Depressive symptoms, depression, and the effect of biologic therapy among patients in Psoriasis Longitudinal Assessment and Registry (PSOLAR)

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Background: Patients with psoriasis are at an increased risk for depression. However, the impact of treatment on this risk is unclear.

Objective: Evaluate the incidence and impact of treatment on depression among patients with moderate-to-severe psoriasis.

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Methods: We defined a study population within the Psoriasis Longitudinal Assessment and Registry and measured the incidence of depressive symptoms (Hospital Anxiety and Depression Scale—Depression score ≥8) and adverse events (AEs) of depression within cohorts receiving biologics, conventional systemic therapies, or phototherapy. Patients were evaluated at approximately 6-month intervals. Multivariate modeling determined the impact of treatment on risk.

Results: The incidence rates of depressive symptoms were 3.01 per 100 patient-years (PYs) (95% confidence interval [CI], 2.73-3.32), 5.85 per 100 PYs (95% CI, 4.29-7.97), and 5.70 per 100 PYs (95% CI, 4.58-7.10) for biologics, phototherapy, and conventional therapy, respectively. Compared with conventional therapy, biologics reduced the risk for depressive symptoms (hazard ratio, 0.76; 95% CI, 0.59-0.98), whereas phototherapy did not (hazard ratio, 1.05; 95% CI, 0.71-1.54). The incidence rates for AEs of depression were 0.21 per 100 PYs (95% CI, 0.15-0.31) for biologics, 0.55 per 100 PYs (95% CI, 0.21-1.47) for phototherapy, and 0.14 per 100 PYs (95% CI, 0.03-0.55) for conventional therapy; the fact that there were too few events (37 AEs) precluded modeling.

Limitations: Incomplete capture of depression and confounders in the patients on registry.

Conclusion: Compared with conventional therapy, biologics appear to be associated with a lower incidence of depressive symptoms among patients with psoriasis. (J Am Acad Dermatol 2018;78:70-80.)

Key words: biologic therapy; depression; phototherapy; PSOLAR; psoriasis; systemic therapy.

Several studies have documented an increased risk for depression and suicidality among patients with psoriasis. Cross-sectional studies with relatively small sample sizes have noted a high prevalence of depression (>60%) and suicidality (>7%) among patients with psoriasis.[1,2] A large cohort study in the General Practice Research Database found an increased risk for depression, anxiety, and suicidality among patients with psoriasis; depression and suicidality risks were higher for patients with severe disease.[3] Another large cohort analysis, using data from the Nurses' Health Study, found an increased risk for depression in women with psoriasis and psoriatic arthritis.[4] A recent meta-analysis reported similar findings, indicating that patients with psoriasis were at least 1.5 times more likely to experience depression than patients without psoriasis.[5]

Depressive symptoms, as opposed to depression, are assessed by the Hospital Anxiety and Depression Scale—Depression (HADS-D) (Table I). Data from clinical trials support a reduction in depressive symptoms with psoriasis treatment. In the pivotal clinical trials for adalimumab, etanercept, ustekinumab, and infliximab, depressive symptoms were decreased.[6-10] However, beyond clinical trials, there is a paucity of well-controlled or real-world data addressing the effect of systemic therapy on comorbid depression and suicidality among patients with psoriasis. Herein we report findings on the prevalence, incidence, and impact of systemic therapy on comorbid depression and depressive symptoms among patients in Psoriasis Longitudinal Assessment and Registry (PSOLAR).[11]

CAPSULE SUMMARY

- Patients with psoriasis have an increased risk for depression/suicidality.
- Biologic agents for psoriasis were associated with a decreased incidence of depressive symptoms versus conventional systemic therapies in the real-world Psoriasis Longitudinal Assessment and Registry.
- Further exploration of the relationship between biologics and depression among patients with psoriasis is warranted to optimize treatment management.

METHODS

Study design

A full description of PSOLAR has been reported previously.[11,12] Briefly, PSOLAR is a prospective, longitudinal, disease-based registry designed to collect safety, efficacy, and health outcomes data from approximately 12,000 patients with psoriasis in 16 countries who are receiving, or are eligible to receive, conventional systemic or biologic therapies. All patients provided written informed consent before the start of the study, and an institutional review board or ethics committee approved the registry protocol at participating sites. This cohort analysis used data obtained through August 23, 2015.

