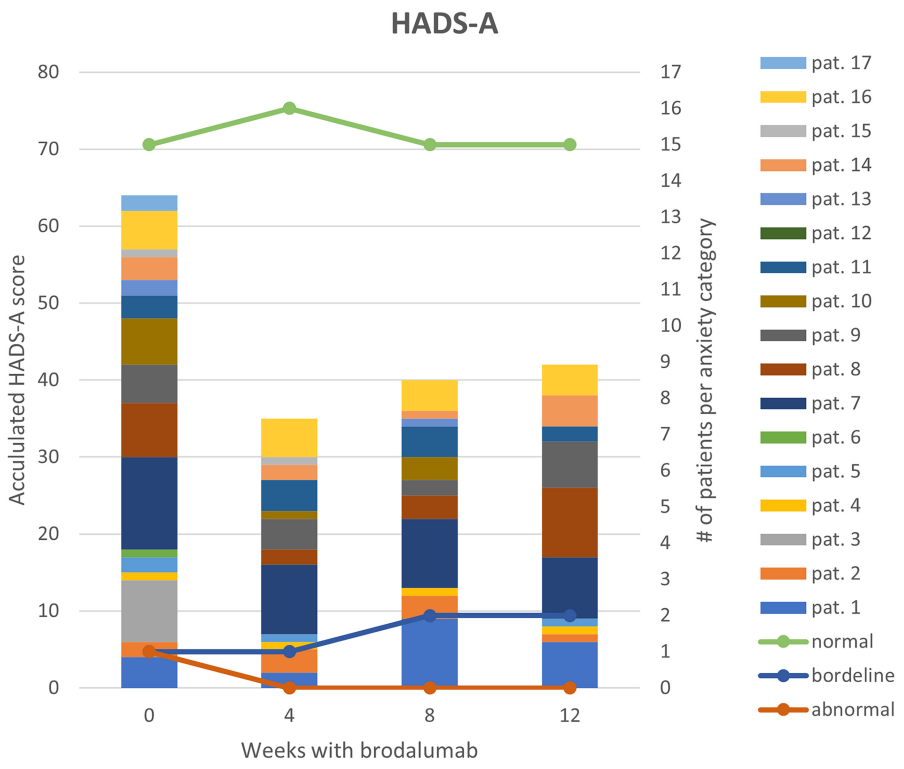
FIGURE 5 Hospital Anxiety and Depression Scale for Depression (HADS-D) scores for the 17 patients that attended all visits. HADS-D contained seven questions. A total score between 0 and 7 is normal, a score between 8 and 10 indicates none to minimal depression (borderline/abnormal), and a score between 11 and 21 indicates depression (abnormal). The upper diagram shows individual total scoring per visit and number of patients in each category. The lower diagram shows mean scores for each emotion in the HADS-D questionnaire [0–3 points].

overview of how these groups scored on the DLQI, HADS-A, HADS-D, and MADRS-S. The groups do not differ significantly in the difference between baseline and week 12 for these variables.

A multiple regression was made with ΔPASI (PASI at 12 weeks minus PASI at baseline) as the dependent variable and ΔHADS-A, ΔHADS-D, ΔDLQI, and ΔMADRS-S as the independent variables. None of the independent variables was significant in the model.

4 | DISCUSSION

In this study we find that when TNF-inhibition has insufficient efficacy, a change of treatment to brodalumab is an effective option to suppress psoriasis and to improve quality of life. These results are fully in line with expectations and reflect the basis for the Swedish guidelines for psoriatic treatment. In addition, we found that the



