Medicine®

OBSERVATIONAL STUDY

OPEN

Depression and Insomnia in Patients With Psoriasis and Psoriatic Arthritis Taking Tumor Necrosis Factor Antagonists

Chun-Ying Wu, MD, PhD, MPH, LLM, Yun-Ting Chang, MD, PhD, Chao-Kuei Juan, MD, Jui-Lung Shen, MD, PhD, Yu-Pu Lin, MS, Jeng-Jer Shieh, PhD, Han-Nan Liu, MD, and Yi-Ju Chen, MD, PhD

Abstract: Psoriasis patients with moderate to severe disease often present with depression and insomnia. Treatment targeting both psoriasis and psychological comorbidities is needed to improve the quality of life of these patients.

In this nationwide cohort study, a total of 980 patients with psoriatic arthritis or psoriasis who had received nonbiological disease-modifying antirheumatic drugs and biologics therapy between 2009 and 2012 were identified. The prevalence rates of patients taking medications for depression and insomnia were compared before and after biologics therapy. Logistic regression method was used to investigate the risk factors for depression and insomnia. Further stratified analyses were performed to examine the prevalence of use of medications for depression and insomnia among different patient subgroups.

The prevalence of patients taking regular antidepressants before starting biologics therapy was about 20%. There was a more than 40% reduction in this prevalence after biologics therapy for 2 years. Age higher than 45 years, female sex, presence of comorbidities, and psoriatic arthritis were independently associated with depression and insomnia. Further stratified analyses revealed a more rapid and significant reduction in depression/insomnia in those undergoing continuous biologics therapy, younger than 45 years, without psoriatic arthritis and not taking concomitant methotrexate, when compared with their counterparts.

The results suggest that biologics therapy may be associated with reduced rates of depression and insomnia, and a reduced rate of regular antidepressants use in psoriasis patients.

(*Medicine* 95(22):e3816)

Abbreviations: BSA = body surface area, CRP = C-reactive protein, DLQI = Dermatology Quality of Life Index, DMARDs = disease-modifying anti-rheumatic drugs, HADRS = Health Anxiety Depressive Rating Scale, HPA = hypothalamus-pituitary-adrenal, ICD-9-CM = International Classification of Diseases, Revision 9, Clinical Modification, IL = interleukin, NHIRD = Taiwan's National Health Insurance Research Database, PASI = psoriasis activity severity index, PUVA = psoralen plus ultraviolet A, TNF = tumor necrosis factor, UVB = ultraviolet B.

INTRODUCTION

Depression and anxiety are estimated to affect more than 30% of psoriasis patients.[1] Low self esteem, social anxiety, embarrassment due to disease stigmata, or absence from work due to painful arthritis may partly explain the psycho-social impact of psoriasis. The prevalence rates of psychological symptoms in psoriasis have been reported to be higher than in many other disfiguring skin diseases[2] and as high as in other major medical diseases, including myocardial infarction, diabetes, hypertension, and cancer.[3]

There is a growing body of evidence to support the association between depressive disorders and inflammation.[4,5] A large meta-analysis has demonstrated that psychological stress elevates proinflammatory markers, such as C-reactive protein (CRP), tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6.[5] Chronic stress has also been reported to exacerbate or induce autoimmune diseases by enhancing hypothalamus-pituitary-adrenal (HPA) axis hyperactivity,[6] which promotes T-cell sensitivity to proinflammatory cytokines, resulting in immune dysregulation.[6] On the other hand, inflammation may also cause depression. Depressive behavior has been induced by injection of IL-1 and lipopolysaccharides in

Editor: Angelo Marzano.
Received: February 24, 2016; revised: May 2, 2016; accepted: May 6, 2016.
From the Faculty of Medicine and Graduate Institute of Clinical Medicine (C-YW, Y-TC, Y-PL, Y-JC), National Yang-Ming University, Taipei; Division of Gastroenterology (C-YW), Taichung Veterans General Hospital; Department of Public Health and Graduate Institute of Clinical Medical Sciences (C-YW), China Medical University; Department of Life Sciences and RongHsing Research Center for Translational Medicine (C-YW), National Chung-Hsing University, Taichung; Department of Dermatology (Y-TC, H-NL), Taipei Veterans General Hospital, Taipei; Department of Dermatology (C-KJ, J-LS, Y-JC), Taichung Veterans General Hospital; Institute of Biomedical Sciences (J-JS), National Chung Hsing University; and Department of Education and Research (J-JS), Taichung Veterans General Hospital, Taichung, Taiwan.

Correspondence: Yi-Ju Chen, Department of Dermatology, Taichung Veterans General Hospital, Taichung and Faculty of Medicine, School of Medicine, National Yang-Ming University, No. 155, Section 2, Linong Street, Taipei 11221, Taiwan (e-mail: yjchenmd@vghtc.gov.tw).

This study is based on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health and managed by the National Health Research Institutes. The interpretations and conclusions contained herein do not represent those of the Bureau of National Health Insurance, Department of Health or the National Health Research Institutes. Y-JC has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Y-JC is an honorary advisory board member of Celegene Ltd.

C-YW and Y-TC contributed equally as first authors. C-YW, Y-TC, and Y-JC conceived the study, provided the concepts, designed the study protocol, acquired the data, analyzed and interpreted the data, and drafted and revised the paper. C-KJ, J-LS, J-JS, and Y-PL participated in the data interpretation, revision of the important intellectual content and drafting of the manuscript. H-NL participated in the data interpretation and revision of the important intellectual content. Y-PL performed the statistical analyses and provided intellectual content. All authors have read and approved the final version of the manuscript.

This study was supported by grants NSC 102-2628-B-010-013 MY2, TCVGH-1036802C, TCVGH-1036803C, TCVGH-1036801B.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000003816

TABLE 1. Demographic Characteristic of Study Subjects

Characteristics	Biologics (N = 980)
Age, y, mean (SD)	45.26 (12.73)
Age, y, median	45.53
N (%)	
0–19	10 (1.0)
20–39	314 (32.0)
40–59	522 (53.3)
60–79	132 (13.5)
≧80	2 (0.002)
Female, N (%)	303 (30.9)
Male, N (%)	677 (69.1)
Duration of follow-ups, y, mean (SD)	1.62 (0.95)
Cumulative duration of biologics, y, mean (SD)	1.15 (0.77)
Psoriatic arthritis, N (%)	783 (79.9)
Continuous biologics treatment*, N (%)	710 (72.4)
Comorbidities, N (%)	
Diabetes mellitus	110 (11.2)
Hypertension	208 (21.2)
Hyperlipidemia	76 (7.8)
Cerebrovascular events	25 (2.6)
Myocardial infarction	63 (6.4)
Liver cirrhosis	11 (1.1)
DMARDs after biologics therapy†, N (%)	
Methotrexate	517 (52.8)
Acitretin	96 (9.8)
Cyclosporine	217 (22.1)
Azathioprine	7 (0.007)

DMARDs = disease-modifying antirheumatic drugs, N = number, SD = standard deviation, y = year.