Abbreviations used:

AE:	adverse event
CI:	confidence intervals
HADS-D:	Hospital Anxiety and Depression Scale—Depression
HR:	hazard ratio
HRQoL:	health-related quality of life
IR:	incidence rate
MedDRA:	Medical Dictionary for Regulatory Activities
PGA:	Physician's Global Assessment
PSOLAR:	Psoriasis Longitudinal Assessment and Registry
PY:	patient-year
TNF—α:	tumor necrosis factor—α

Objectives

The primary objectives of this analysis were to calculate the prevalence and incidence of depression and symptoms suggestive of depression among PSOLAR patients with moderate-to-severe psoriasis and to assess the effect of systemic treatment on the risk for development of these outcomes. Symptoms suggestive of depression were evaluated using the HADS-D (Table I).[13] Incidence of depression was based on reports of adverse events (AEs) of depression. An additional objective was to describe suicidality, including completed suicide, suicide attempt, or suicidal ideation.

Cohorts, exposures, outcomes, and statistical methods

To study the incidence of depression and symptoms of depression, the study population was defined by using the following criteria: no medical history of depression, a HADS-D score lower than 8 at baseline, and exposure to only 1 study therapy (ie, monotherapy). Exposure cohorts were defined as patients treated with (1) biologics (etanercept, adalimumab, infliximab, and ustekinumab), (2) phototherapy (including ultraviolet B and psoralens plus ultraviolet A light), or (3) conventional systemic agents (including methotrexate, cyclosporine, systemic corticosteroids, fumarates, mycophenolate mofetil, and oral retinoids).

Exposure started at the date of the first dose of a cohort-defining therapy on registry (or at enrollment for those who entered the registry while undergoing therapy) and ended at the date of the last cohort-defining therapy dose, the date of switching to a different therapy, discontinuation from the registry, data extraction (August 23, 2015), or death. Outcomes included symptoms suggestive of depression (HADS-D score $\geq$8) and an AE of depression (according to the Medical Dictionary for Regulatory Activities [MedDRA], version 17.1, Standardized MedDRA Queries for Depression and Suicide/Self-injury). These outcomes were considered separately, and patients were followed only until the first occurrence of either outcome. HADS-D data were to be collected at baseline, every 6 months for the next 18 months, and every 12 months thereafter. AEs were to be collected every 6 months; depression was considered an AE of special interest and subjected to enhanced reporting efforts. Suicidality was assessed on the basis of reporting of terms from the Suicide/Self-injury Standardized MedDRA Query; individual cases were classified as completed suicide, suicide attempt, or suicidal ideation.

Incidence rates (IRs) were calculated for depressive symptoms (an initial HADS-D score $\geq$8) or AE of depression for each of the 3 cohorts (combined biologics, phototherapy, or conventional systemic therapy) and for each individual biologic agent. Cox proportional hazards regression models were used to estimate risk on the basis of time to first outcome for each of the treatment cohorts after adjustment for a predefined list of potential confounders as discussed in the Results. Each covariate was independently tested for association with each outcome (univariate P value $< .20$) and included in the final model if an association was confirmed. Hazard ratios (HRs), confidence intervals (CIs), and P values (based on a Wald χ^2 test) were calculated independently for the combined biologics and phototherapy cohorts versus the conventional therapy reference cohort. Each biologic was also separately compared with the conventional therapy reference cohort. To evaluate their potential confounding effect, a post hoc analysis excluding patients with concomitant oral retinoid (acitretin and etretinate) use from the conventional systemics cohort was conducted. Missing values for covariates were imputed (ie, means for continuous factors and medians for categoric factors).

RESULTS

The demographic and clinical characteristics of the 7490 patients in the study population (Table II) were generally similar to those of the overall PSOLAR population (data not shown). The following characteristics were enriched among patients who developed symptoms suggestive of depression compared with the study population: nonwhite race, medical and psychiatric comorbidities, lower

education level, and public insurance. Among patients who reported an AE of depression, the following characteristics were enriched: psychiatric comorbidities (anxiety), lower education level, private insurance, current/past smoking, and less severe psoriasis as assessed by body surface area and the Physician's Global Assessment (PGA).

Incidence of depression

A total of 532 study patients developed symptoms suggestive of depression (HADS-D score ≥8 [Table III]). The IR was lower for the biologics cohort (IR, 3.01; 95% CI, 2.73-3.32) than for the phototherapy cohort (IR, 5.85; 95% CI, 4.29-7.97) and the conventional systemic cohort (IR, 5.70; 95% CI, 4.58-7.10). The IRs for the individual biologic therapy cohorts (ustekinumab, infliximab, etanercept, and adalimumab) were similar to those for the overall biologic cohort and lower than those for the phototherapy and conventional systemic cohorts.

A total of 37 AEs of depression were reported in the study population (Table IV). The IRs for the biologic (IR, 0.21; 95% CI, 0.15-0.31), phototherapy (IR, 0.55; 95% CI, 0.21-1.47), and conventional systemic agent cohorts (IR, 0.14; 95% CI, 0.03-0.55) were lower than those for depressive symptoms. The IRs of AEs of depression were similar among groups; however, the analysis was limited by the low numbers of events and the wide CIs.