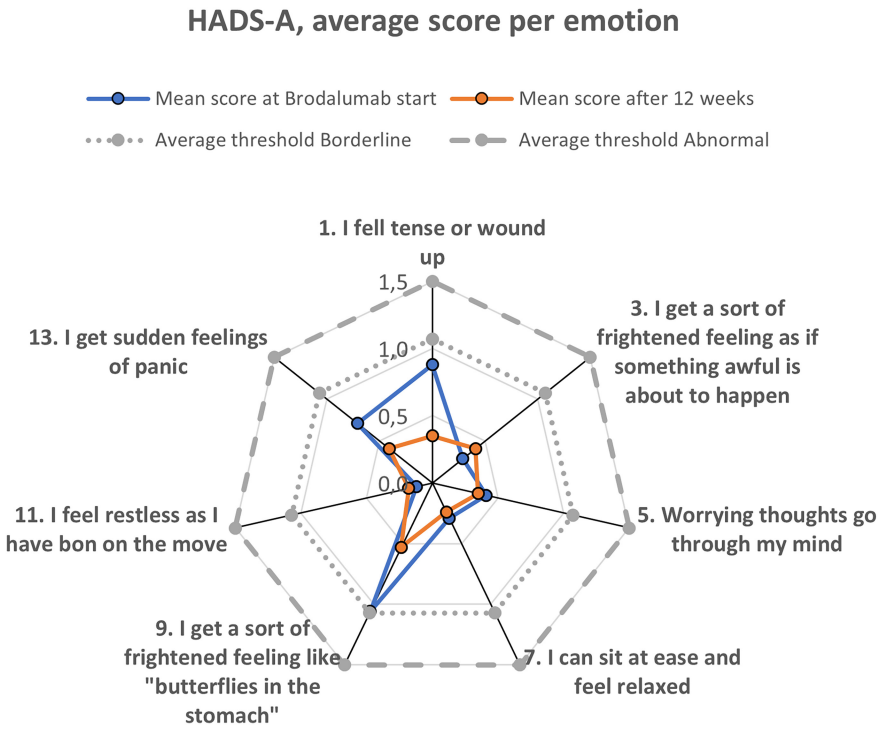


FIGURE 6 Hospital Anxiety and Depression Scale for Anxiety (HADS-A) scores for the 17 patients that attended all visits. A score between 0 and 7 is normal, a score between 8 and 10 indicates none to minimal anxiety (borderline/abnormal) and a score between 11 and 21 indicates anxiety (abnormal). The upper diagram shows individual total scoring per visit and number of patients in each category. The lower diagram shows mean scores for each emotion in the HADS-A questionnaire [0–3 points].

change of treatment had positive effects on anxiety and depression symptoms. This is in line with other studies.[35–39]

Depression was assessed with both the MADRS-S and HADS-D in this study. Although the MADRS-S is regarded as more robust and less sensitive to temporary physical circumstances than the HAS-D, they provided similar results. The most appropriate tool for assessing depression for psoriatic patients is a topic for further studies. This study contributes to the growing evidence aiming to exemplify the utility of these tools for assessment of depression and anxiety that could be used to support dermatologists in their clinic work when assessing mental health in patients with psoriasis.

The relatively quick, and positive response in MADRS-S, HADS-A, and HADS-D indicate that anxiety and depression should be appropriately accounted for. In relation to the Swedish guidelines,

TABLE 3 Spearman's correlations between variable 1 and 2 and *p*-values from Spearman's correlation test.

Variable 1	Variable 2	Spearman's r	*p*-value	Adjusted *p*-value
PASI at brodalumab start	DLQI at brodalumab start	0.16	0.49	1
	MADRS-S at brodalumab start	−0.16	0.49	1
	HADS-D at brodalumab start	−0.22	0.34	1
	HADS-A at brodalumab start	0.023	0.92	1
	VAS at brodalumab start	0.39	0.10	1
	PaGA at brodalumab start	0.30	0.21	1
	sPGA at brodalumab start	0.53	0.024	0.56
DLQI at brodalumab start	PASI at brodalumab start	0.16	0.49	1
	MADRS-S at brodalumab start	0.49	0.034	0.74
	HADS-D at brodalumab start	0.29	0.21	1
	HADS-A at brodalumab start	0.32	0.16	1
	VAS at brodalumab start	0.79	0.0008	**0.021**
	PaGA at brodalumab start	0.70	0.004	0.094
	sPGA at brodalumab start	0.28	0.23	1
Change in PASI from brodalumab start to 12 weeks after	Change in DLQI from brodalumab start to 12 weeks after	0.38	0.13	1
	Change in MADRS-S from brodalumab start to 12 weeks after	−0.34	0.17	1
	Change in HADS-D from brodalumab start to 12 weeks after	0.058	0.82	1
	Change in HADS-A from brodalumab start to 12 weeks after	0.018	0.94	1
	Change in VAS from brodalumab start to 12 weeks after	0.38	0.13	1
	Change in PaGA from brodalumab start to 12 weeks after	0.71	0.006	0.14
	Change in sPGA from brodalumab start to 12 weeks after	0.87	0.0005	**0.015**
Change in DLQI from brodalumab start to 12 weeks after	Change in PASI from brodalumab start to 12 weeks after	0.38	0.13	1
	Change in MADRS-S from brodalumab start to 12 weeks after	−0.35	0.16	1
	Change in HADS-D from brodalumab start to 12 weeks after	0.057	0.82	1
	Change in HADS-A from brodalumab start to 12 weeks after	0.41	0.10	1
	Change in VAS from brodalumab start to 12 weeks after	0.77	0.002	0.051
	Change in PaGA from brodalumab start to 12 weeks after	0.50	0.053	1
	Change in sPGA from brodalumab start to 12 weeks after	0.33	0.19	1

Note: The adjusted *p*-value is using Holm's method. The bold values are to highlight adjusted p-values lower than 0.05.