*Indicates continuous biologics treatment without interruption, or being interrupted for less than 3 months.

†Only those receiving drugs of interest for more than 30 days would be included.

rats.[7] One longitudinal cohort study has demonstrated that circulating low-grade inflammatory markers, such as CRP and IL-6, effectively predict future depression after 12-year follow-up.[8] Finally, a randomized control trial has indicated that etanercept, a TNF-α inhibitor, improves depression symptoms and fatigue in psoriasis patients.[9] There is a lack of observational studies investigating the long-term impact of biologics on the prevalence of antidepressant prescriptions in daily practice.

The aims of the present study are to examine the effects of biologics therapy, mostly anti-TNF therapy, on decreasing depression and insomnia rates in patients with psoriasis and psoriatic arthritis based on a nationwide cohort and to identify the subgroups of patients who benefit from biologics therapy.

METHODS

Study Design

We conducted a nationwide cohort study by retrieving information from all patients with a diagnosis of psoriasis or psoriatic arthritis from Taiwan's National Health Insurance Research Database (NHIRD). The NHIRD has been utilized extensively in epidemiologic studies in Taiwan.[10–12] It consists of detailed health care data from more than 25 million enrollees, representing more than 99% of Taiwan's entire population. In this database, the diagnostic codes are in the format of the International Classification of Diseases, Revision 9, Clinical Modification (ICD-9-CM) with diagnoses made by board-certified physicians in the corresponding specialties. The accuracy of diagnosis of major diseases in the NHIRD, such as diabetes and ischemic stroke, has been validated.[13–15] Personal information including body weight, height, family history, laboratory examination results, lifestyle, and social habits such as smoking or alcohol use was not available from the NHIRD. This study was approved by the ethical review board of Taichung Veterans General Hospital, Taichung, Taiwan.

Study Cohorts

All patients with a primary diagnosis of psoriasis or psoriatic arthritis (ICD-9-CM codes 696.0, 696.1, and 696.8) for the first time and who had received biologics between 1997 and March 2012 were eligible for inclusion in this study. We included only those subjects who had been admitted for psoriasis or received a diagnosis of psoriasis or psoriatic arthritis more than 3 times by dermatologists or rheumatologists, as previously described.[11] A total of 12,7928 patients with a diagnosis of psoriasis or psoriatic arthritis were identified between 1997 and March 2012. Among them, 27,229 patients had received nonbiologic DMARDs and 1043 patients had received biologics. Patients receiving biologics therapy for less than 1 month were excluded. A total of 980 patients who received biologics between 2009 and 2012 were identified.

TABLE 2. Multivariate Analysis for Predicting Factors of Depression and Insomnia in Psoriasis Patients Taking Biologics Therapy

	N	E	aOR*	95% CI	*P* Value*
Age ≥45	506	227	2.35	(1.79–3.08)	<0.0001
Female sex	303	132	1.64	(1.24–2.16)	0.0005
Diabetes	110	50	1.59	(1.06–2.38)	0.02
Hypertension	208	94	1.67	(1.22–2.28)	0.001
Hyperlipidemia	76	39	2.02	(1.26–3.23)	0.003
CVA	25	14	2.36	(1.06–5.25)	0.03
MI/ACS	63	33	2.09	(1.25–3.49)	0.004
Liver cirrhosis	11	6	2.19	(0.66–7.23)	0.19
Chronic renal failure	7	3	1.36	(0.30–6.10)	0.69
Interrupted biologics therapy†	190	61	0.82	(0.59–1.15)	0.26
Psoriatic arthritis	783	291	1.42	(1.01–1.99)	0.04

ACS = acute coronary syndrome, aOR = adjusted odds ratio, CI = confidence intervals, CVA = cerebrovascular events, E = number of events, MI = myocardial infarction, N = total number of patients.

*Adjusting for covariate factors listed in the table above by logistic regression model.

†Interrupted biologics therapy indicates that biologics treatment ever being discontinued for more than 3 months.