Factors predictive of symptoms suggestive of depression

On the basis of the Cox model, treatment with biologics reduced the risk for depressive symptoms (HR, 0.76; 95% CI, 0.59−0.98) compared with conventional systemic therapy, whereas phototherapy did not affect risk (HR, 1.05; 95% CI, 0.71-1.54]) (Table V). Among the individual biologics, only adalimumab significantly lowered the risk for depressive symptoms (HR, 0.63; 95% CI, 0.46-0.86). Ustekinumab and infliximab did not lower risk, but the upper limits of the CIs were only slightly higher than 1.00 (HR, 0.80; 95% CI, 0.60−1.06 and HR, 0.70; 95% CI, 0.47-1.03, respectively). Etanercept did not appear to lower risk (HR, 0.91; 95% CI, 0.67-1.23). Given that oral retinoids have been associated with depressive symptoms and depression,[14] we conducted a sensitivity analysis excluding patients with concomitant retinoid use from all cohorts. The results of the primary analysis were minimally affected. Although combined biologics treatment was no longer associated with reduced risk for depressive symptoms (HR, 0.77; 95% CI, 0.58-1.00; $P = .0542$ [data not shown]), the point estimate and CI were very similar to those in the primary analysis (HR, 0.76 and 95% CI, 0.59-0.98, respectively). Furthermore, the reduced risk for depressive symptoms with adalimumab treatment persisted (HR, 0.63; 95% CI, 0.46-0.87; $P = .0053$ [data not shown]). Factors that increased risk for depressive symptoms included increasing age, nonwhite race, history of anxiety, psoriatic arthritis, higher baseline PGA score, and chronic obstructive pulmonary disease. Factors that decreased the risk included the following: having a college/university education; increasing years since psoriasis began; having a decreased, stable, or 1-point or less increase in PGA; and having private insurance. The low numbers of events precluded Cox modeling of the AEs of depression.

Suicidality

A total of 21 patients in the overall PSOLAR population completed suicide, attempted suicide, or experienced suicidal ideation (IR, 43.0 per 100,000 patient-years [PYs]) (Table VI). Of note, not all of these patients met the inclusion criteria for the study population in the analysis of IRs and HRs reported earlier. Of these 21 patients, 3 completed suicide (IR, 6.1 per 100,000 PYs), 8 attempted suicide, and 10 experienced suicidal ideation (Table VI). All 3 patients who completed suicide were male; 1 patient was being treated with ustekinumab at the time of suicide (within 91 days) and 1 each had been treated previously with ustekinumab and adalimumab, etanercept, or alefacept, respectively (see Table VI for additional details). Of the 8 patients who attempted suicide, 3 were receiving etanercept, 2 infliximab, and 1 adalimumab and 2 were not receiving any systemic psoriatic treatment at the time of the event. All but 1 of the patients who attempted suicide had previously received biologics. Of the 10 patients with suicidal ideation, 5 were receiving ustekinumab, 2 etanercept, and 1 adalimumab and 2 were not receiving any treatment at the time of the event. All patients who experienced suicidal ideation had previously received biologic therapy.

DISCUSSION

Our study indicates that, compared with conventional systemic therapy, biologic therapy is associated with a decreased risk for development of depressive symptoms among patients with moderate-to-severe psoriasis. Of the biologics examined, adalimumab had the strongest association with

Table I. Summary of the Hospital Anxiety and Depression Scale-Depression

A/D	Question	Range
A	I feel tense or "wound up."	0 = Not at all 1 = From time to time, occasionally 2 = A lot of the time 3 = Most of the time
D	I still enjoy the things I used to enjoy.	0 = Definitely as much 1 = Not quite as much 2 = Only a little 3 = Hardly at all
A	I get a sort of frightened feeling as if something awful is about to happen.	0 = Not at all 1 = A little, but it doesn't worry me 2 = Yes, but not too badly 3 = Very definitely and quite badly
D	I can laugh and see the funny side of things.	0 = As much as I always could 1 = Not quite so much now 2 = Definitely not so much now 3 = Not at all
A	Worrying thoughts go through my mind.	0 = Only occasionally 1 = From time to time, but not too often 2 = A lot of the time 3 = A great deal of the time
D	I feel cheerful.	0 = Most of the time 1 = Sometimes 2 = Not often 3 = Not at all
A	I can sit at ease and feel relaxed.	0 = Definitely 1 = Usually 2 = Not often 3 = Not at all
D	I feel as if I am slowed down.	0 = Not at all 1 = Sometimes 2 = Very often 3 = Nearly all the time
A	I get a sort of frightened feeling like "butterflies" in the stomach.	0 = Not at all 1 = Occasionally 2 = Quite often 3 = Very often
D	I have lost interest in my appearance.	0 = I take just as much care as ever 1 = I may not take quite as much care 2 = I don't take as much care as I should 3 = Definitely
A	I feel restless as I have to be on the move.	0 = Not at all 1 = Not very much 2 = Quite a lot 3 = Very much indeed
D	I look forward with enjoyment to things.	0 = As much as I ever did 1 = Rather less than I used to 2 = Definitely less than I used to 3 = Hardly at all
A	I get sudden feelings of panic.	0 = Not at all 1 = Not very often 2 = Quite often 3 = Very often indeed