Abbreviations: DLQI, Dermatology Life Quality Index; HADS-A, Hospital Anxiety and Depression scale-anxiety; HADS-D, Hospital Anxiety and Depression scale-depression; MADRS-S, Montgomery-Asberg Depression Rating Scale-Self assessment; PaGA, Patient Global Assessment form; PASI, Psoriasis Area and Severity Index; sPGA, static Physician's Global Assessment form; VAS, visual analogue scale.

this might lead to switching to a more potent treatment like brodalumab at an earlier stage for certain patients compared to the current criteria.

In our study it was interesting to see that the response to brodalumab treatment in DLQI, HADS-A, HADS-D, and MADRS-S is rather similar between those with a PASI improvement of <75% and

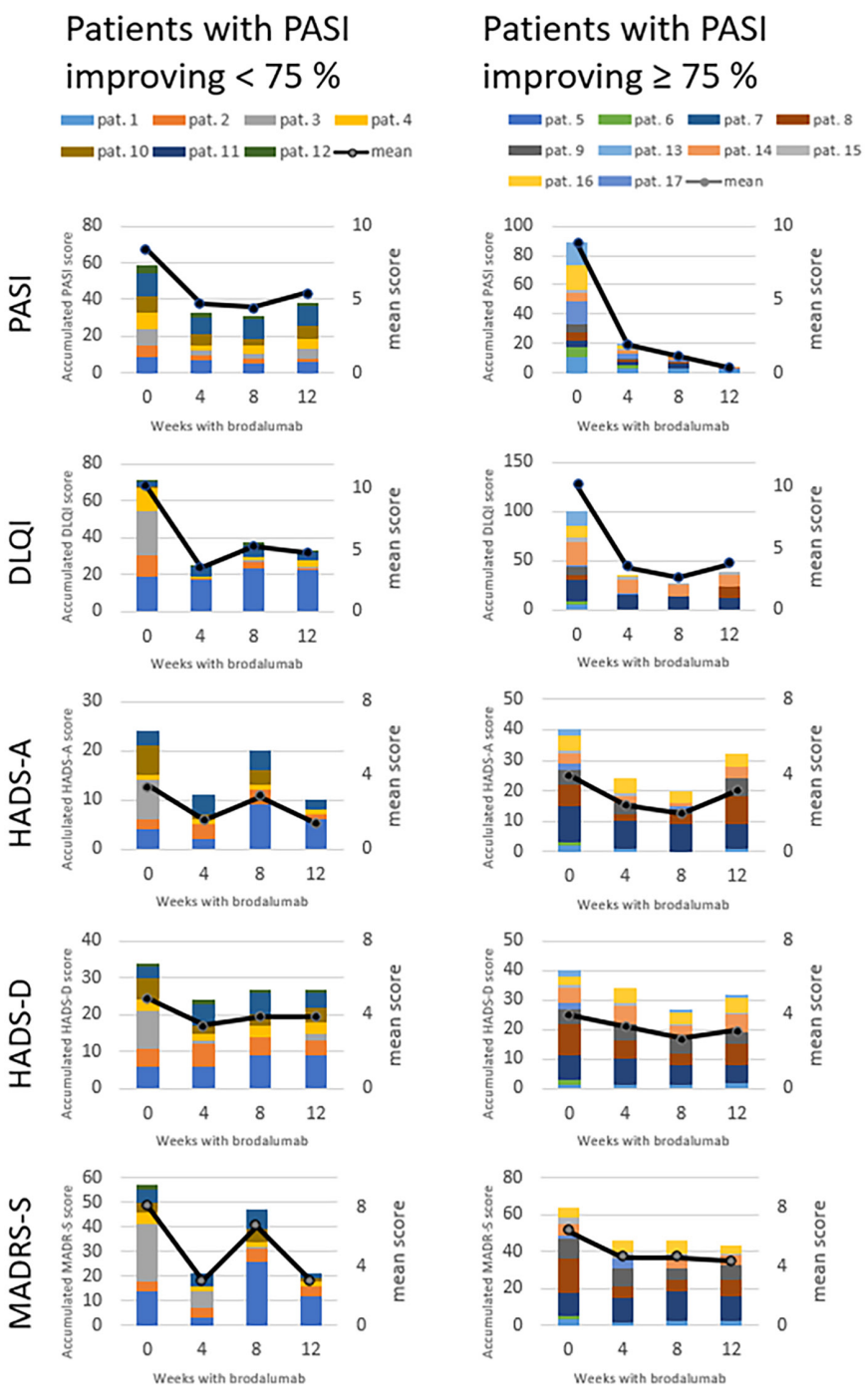


FIGURE 7 Individual and mean comparison in PASI, DLQI, HADS-A, HADS-D and MADRS-S scores between those that registered PASI improvement <75% and ≥75%.

≥75%. This seems to support the growing evidence that IL-17 inhibition affects depression and anxiety in a more direct way, and not only indirectly through psoriatic improvement.

Further, the results of MADRS-S and HADS indicate that certain emotions, reflected in these questionnaires, seem more directly linked with the treatment than others. A few seem not to be affected and one or two even worsened (see spider diagrams in Figures 4–6 and Table 2). It would be of interest in future studies to investigate if certain subsets of emotions relate differently, or not at all, to psoriasis or specific psoriatic treatments.

Pruritus VAS also improved after switching to brodalumab. Pruritus is often not directly linked to psoriatic severity,[40,41] but it has been shown that pruritus increases vulnerability to anxiety and depression.[42] Significance in the correlation between pruritus and depression or anxiety was not established in this study. However, it was established for DLQI, which provides an indication of support for these dependencies.

This study has several limitations. Obviously, the number of participants was small, which limits the statistical significance. Furthermore, the study was open labeled, which may affect the mental well-being measured by DLQI, MADRS-S, and HADS.