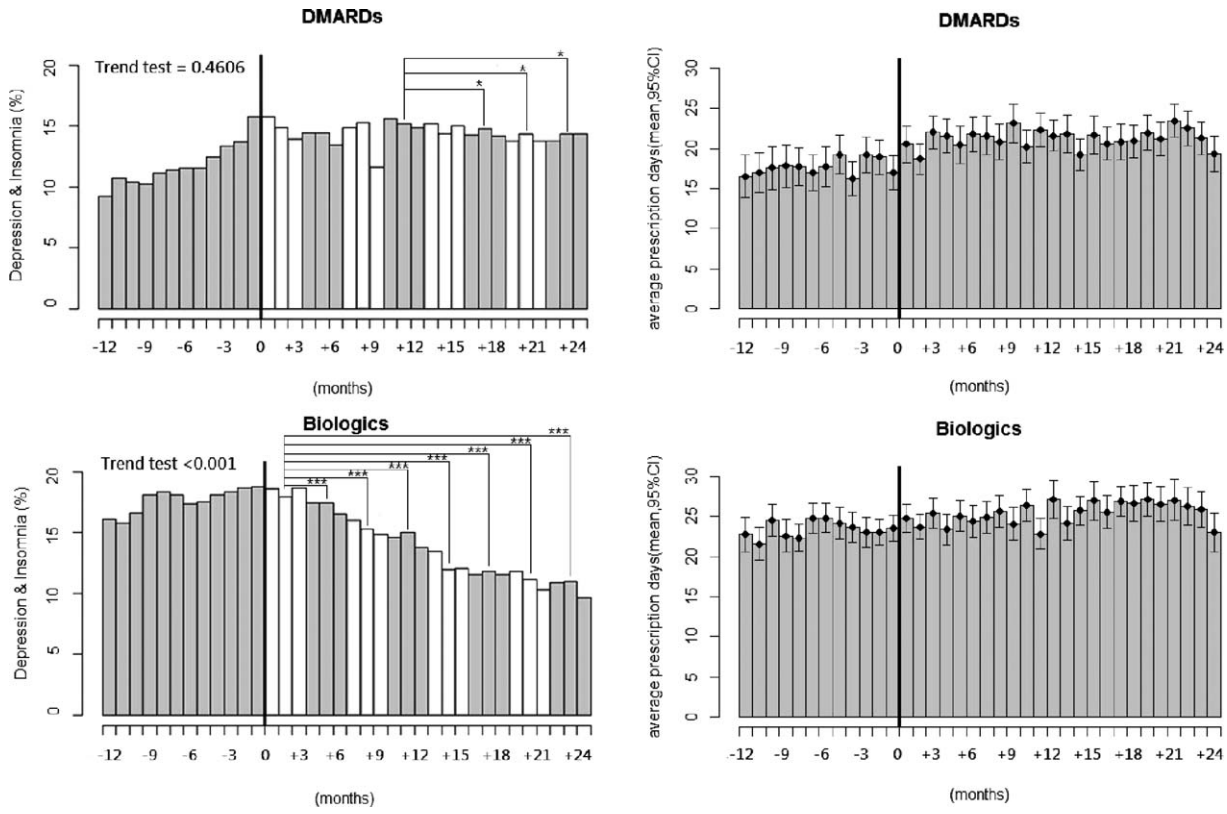

FIGURE 1. Prevalence rates of depression and insomnia 1 year before and after 2 years of biologics or DMARDs treatment. The average prescription days each month were presented. * denotes $P<0.05$; ** denotes $P<0.01$; *** denotes $P<0.0001$, on Student *t* test, with the rate within 1 month of biologics as the reference.

Biologics Therapy for Psoriasis

Biologics available for the management of psoriasis and psoriatic arthritis in Taiwan include etanercept, adalimumab, golimumab, and ustekinumab. Reimbursement for biologics for psoriasis management began in 2009. Only those with moderate to severe psoriasis with failed treatment for at least 6 months with more than 2 nonbiologic DMARDs (mainly methotrexate, cyclosporine, and acitretin) and at least 24 sessions of phototherapy (including psoralen plus ultraviolet violet A [PUVA] and ultraviolet violet B [UVB] phototherapy) 2 or 3 times per week over a period of 6 months or those with active psoriatic arthritis (3 or more swollen joints at least 2 times, recorded at least 1 month apart, and with radiologic and laboratory evidence) with failed treatment for at least 6 months with more than 2 nonbiologic DMARDs (drugs mentioned above plus leflunomide or salazopyrine) can apply for reimbursement for biologics. Patients with prior history of premalignant or malignant diseases or with active infection are not eligible to receive biologics. Since ustekinumab has not been reimbursed for psoriasis until May 2012, we did not include patients taking ustekinumab into our cohort.

Until April 2015, according to the NHI regulations, all patients with moderate to severe psoriasis meeting the above criteria were to be reimbursed for biologics therapy for 6 months. Repeated assessment would be performed after 6 months of biologics therapy. Patients would stop current biologics or switch to another class of biologics due to the following reasons: severe infection, intolerance to biologics, pregnancy, malignant disease, or poor response to current biologics (less than psoriasis activity severity index [PASI]50 or body surface area [BSA] 50% improvement). For those with good response, that is, PASI score of less than 10, biologics may also have been temporarily discontinued until psoriasis recurrence. Biologic reimbursement may have been discontinued from the time of clearance of skin lesions to psoriasis recurrence. In general, patients who achieved fair to good response and had no serious adverse effect may receive continuous biologics reimbursement for psoriasis.

Information regarding medications was retrieved from the pharmacy prescription database. Reliability of the retrieved information was independently verified by 2 statisticians.

Main Outcome Measurements

Patients with depression and insomnia were defined as those who had received the diagnoses of depression (ICD9 codes 296.2, 296.3, 298.0, 300.4, 309.28, 311, and V790) or insomnia (ICD9 codes 307, 327, 780.52) and had taken antidepressants as listed in supplementary Table 1, http://links.lww.com/MD/B5. The prevalence rates of depression/insomnia or antidepressant use were compared 1 year before starting biologics and after 2 years of biologic use. The average prescription days of antidepressants per month was also measured.