Continued

Table I. Cont'd

A/D	Question	Range
D	I can enjoy a good book or radio or TV program.	0 = Often 1 = Sometimes 2 = Not often 3 = Very seldom

Patients were asked to complete the HADS questionnaire on the basis of their feelings experienced in the past week. Anxiety and depression were assessed on the basis of the total score, a summation of the individual scores (HADS-D questions marked by a *D*). Scores of 8 or higher for the HADS-D scale were considered elevated.
A, Anxiety; *D*, depression; *HADS-D*, Hospital Anxiety and Depression Scale—Depression; *TV*, television.

lower risk, with the findings for ustekinumab and infliximab trending toward lower risk but not achieving statistical significance. We were unable to assess risk for AEs of depression on account of the low number of events.

In addition, socioeconomic factors appeared to be important considerations. The modeled analysis showed that having achieved a higher level of education appears to reduce the risk for development of depressive symptoms, as has been demonstrated in other studies.[15,16] Having private insurance also decreased the risk for development of depressive symptoms in our analysis.

Depressive symptoms were assessed by using the HADS-D instrument (Table I). The sensitivity and specificity of this instrument for capturing true depression is estimated at around 0.8 when a cutoff score of 8 or higher is used. However, the HADS-D has not been validated in psoriasis, and it is important to note that responses to some of the questions may reflect aspects of psoriasis rather than frank depression.

Given the relatively high incidence of depressive symptoms (occurring in 532 patients), it is surprising that relatively few patients reported an AE of depression (37 events). There are several possible explanations for this discrepancy, including potential under-reporting or underdiagnosis of depression, the impact of treatment on depression, and elements of the study design. In particular, patients were followed only until their first occurrence of either depressive symptoms or AE of depression. Some patients who developed depressive symptoms may have progressed to also have an AE of depression; however, the latter would not have been captured in this analysis. In addition, clinical depression may be underdiagnosed or under-reported in a dermatology setting. PSOLAR does not capture whether patients with elevated HADS-D scores were specifically evaluated for depression by a mental health specialist or primary care provider. An earlier review noted that the 2-question Patient Health Questionnaire-2 ("Over the past 2 weeks, have you felt down, depressed, or hopeless?" and "Over the past 2 weeks, have you felt little interest or pleasure in doing things?") may be as effective as more complex tools for depression screening.[17] A simple, practical approach for depression screening may be more feasible than use of the HADS-D instrument in an outpatient dermatology setting and may promote appropriate referrals for patients at risk.

Despite possible confounding factors or study design, it is possible that biologic therapy reduces the risk for frank depression in patients with psoriasis. We were unable to model this risk on account of the low numbers of AEs of depression. Two potential reasons could explain why biologics may reduce these risks. First, dysregulated systemic inflammation may promote depression.[18] Cytokines can access the central nervous system and elevated tumor necrosis factor-α (TNF-α) levels have been detected in the serum of patients with depression.[19] Consequently, neutralization of inflammatory mediators that are common to psoriasis and depression could alleviate depressive symptoms and prevent progression to depression. Second, various psychosocial factors associated with psoriasis may promote depression. For example, the visibility of psoriasis lesions may lead to social stigmatization.[20] Furthermore, the overall impact of psoriasis on health-related quality of life (HRQoL) has been shown to be similar to that of other major chronic illnesses.[21] Thus, improvement in psoriasis may be expected to enhance social functioning and HRQoL, which may in turn reduce risk for development of depressive symptoms and depression.