The follow-up period was limited to 12 weeks. For several emotions, we observed a rather immediate and transient effect, but 12 weeks may not be enough to monitor the full effect on depression and anxiety. Likewise, it is difficult to draw conclusions regarding those emotions that did not respond to the treatment. Was it due to non-correlation or that the follow up time was simply too short to measure those effects? A similar, but longer-term, study by Ohata et al.[35] with assessments at baseline, +12 weeks, and +48 weeks reported that depression continued to improve in the latter period whilst anxiety was rather stable after 12 weeks.

Depression is a common comorbidity in psoriasis, but also in other physical diseases such as diabetes, heart failure, attention deficit hyperactivity disorder, and other psychiatric diseases. A lot of factors play a part in their etiology such as sex, age, BMI, heredity, socioeconomic factors, education, social status, friends, marital status, pain, smoking, and medications. Some were considered, but most were not analyzed in this study.

In summary, brodalumab treatment for 3 months markedly improved psoriasis severity and symptoms of depression in patients with insufficient response to TNF-a inhibitors. The present results indicate that effectively treating psoriasis has a rapid positive impact on mental well-being. In addition, there may be direct links between specific treatments, like IL-17 inhibitors and mental well-being. Consequently, it is important to evaluate and consider depressive symptoms as part of the treatment regime for psoriasis.

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CONFLICT OF INTEREST STATEMENT

Ylva Andersch-Björkman, Oliver Seifert, Martin Gillstedt are note associated with any advisory board. Sol-Britt Lonne-Rahm is associated with advisory board for Abvvie and LEO-Pharma Emanuela Micu is not associated with any advisory board but is now in a clinical trial for Janssen-Cilag. Amra Osmancevic; Advisory boards for AbbVie, Almirall, Celgene/Amgen, Janssen Cilag, Eli Lilly, UCB-Pharma, LEO Pharma, Pfizer, Novartis, Kyowa Kirin, Bristol Myers Squibb, Meda, Boehringer Ingelheim, Recordati Rare Diseases and Therakos. Clinical trials: with AbbVie, Novartis, LEO Pharma, Janssen-Cilag, UCB-pharma, Pfizer and Boehringer Ingelheim. Participated in clinical trials with Novartis, Abbvie, LEO Pharma, Celgene, Janssen Cilag, UCB-Pharma och Boehringer Ingelheim.

ETHICS STATEMENT

The Ethics Committee in Gothenburg approved the study (Dnr: 473-18, Dnr: 2019-03270).

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