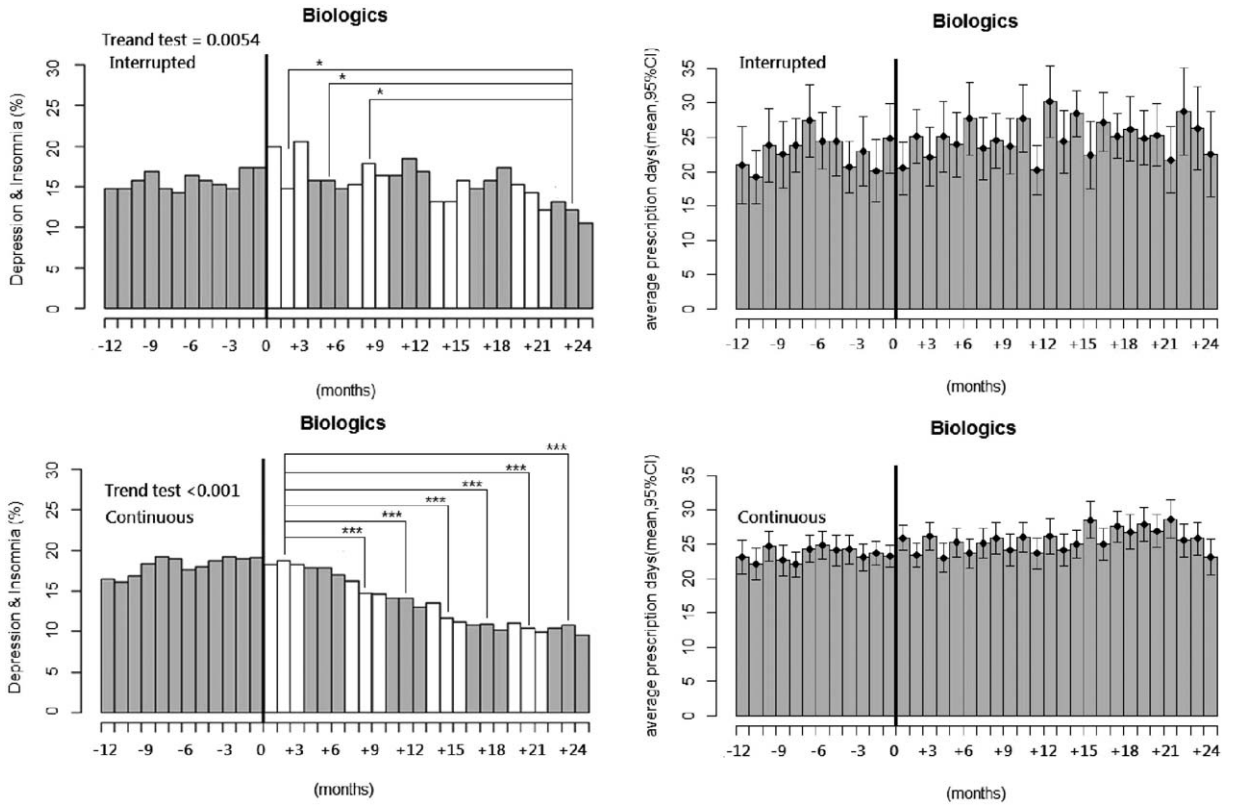

FIGURE 2. Prevalence rates of depression and insomnia between subjects with continuous biologics therapy and subjects with interrupted biologics therapy. The average prescription days each month were presented.* denotes $P < 0.05$; ** denotes $P < 0.01$; ***denotes $P < 0.0001$, on Student *t* test, with the rate within 1 month of biologics as the reference. Interrupted biologics therapy indicates receiving biologics therapy with interruption for more than 3 months; continuous biologics therapy indicates receiving biologics therapy without interruption or interrupted for less than 3 months during the observation period of time.

Covariate Factors

Certain demographic factors, such as age, sex, comorbidities including hypertension, diabetes mellitus, and hyperlipidemia, DMARD treatment, and treatment patterns of biologics were considered potential confounders. DMARDs included methotrexate, cyclosporine, acitretin, azathioprine, mycophenolatemofetil, leflunomide, and sulfasalazine. Biologics treatment patterns included continuous (without interruption or with interruption for less than 3 months) and interrupted (interrupted for more than 3 months). Other confounders included use of nonbiologic DMARDs, presence of psoriatic arthritis, use of corticosteroids, and use of phototherapies including PUVA and UVB therapies prior to the index date (Table 1).

Statistical Analysis

The demographic data of the study population were first analyzed. We compared the prevalence rates of disease of outcomes before and after biologic therapy by χ^2 method. We next performed multivariate analysis by adjusting several covariate factors to examine the risk factors for depression and insomnia utilizing the logistic regression method.

The differences in prevalence rates of depression/insomnia were further explored by stratification according to disease, age, sex, use of DMARDs, and biologics treatment patterns to examine whether the main findings are robust across different subgroups of patients. The differences in average prevalence rates every 3 months after biologics therapy were compared using Student *t* test, with the rate within 1 month of biologics use serving as the reference.

All data management was performed with SAS 9.4 software (SAS Institute Inc, Cary, NC). Calculations of cumulative incidences and Cox models were carried out with the ''cmprsk'' package of R (http://cran.r-project.org/web/packages/cmprsk/index.html). Calculated results are expressed as the estimated number together with 95% confidence interval (CI).

RESULTS

Demographic Characteristics

The demographic characteristics and associated comorbidities are shown in Table 1. Male patients constituted about 70% of study subjects. Approximately 52% of patients received methotrexate in combination with biologic, followed by cyclosporine. About 80% of patients presented with psoriatic arthritis. In addition, 72.4% of patients received continuous biologic therapy. All of these patients received DMARDs before biologic therapy.

A total of 349 patients (35.61%) with depression or insomnia taking antidepressants were identified within 1 year

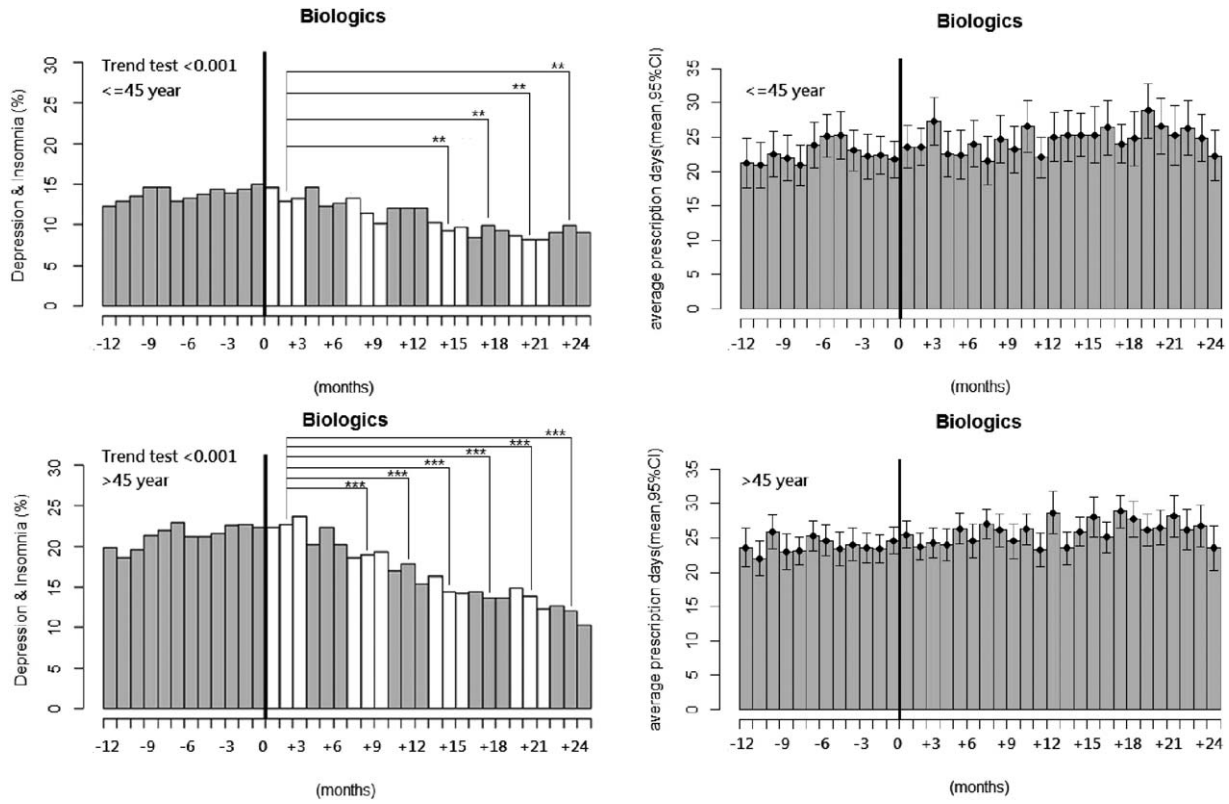

FIGURE 3. Prevalence rates of depression and insomnia between subjects ≥45 years and subjects <45 years. The average prescription days each month were presented. * denotes $P < 0.05$; ** denotes $P < 0.01$; *** denotes $P < 0.0001$, on Student *t* test, with the rate within 1 month of biologics as the reference.

of the index date and during the observation period. Only 30 (3.06%) were found to have depression or insomnia as the major diagnosis.