Our data are in line with the data from pivotal clinical trials for etanercept, adalimumab, infliximab, and ustekinumab, which show improvement of depressive symptoms with treatment. Both depressive symptoms and HRQoL measures improved in parallel with Psoriasis Area and Severity Index responses.[7-10] Major strengths of our analysis, as compared with analyses of tertiary study

Table II. Demographic and clinical characteristics of the study population

	Developed symptoms suggestive of depression*		Reported AE of depression†		
	No	Yes	No	Yes	Total
Characteristic	(n = 6958)	(n = 532)	(n = 7453)	(n = 37)	(n = 7490)
Age, years, mean ± SD	47.8 ± 13.8	51.0 ± 13.5	48.0 ± 13.8	46.4 ± 13.4	48.0 ± 13.8
Sex, female	2792 (40.1)	214 (40.2)	2985 (40.1)	21 (56.8)	3006 (40.1)
Race					
White	5812 (83.5)	407 (76.5)	6186 (83.0)	33 (89.2)	6219 (83.0)
Black	256 (3.7)	23 (4.3)	277 (3.7)	2 (5.4)	279 (3.7)
Asian	272 (3.9)	45 (8.5)	317 (4.3)	-	317 (4.2)
Hispanic	437 (6.3)	42 (7.9)	479 (6.4)	-	479 (6.4)
Other	180 (2.6)	15 (2.8)	193 (2.6)	2 (5.4)	195 (2.6)
BMI, mean ± SD	30.5 ± 6.8	30.7 ± 7.3	30.5 ± 6.8	32.2 ± 9.1	30.5 ± 6.9
Duration of PsO, mean ± SD	17.9 ± 13.1	17.5 ± 13.2	17.8 ± 13.1	19.3 ± 12.7	17.8 ± 13.1
PGA score, mean ± SD	1.9 ± 1.2	1.9 ± 1.2	1.9 ± 1.2	1.4 ± 1.3	1.9 ± 1.2
PGA score distribution					
0 = clear	933 (13.6)	76 (14.4)	998 (13.6)	11 (29.7)	1009 (13.7)
1 = minimal	1750 (25.5)	126 (23.9)	1864 (25.4)	12 (32.4)	1876 (25.4)
2 = mild	1927 (28.1)	131 (24.8)	2053 (28.0)	5 (13.5)	2058 (27.9)
3 = moderate	1721 (25.1)	147 (27.8)	1862 (25.4)	6 (16.2)	1868 (25.3)
4 = marked	443 (6.5)	42 (8.0)	482 (6.6)	3 (8.1)	485 (6.6)
5 = severe	80 (1.2)	6 (1.1)	86 (1.2)	—	86 (1.2)
% BSA, mean ± SD	10.6 ± 16.0	14.0 ± 19.7	10.9 ± 16.3	6.0 ± 12.3	10.8 ± 16.3
PsA, yes	2292 (33.0)	226 (42.5)	2504 (33.7)	14 (37.8)	2518 (33.7)
PsA, confirmed yes	865 (12.5)	99 (18.6)	960 (12.9)	4 (10.8)	964 (12.9)
CAD/MI/ACVD/stroke/TIA, yes	415 (6.0)	40 (7.5)	454 (6.1)	1 (2.7)	455 (6.1)
Cardiovascular disease					
Atherosclerotic disease	237 (3.4)	26 (4.9)	262 (3.5)	1 (2.7)	263 (3.5)
Coronary artery disease	207 (3.0)	20 (3.8)	227 (3.1)	—	227 (3.0)
Myocardial infarction	155 (2.2)	14 (2.6)	169 (2.3)	—	169 (2.3)
TIA/CVA/stroke	69 (1.0)	9 (1.7)	78 (1.1)	—	78 (1.0)
Pulmonary disease					
Obstructive pulmonary	82 (1.2)	13 (2.4)	94 (1.3)	1 (2.7)	95 (1.3)
Diabetes, type I or II	755 (10.9)	81 (15.2)	833 (11.2)	3 (8.1)	836 (11.2)
Cancer, other/skin melanoma‡	259 (3.7)	26 (4.9)	285 (3.8)	—	285 (3.8)
Psychiatric illness					
Anxiety	391 (5.6)	43 (8.1)	430 (5.8)	4 (10.8)	434 (5.8)
Bipolar	42 (0.6)	8 (1.5)	50 (0.7)	—	50 (0.7)
Schizophrenia	10 (0.1)	2 (0.4)	12 (0.2)	—	12 (0.2)
Suicidal ideation	2 (0.0)	1 (0.2)	3 (0.0)	—	3 (0.0)
Prior treatments					
Phototherapy	3931 (56.5)	283 (53.2)	4192 (56.3)	22 (59.5)	4214 (56.3)
Immunomodulators§	3285 (47.2)	259 (48.7)	3526 (47.3)	18 (48.7)	3544 (47.3)
Biologics					
Adalimumab	2148 (30.9)	159 (29.9)	2294 (30.8)	13 (35.1)	2307 (30.8)
Etanercept	2958 (42.5)	224 (42.1)	3167 (42.5)	15 (40.5)	3182 (42.5)
Infliximab	1076 (15.5)	95 (17.9)	1167 (15.7)	4 (10.8)	1171 (15.6)
Ustekinumab	1490 (21.4)	122 (22.9)	1598 (21.4)	14 (37.8)	1612 (21.5)
Insurance					
None	465 (6.7)	49 (9.2)	512 (6.9)	2 (5.4)	514 (6.9)
Public	1085 (15.6)	148 (27.8)	1223 (16.4)	10 (27.0)	1233 (16.5)
Private	5001 (72.0)	291 (54.7)	5269 (70.8)	23 (62.2)	5292 (70.8)
Both public/private	397 (5.7)	44 (8.3)	439 (5.9)	2 (5.4)	441 (5.9)

Continued

Table II. Cont'd

Characteristic	Developed symptoms suggestive of depression* No (n = 6958)	Developed symptoms suggestive of depression* Yes (n = 532)	Reported AE of depression† No (n = 7453)	Reported AE of depression† Yes (n = 37)	Total (n = 7490)
Education					
Less than high school	383 (5.6)	59 (11.2)	438 (5.9)	4 (10.8)	442 (6.0)
High school	2108 (30.5)	189 (35.9)	2283 (30.9)	14 (37.8)	2297 (30.9)
College/university	3613 (52.3)	224 (42.5)	3820 (51.7)	17 (46.0)	3837 (51.6)
Graduate/professional	800 (11.6)	55 (10.4)	853 (11.5)	2 (5.4)	855 (11.5)
Smoking, current/past	3755 (54.0)	315 (59.2)	4044 (54.3)	26 (70.3)	4070 (54.4)

Data are presented as number (%), unless otherwise specified.
AE, Adverse event; *ACVD*, atherosclerotic cardiovascular disease; *BMI*, body mass index; *BSA*, body surface area; *CAD*, coronary artery disease; *CVA*, cerebrovascular accident; *MI*, myocardial infarction; *n*, number of patients; *PGA*, Physician's Global Assessment; *PsA*, psoriatic arthritis; *PsO*, psoriasis; *SD*, standard deviation; *TIA*, transient ischemic attack.
*Symptoms suggestive of depression were defined as a score of 8 or higher on the Hospital Anxiety and Depression Scale—Depression questionnaire.
†AEs of depression were collected using Standardized Medical Dictionary for Regulatory Activities Queries for Depression and Suicide/Self-injury.
‡Other/skin melanoma was defined as patients with basal cell carcinoma, squamous cell carcinoma, melanoma, unknown skin cancer, or other cancer.
§Immunomodulators included cyclosporine, methotrexate, mycophenolate mofetil, oral tacrolimus, and other.

Table III. Incidence (events per 100 PYs) of symptoms suggestive of depression (HADS-D score ≥8) by monotherapy in patients with no symptoms suggestive of depression (HADS-D score <8) or self-reported history of depression at enrollment in PSOLAR

Therapy	No. of cases	Total PYs	Incidence rate (95% CI)
Biologic agents	412	13681	3.01 (2.73-3.32)
Ustekinumab	173	5739	3.01 (2.60-3.50)
Infliximab	44	1461	3.01 (2.24-4.05)
Etanercept	98	2776	3.53 (2.90-4.30)
Adalimumab	97	3705	2.62 (2.15-3.19)
Phototherapy	40	684	5.85 (4.29-7.97)
Conventional systemics	80	1403	5.70 (4.58-7.10)

CI, Confidence interval; *HADS-D*, Hospital Anxiety and Depression Scale—Depression; *PSOLAR*, Psoriasis Longitudinal Assessment and Registry; *PY*, patient-year.

Table IV. Incidence (events per 100 PYs) of adverse events of depression reported during monotherapy in patients with no symptoms suggestive of depression (HADS-D score <8) or self-reported history of depression at enrollment in PSOLAR

Therapy	No. of cases	Total PYs	Incidence rate (95% CI)
Biologic agents	31	14427	0.21 (0.15-0.31)
Ustekinumab	13	6054	0.21 (0.12-0.37)
Infliximab	2	1554	0.13 (0.03-0.51)
Etanercept	5	2968	0.17 (0.07-0.40)
Adalimumab	11	3850	0.29 (0.16-0.52)
Phototherapy	4	727	0.55 (0.21-1.47)
Conventional systemics	2	1452	0.14 (0.03-0.55)

The overall total of PYs for biologic agents has been rounded to the nearest whole number.
CI, Confidence interval; *HADS-D*, Hospital Anxiety and Depression Scale—Depression; *PSOLAR*, Psoriasis Longitudinal Assessment and Registry; *PY*, patient-year.

populations and clinical trials, include longer duration of follow-up, a representative study population, and an observational real-world setting design. Weaknesses include the following: the inherent limitations of the HADS-D instrument, as noted earlier; patient self-reporting of AEs of depression; possible inadequate capture of depressive events; and lack of data regarding alcohol consumption and other medications (such as antidepressants). Of note, although oral retinoids have been associated with depression, the results of a sensitivity analysis provided evidence against confounding by retinoid use. In addition, there are biases inherent to the longitudinal cohort design, such as the inability to account for all baseline differences between cohorts that might affect outcome. Lastly, smaller sample sizes may limit the ability to interpret some analyses, (eg, the post hoc analysis excluding patients with concomitant retinoid use).