Multivariate Analysis for Risk Factors of Depression/Insomnia

We next conducted multivariate analysis to identify the predicting factors for depression/insomnia in these patients. Older age, female sex, major comorbidities including diabetes, hypertension, hyperlipidemia, acute coronary syndrome, and presence of psoriatic arthritis were significant predicting factors for depression and insomnia (Table 2).

Prevalence Rates of Depression/Insomnia

The prevalence of depression/insomnia under regular treatment was estimated to be up to 20% before biologic therapy. The prevalence rates decreased soon within 3 months of biologic treatment, and then steadily decreased during the follow-up period. A 43.8% decrease was observed after 24 months of biologic therapy ($P < 0.001$), compared with only 10% to 11% decrease after 24 months of DMARDs treatment ($P = 0.46$) (Figure 1, supplementary Table 2, http://links.lww.com/MD/B5).

Stratified Analyses

We next compared the prevalence rates between those with continuous biologic treatment (N = 790) and those with interrupted biologic treatment (N = 190) (Figure 2). Similar rates of antidepressant use were found in both study groups before starting biologics. We found a steady decrease in depression/insomnia rates in patients taking continuous biologic treatment. However, a fluctuating rate was observed among those with interrupted biologic treatment. We found decreases of 45% and 47% after 16 and 24 months of continuous biologic treatment, respectively. On the contrary, only a 30% decrease was observed in those with interrupted biologic treatment after 24 months (Figure 2, supplementary Table 2, http://links.lww.com/MD/B5).

A similar decreasing trend was seen in those younger than 45 years (N = 474) and those 45 years and older (N = 506). Patients 45 years and older tended to have higher prevalence of depression and insomnia. The prevalence rate decreased more rapidly in those younger than 45 years. Nevertheless, both age groups achieved up to 40% decrease after 24 months of biologic treatment (Figure 3, supplementary Table 2, http://links.lww.com/MD/B5).

Female patients (N = 303) tended to have higher prevalence of depression/insomnia than male patients (N = 677). Likewise, a decreasing trend in prevalence rate was observed in both sex groups (Figure 4, supplementary Table 2, http://links.lww.com/MD/B5).

Patients with psoriatic arthritis (N = 783) had higher prevalence of depression/insomnia than those without psoriatic arthritis (N = 197). We found a rapid decrease in prevalence rate among those without psoriatic arthritis when compared with those with psoriatic arthritis (Figure 5, supplementary Table 2, http://links.lww.com/MD/B5). Likewise, a significant

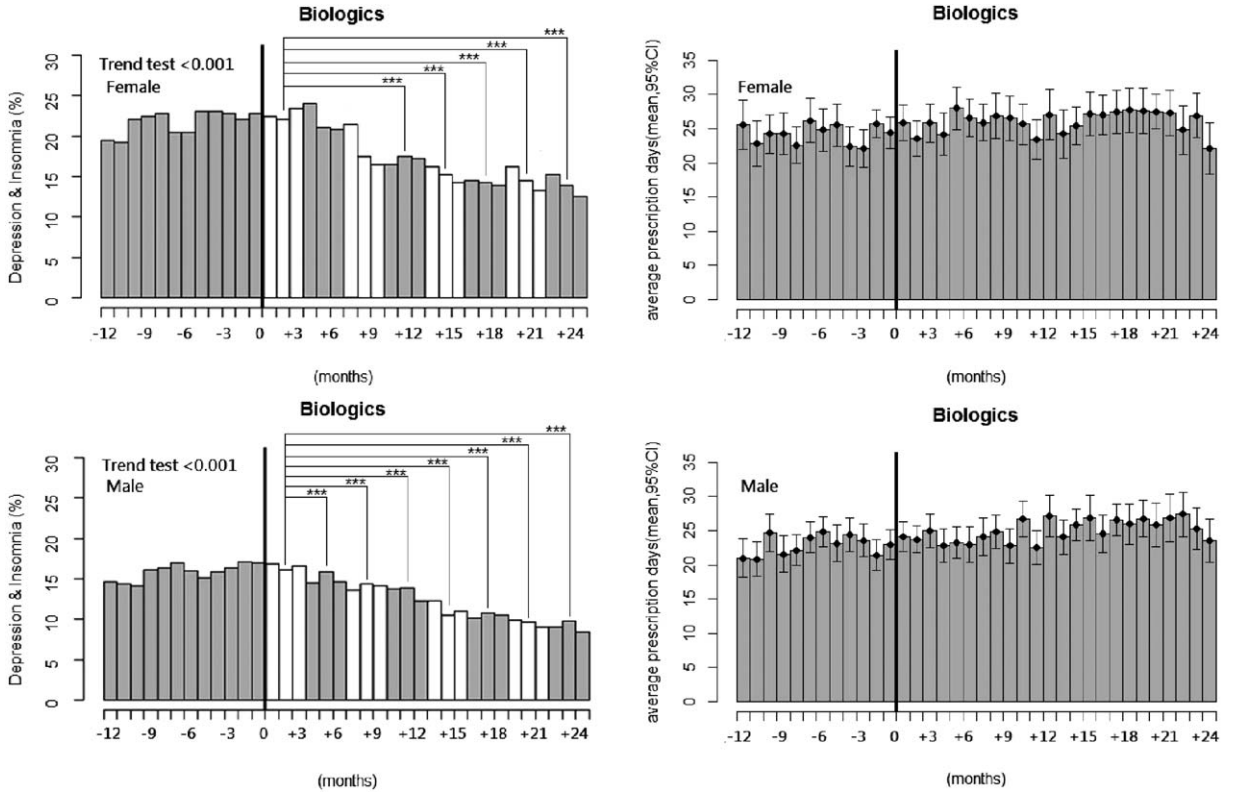

FIGURE 4. Prevalence rates of depression and insomani between female and male patients. The average prescription days each month were presented.* denotes $P < 0.05$; ** denotes $P < 0.01$; ***denotes $P < 0.0001$, on Student *t* test, with the rate within 1 month of biologics as the reference.

decrease was observed more in those not taking concomitant methotrexate than those taking methotrexate (Figure 6, supplementary Table 2, http://links.lww.com/MD/B5).