We also presented a descriptive analysis of suicidality among patients enrolled in PSOLAR. Overall, the IR of suicidal ideation, attempted suicide, or completed suicide was low (43.0 per 100,000 PYs). Although it is difficult to directly compare this rate with other published data, the

Table V. Multivariate Cox model for symptoms suggestive of depression

Covariate*	Hazard Ratio (95% CI)	*P* value
Exposure		
Biologic agents vs conventional systemic agents	**0.76 (0.59-0.98)**	**.0367**
Ustekinumab vs conventional systemic agents	0.80 (0.60-1.06)	.1208
Infliximab vs conventional systemic agents	0.70 (0.47-1.03)	.0699
Etanercept vs conventional systemic agents	0.91 (0.67-1.23)	.5220
Adalimumab vs conventional systemic agents	**0.63 (0.46-0.86)**	**.0034**
Phototherapy vs conventional systemic agents	1.05 (0.71-1.54)	.8159
Age/10 y	**1.12 (1.05-1.21)**	**.0015**
Sex: male vs female	1.09 (0.91-1.30)	.3644
Race: nonwhite vs white	**1.72 (1.39-2.13)**	**<.0001**
Years since psoriasis	**0.99 (0.98-1.00)**	**.0026**
Baseline PGA		
2-3	**1.45 (1.17-1.79)**	**.0005**
4-5	**2.36 (1.62-3.43)**	**<.0001**
Change in PGA (HADS-D score)		
−2 or lower	**0.44 (0.33-0.59)**	**<.0001**
−1	**0.66 (0.52-0.84)**	**.0006**
1	**0.69 (0.52-0.91)**	**.0101**
≥2	1.01 (0.70-1.44)	.9734
Psoriatic arthritis: yes vs no	**1.58 (1.32-1.88)**	**<.0001**
Diabetes: yes vs no	1.15 (0.90-1.48)	.2685
Schizophrenia: yes vs no	2.16 (0.53-8.79)	.2818
Anxiety: yes vs no	**1.64 (1.19-2.25)**	**.0024**
Bipolar disease: yes vs no	2.01 (0.99-4.09)	.0547
Chronic obstructive pulmonary disease: yes vs no	**2.10 (1.19-3.71)**	**.0105**
CAD/MI/ACVD/stroke/TIA: yes vs no	0.81 (0.57-1.15)	.2440
Insurance		
Public vs none	1.29 (0.92-1.81)	.1455
Private vs none	**0.62 (0.45-0.85)**	**.0029**
Both public and private vs none	0.94 (0.60-1.46)	.7806
Education: ≥college/university vs <high school	**0.79 (0.66-0.95)**	**.0114**

Boldface indicates statistical significance.

ACVD, Atherosclerotic cardiovascular disease; *CAD*, coronary artery disease; *CI*, confidence interval; *HADS-D*, Hospital Anxiety and Depression Scale—Depression; *MI*, myocardial infarction; *PGA*, Physician's Global Assessment; *TIA*, transient ischemic attack.

*Potential covariates included age, sex, ethnicity, educational status, psychiatric history, type of insurance, body mass index, duration of psoriasis, historic peak PGA, baseline PGA, change in disease severity (defined as change in PGA from peak or baseline to time of event or last available PGA score), comorbidities (including psoriatic arthritis, diabetes, chronic obstructive pulmonary disease, and cardiovascular disease [defined as CAD, MI, ACVD, stroke, and TIA]), and smoking status. All covariates with an overall univariate *P* value less than .2 were included in the Cox model.

suicide rate among patients with psoriasis in the General Practice Research Database was 90 per 100,000 PYs.[3]

Although biologic therapies have been associated with a low risk for suicidality,[22] an imbalance in suicide and suicidal ideation has been previously observed among patients treated with an interleukin 17 receptor inhibitor.[23] It is important to note that causality remains uncertain[22] and differences in study design could be contributing to the perceived imbalance. Our studies do not assess interleukin 17 inhibitors, and more data from other registries that capture the use of this class of drug are needed to understand this potential risk. With consideration of the role of TNF−α in depression, further study may be beneficial to determine whether biologic therapies targeting other cytokines may have a different impact on depression and suicide relative to anti−TNF−α agents.[19]

Overall, this study contributes to the body of literature suggesting that treatment with biologic agents may reduce the risk for development of depressive symptoms among patients with moderate-to-severe psoriasis. It also provides a longitudinal description of depressive symptoms, depression events, and suicidality in a large cohort of patients with psoriasis. Further studies are needed to fully understand how biologics, including novel agents, affect the risk for depression and suicide among patients with psoriasis.

Table VI. Characteristics of patients who completed suicide, attempted suicide, or had suicidal ideation

Event	Age, y/sex	Elevated HADS-D score (baseline)*	History of depression†	Elevated HADS-D score (registry)*	Depression (registry)†	Biologic agents (ever exposed)‡	Nonbiologic immunomodulators (ever exposed)‡	Phototherapy (ever exposed)‡	Biologic agents at time of event§	Other treatment at time of event§
S	31/M	N	NA	N	N	UST‖	—	—	UST	—
S	46/M	N	Y	N	Y	ADA, ALE, ETN¶	—	—	—	—
S	46/M	N	Y	NA	N	UST#	—	—	—	—
SA	43/F	N	Y	Y	Y	ADA, ETN, IFX	MTX	—	ETN	—
SA	34/F	Y	Y	N	N	EFA, ETN, IFX	—	—	IFX	—
SA	41/F	N	Y	Y	N	ETN	—	—	ETN	—
SA	72/M	Y	Y	Y	Y	—	—	UVB	—	NA
SA	58/M	N	NA	N	Y	ADA, ETN	Systemic steroids	—	—	—
SA	52/F	N	NA	N	N	ADA, EFA, ETN, IFX, UST	—	—	IFX	MTX
SA	49/M	Y	Y	Y	N	ADA, ETN	—	—	ETN	—
SA	40/M	Y	Y	N	N	ADA	—	—	ADA	—
SI	44/F	Y	NA	N	N	UST	—	—	UST	UST
SI	50/F	N	NA	N	Y	ALE, UST	—	—	UST	—
SI	54/F	N	NA	N	Y	UST	Systemic steroids	—	UST	Systemic steroids
SI	61/F	N	Y	Y	N	ADA	—	—	—	—
SI	43/F	N	N	Y	N	ADA, ETN, IFX, UST	ACT, CsA, MTX, AZA	—	UST	—
SI	54/F	Y	Y	Y	Y	ETN	—	—	ETN	—
SI	44/F	N	Y	Y	N	UST	MTX	UVB	UST	—
SI	54/F	N	Y	Y	N	ADA ETN	—	—	—	—
SI	68/F	N	NA	N	Y	ADA	—	—	ADA	—
SI	70/M	Y	NA	Y	Y	ADA, ETN, IFX	—	—	ETN	—

ACT, Acitretin; *ADA*, adalimumab; *ALE*, alefacept; *AZA*, azathioprine; *CsA*, cyclosporine A; *EFA*, efalizumab; *ETN*, etanercept; *F*, female; *HADS-D*, Hospital Anxiety and Depression Scale—Depression; *IFX*, infliximab; *M*, male; *MTX*, methotrexate; *N*, no; *NA*, not available; *S*, suicide; *SA*, suicide attempt; *SI*, suicidal ideation; *UST*, ustekinumab; *UVB*, ultraviolet B; *Y*, yes.

*Patients had an elevated HADS-D score (baseline) if their HADS-D score was 8 or higher at enrollment, and they had an elevated HADS-D score (registry) if their HADS-D score was 8 or higher at any other time point.

†A history of depression was based on medical history at the time of enrollment. Depression (registry) was defined as an adverse event of depression during enrollment.

‡Patients who were ever exposed to biologics (ADA, ETN, IFX, UST, ALE, EFA, and/or golimumab), nonbiologic immunomodulators (MTX, CsA, oral tacrolimus, mycophenolate mofetil, sulfasalazine, retinoids [ACT, etretinate, isotretinoin], and/or systemic steroids), and phototherapy (psoralens plus ultraviolet light and/or UVB) may have been treated before and/or during enrollment.

§Biologic and other treatments at time of event were defined as those received by the patient if the last dose occurred within the past 91 days.

‖This patient had a history of alcohol use (quantity and frequency unknown) and was suspected of drug intoxication. The last dose of a biologic (UST) was received 34 days before the suicide.

¶This patient had a history of anxiety, depression, and alcoholism. The last dose of a biologic (ADA) was received 216 weeks before the suicide.

#This patient had a history of alcohol use and depression. The last dose of a biologic (UST) was received 17 weeks before the suicide.

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