DISCUSSION

Our study provided nationwide-based evidence of a significantly decreasing prevalence rate of depression and insomnia in patients with psoriasis or psoriatic arthritis following biologics therapy, as shown in Figure 1. We performed multivariate analysis and stratified analysis to examine the effects among different subsets of patients. Older age (45 years or higher), female sex, presence of several comorbidities, and psoriatic arthritis were found to be independently associated with depression and insomnia, as seen in Table 2. In addition, a significantly reduced rate was seen after biologics therapy across almost all subsets of patients, as shown in all figures.

Depression or insomnia is commonly seen in patients with psoriasis or psoriatic arthritis, ranging from 20% to 50% in the literature.[16] Major depression has been reported in 16.5% of psoriasis patients.[17] Risk of major depression has been found in association with psoriasis severity.[17] More than 30% of patients in our biologic cohort had taken antidepressants, yet only 3% had received proper diagnosis of depression or insomnia. This implies that depression and insomnia are under-diagnosed in this patient population.

Recent systemic review and meta-analysis have revealed that both TNF-α antagonists and ustekinumab are associated with a significant reduction in depression symptoms using various scales including Health Anxiety Depressive Rating Scale (HADRS) and Dermatology Quality of Life Index (DLQI) following 12 or 24 weeks of treatment.[16,18,19] Few studies have investigated the long-term impact of biologics on psychological health among psoriasis patients. Here, we first demonstrated an up to 47% decrease in patients with depression and insomnia after 2-year biologics treatment, based on real-world data from daily practice in Taiwan. Instead of questionnaires, we utilized antidepressant prescriptions as the outcome of disease in this study. And, the identified depression/insomnia patients were found to take regular antidepressants, for about 20 to 25 days per month, as shown in all figures. We might therefore have identified the patients with more severe depression and insomnia who need regular visits.

TNF-α has been shown to play a key role in the pathophysiology of depression. Prior studies have reported elevated plasma TNF-α and soluble receptors in acutely depressed patients.[20] Another study has shown that experimental injection of Salmonella abortus equi endotoxin stimulates TNF-α production and leads to depression-like emotional and cognitive behaviors in humans.[21] Recent animal studies have further demonstrated the antidepressant effect of etanercept, an anti-TNF-α drug. Anti-TNF-α treatment might enhance serotonergic or noradrenergic neurotransmission or normalize stress hormone secretion, which leads to antidepressive effect.[22] The exact mechanisms need to be investigated in future studies.

Psoriasis patients reimbursed for biologics may discontinue their treatment for several reasons. One recent large-scale study, based on national pharmacovigilance cohort from the

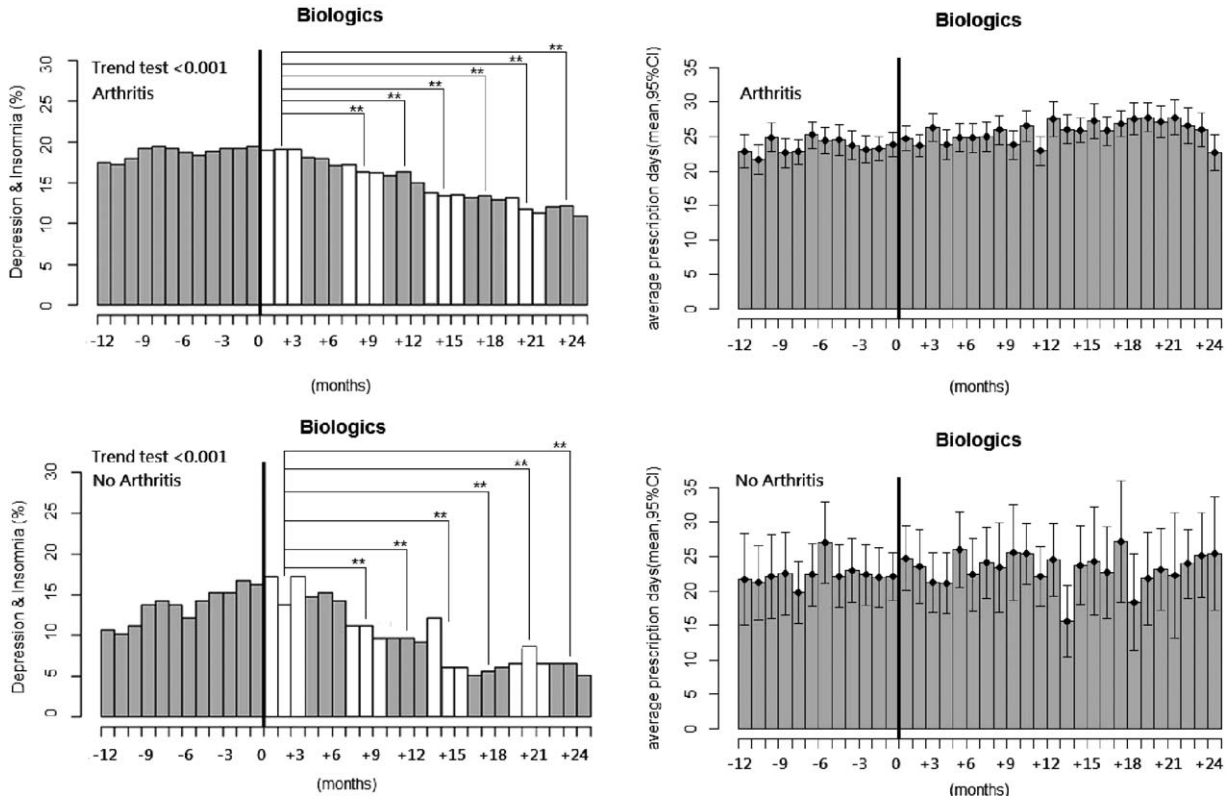

FIGURE 5. Prevalance rates of depression and insomnia between subjects with psoriatic arthritis and those without psoriatic arthritis. The average prescription days each month were presented. * denotes $P < 0.05$; ** denotes $P < 0.01$; *** denotes $P < 0.0001$, on Student *t* test, with the rate within 1 month of biologics as the reference.

British Association of Dermatologists Biologic Intervention Registry, has indicated that about 77% of patients receive continuous biologic treatment in the first year. Female sex, current smoker, higher baseline DLQI, concomitant methotrexate use, and concomitant cyclosporine use are independent factors for discontinuation of biologics. However, baseline PASI score is not independently associated with biologic discontinuation.[23]

Until 2015, based on the reimbursement policy in Taiwan, patients with relatively good response to 6 months of biologic therapy (i.e., PASI < 10) might not be allowed to receive next reimbursement of biologics. On the contrary, for patients with unsatisfactory or poor responses to the previous biologics, physicians tended to switch to different classes of biologics, instead of halting biologics therapy. We therefore postulated that except for patients who developed unfavorable adverse effects or could not tolerate biologics well, most patients might discontinue biologic therapy because of a more favorable response to biologics than those with continuous therapy. Accordingly, a more reduction for rate of depression and insomnia in these patients were expected.

However, the present study revealed alternative findings. We found a more rapid and sustained reduction in depression and insomnia rates in the continuous group, compared with a fluctuation in the interrupted group (Figure 2). These results implied that the reduced rate of depression or insomnia might not be solely associated with clinical disease improvement. We postulated that patients might be more anxious or depressed when they realized that they could not get next reimbursement until their skin condition became bad enough. The severity of psoriasis may also fluctuate between treatment and nontreatment. Clinical remission has been reported to be associated with less depression and anxiety in early RA patients.[24] However, measurements of psoriasis disease severity such as PASI score and BSA involvement were not recorded in the database. Thus, we could not correlate the disease severity with the prevalence of depression/insomnia in the current study.

More than 50% of patients received concomitant methotrexate with biologics in our study. Our stratified analysis revealed a significant but slower decrease in the prevalence of depression/insomnia in patients taking concomitant methotrexate, than patients not taking methotrexate. It has been hypothesized that methotrexate precipitates bipolar disorder by interfering with folate metabolism, which leads to folic acid deficiency and alters the metabolic pathways of S-adenylmethoinine/S-adenylhomocystein, homocysteine and biopterin. These biochemical abnormalities have been associated with symptoms of depression and anxiety.[25] Methotrexate has been reported to be associated with mild psychological distress in patients with psoriasis, in addition to female sex, larger BSA involvement, self-distraction, and behavior disengagement.[26] On the contrary, low dose and short-term cyclosporine has recently been demonstrated to improve symptoms of depression and anxiety.[27] However, we could not adequately stratify patients by nonbiological DMARD other than methotrexate due to the limited number of study subjects. Different study design would be needed to investigate the relationship between nonbiological DMARDs and depression.

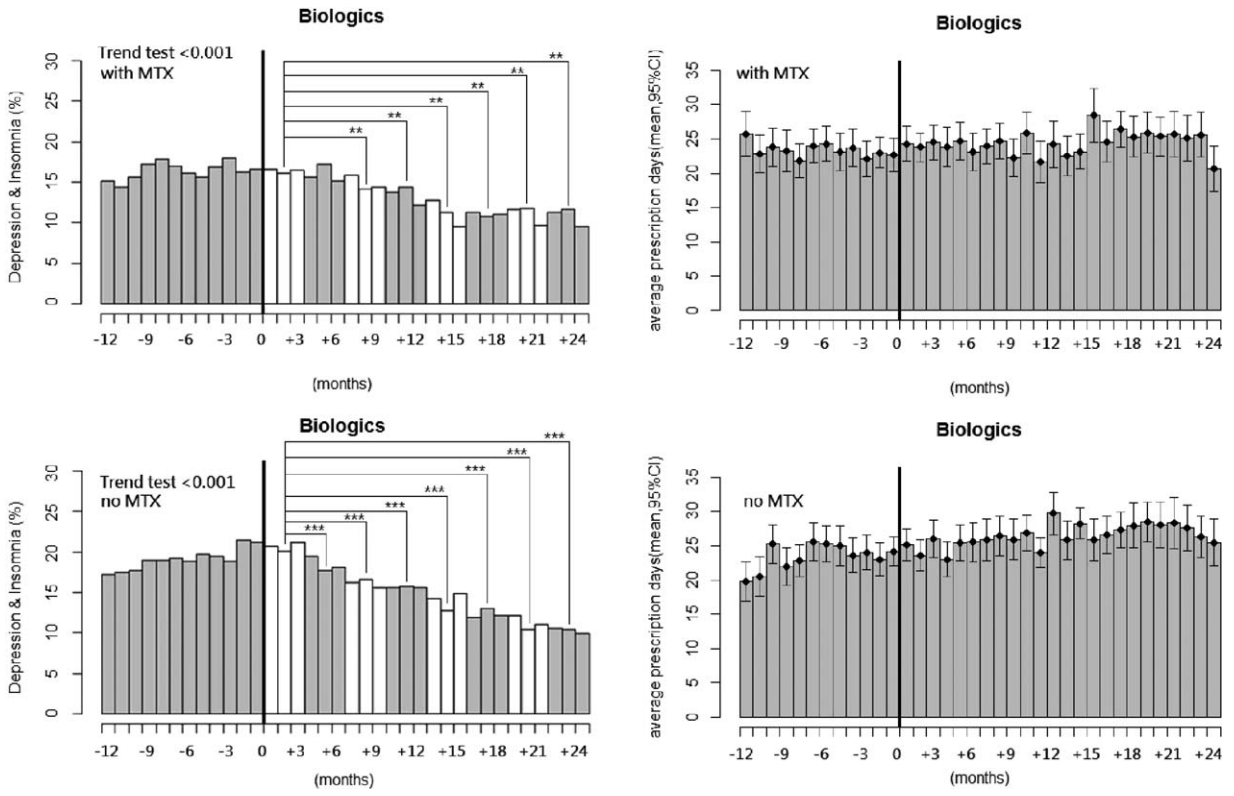

FIGURE 6. Prevalence rates of depression and insomnia between subjects taking concomitant methorexate and those not taking concomitant methotrexate. The average prescription days each month were presented.* denotes $P < 0.05$; ** denotes $P < 0.01$; ***denotes $P < 0.0001$, on Student *t* test, with the rate within 1 month of biologics as the reference. Patients taking concomitant methotrexate indicates those taking methotrexate for more than 30 days during observation.

The strengths of the current study included utilization of the nationwide NHIRD to avoid selection bias, which is a major concern in observational studies. In addition, the large sample size in the NHIRD allowed us to examine effects across different patient subgroups.

There are also limitations to the present study. First, it is difficult to infer causation between a drug of interest (biologics in this study) and risk of outcomes (depression and insomnia) based on an observational study, without a random assignment of treatments. Confounding by indication may exist and account for differences in outcomes. For example, patients may have switched to or added TNF-α antagonist due to unsatisfactory efficacy or intolerance to the adverse events of nonbiologic DMARDs. Therefore, subjects in the biologic cohort may be those with refractory disease, at risk of multiple comorbidities or taking more immunosuppressant drugs, which can lead to depression, anxiety, and insomnia. To avoid the selection bias, instead of selecting a reference cohort, we compared the prevalence rates before and after biologic therapy in the biologic cohort. We further conducted stratified analyses to examine antidepressant effect among different subgroups of patients. However, subgroups of patients may differ in many measured or unmeasured ways, which may affect disease outcomes. Certain subtypes of severe psoriasis could also affect the quality of life. However, due to a lack of specific diagnostic codes for pustular psoriasis or erythrodermic psoriasis, we could not adequately identify these disease subtypes for analyses. We did not have access to personal information such as lifestyle, family history, laboratory or serologic information, or records of disease severity score, which may contribute to depression or insomnia. Finally, coding error is possible in a database. To avoid such error, the diagnosis of psoriasis was made at least 3 times by dermatologists or rheumatologists.

In conclusion, our results suggested a sustained benefit of biologic therapy in reducing antidepressant use among psoriasis patients over a 2-year observation period. The results should be interpreted carefully in that only patients taking anti-TNF treatment were included in our analyses. Older age, female sex, presence of comorbidities and psoriatic arthritis were independent risk factors for depression and insomnia. Further stratified analyses demonstrated similar beneficial effect across different patient subgroups. Finally, the beneficial effect was more significant in those receiving continuous biologics, without psoriatic arthritis and without concomitant methotrexate.

REFERENCES

1. Dowlatshahi EA, Wakkee M, Arends LR, et al. The prevalence and odds of depressive symptoms and clinical depression in psoriasis patients: a systematic review and meta-analysis. *J Invest Dermatol.* 2014;134:1542–1551.
2. Narita M, Nishizawa Y, Iwaya S, et al. Ustekinumab improves psoriasis without suppressing tumor antigen-specific cytotoxic T lymphocytes. *Int Arch Allergy Immunol.* 2014;165:52–60.

3. Rapp SR, Feldman SR, Exum ML, et al. Psoriasis causes as much disability as other major medical diseases. *J Am Acad Dermatol.* 1999;41:401–407.
4. Rosenblat JD, Cha DS, Mansur RB, et al. Inflamed moods: a review of the interactions between inflammation and mood disorders. *Prog Neuropsychopharmacol Biol Psychiatry.* 2014;53:23–34.
5. Steptoe A, Hamer M, Chida Y. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. *Brain Behav Immun.* 2007;21:901–912.
6. Dhabhar FS. Enhancing versus suppressive effects of stress on immune function: implications for immunoprotection and immunopathology. *Neuroimmunomodulation.* 2009;16:300–317.
7. Dunn AJ, Swiergiel AH, de Beaurepaire R. Cytokines as mediators of depression: what can we learn from animal studies? *Neurosci Biobehav Rev.* 2005;29:891–909.
8. Gimeno D, Kivimaki M, Brunner EJ, et al. Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. *Psychol Med.* 2009;39:413–423.
9. Tyring S, Gottlieb A, Papp K, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet.* 2006;367:29–35.
10. Wu CY, Chen YJ, Ho HJ, et al. Association between nucleoside analogues and risk of hepatitis B virus-related hepatocellular carcinoma recurrence following liver resection. *JAMA.* 2012;308:1906–1914.
11. Chen YJ, Chang YT, Shen JL, et al. Association between systemic antipsoriatic drugs and cardiovascular risk in patients with psoriasis with or without psoriatic arthritis: a nationwide cohort study. *Arthritis Rheum.* 2012;64:1879–1887.
12. Wu CY, Kuo KN, Wu MS, et al. Early Helicobacter pylori eradication decreases risk of gastric cancer in patients with peptic ulcer disease. *Gastroenterology.* 2009;137:1641–1648.
13. Lin CC, Lai MS, Syu CY, et al. Accuracy of diabetes diagnosis in health insurance claims data in Taiwan. *J Formos Med Assoc.* 2005;104:157–163.
14. Cheng CL, Kao YH, Lin SJ, et al. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. *Pharmacoepidemiol Drug Saf.* 2011;20:236–242.
15. Hsieh CY, Chen CH, Li CY, et al. Validating the diagnosis of acute ischemic stroke in a National Health Insurance claims database. *J Formos Med Assoc.* 2015;114:254–259.
16. Fleming P, Roubille C, Richer V, et al. Effect of biologics on depressive symptoms in patients with psoriasis: a systematic review. *J Eur Acad Dermatol Venereol.* 2015;29:1063–1070.
17. Dommasch ED, Li T, Okereke OI, et al. Risk of depression in women with psoriasis: a cohort study. *Br J Dermatol.* 2015;173:975–980.
18. Guenther L, Han C, Szapary P, et al. Impact of ustekinumab on health-related quality of life and sexual difficulties associated with psoriasis: results from two phase III clinical trials. *J Eur Acad Dermatol Venereol.* 2011;25:851–857.
19. Langley RG, Feldman SR, Han C, et al. Ustekinumab significantly improves symptoms of anxiety, depression, and skin-related quality of life in patients with moderate-to-severe psoriasis: Results from a randomized, double-blind, placebo-controlled phase III trial. *J Am Acad Dermatol.* 2010;63:457–465.
20. Himmerich H, Fulda S, Linseisen J, et al. Depression, comorbidities and the TNF-alpha system. *Eur Psychiatry.* 2008;23:421–429.
21. Reichenberg A, Yirmiya R, Schuld A, et al. Cytokine-associated emotional and cognitive disturbances in humans. *Arch Gen Psychiatry.* 2001;58:445–452.
22. Krugel U, Fischer J, Radicke S, et al. Antidepressant effects of TNF-alpha blockade in an animal model of depression. *J Psychiatr Res.* 2013;47:611–616.
23. Warren RB, Smith CH, Yiu ZZ, et al. Differential drug survival of biologic therapies for the treatment of psoriasis: a prospective observational cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *J Invest Dermatol.* 2015;135:2632–2640.
24. Kekow J, Moots R, Khandker R, et al. Improvements in patient-reported outcomes, symptoms of depression and anxiety, and their association with clinical remission among patients with moderate-to-severe active early rheumatoid arthritis. *Rheumatology (Oxford).* 2011;50:401–409.
25. Vezmar S, Becker A, Bode U, et al. Biochemical and clinical aspects of methotrexate neurotoxicity. *Chemotherapy.* 2003;49:92–104.
26. Colombo D, Caputo A, Finzi A, et al. Evolution of and risk factors for psychological distress in patients with psoriasis: the PSYCHAE study. *Int J Immunopathol Pharmacol.* 2010;23:297–306.
27. Okubo Y, Natsume S, Usui K, et al. Low-dose, short-term ciclosporin (Neoral(R)) therapy is effective in improving patients' quality of life as assessed by Skindex-16 and GHQ-28 in mild to severe psoriasis patients. *J Dermatol.* 2011;38:465–472.