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ORIGINAL RESEARCH

Psychological Well-Being of Patients with Moderate-to-Severe Plaque Psoriasis Treated with Tildrakizumab: 28-Week Interim Results from a Multicenter Observational Study in Italy Using the DASS-21 Questionnaire, the BLUE Study

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ABSTRACT

Introduction: Psoriasis is a chronic inflammatory skin disease associated with significant physical and psychological burden. Tildrakizumab, an interleukin-23 p19 inhibitor, has demonstrated efficacy in treating moderate-to-severe plaque psoriasis both in clinical trials and real-world setting. However, limited data are available on the impact of the effective treatment of psoriasis on the psychological health of patients. The aim of this study was to assess changes in psychological well-being, as well as clinical and quality-of-life outcomes, in patients with moderate-to-severe plaque psoriasis treated

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with tildrakizumab in routine clinical practice in Italy.

Methods: This was an interim analysis (IA) of a 52-week multicenter, prospective, observational study. Adults with moderate-to-severe plaque psoriasis initiating tildrakizumab were enrolled. Endpoints focused on well-being and psychological health and included changes, from baseline to week 28, in Depression, Anxiety, and Stress Scale-21 (DASS-21) scores, Dermatology Life Quality Index (DLQI), European Social Survey (ESS) items, and World Health Organization-Five Well-Being Index (WHO-5). Effectiveness was also monitored via Psoriasis Area and Severity Index (PASI), and safety via treatment-emergent adverse event reporting.

Results: A total of 115 patients were included (mean age 52.5 years, 60.8% male), 102 receiving ≥ 1 dose of tildrakizumab and completing DASS-21 evaluations at baseline and week 28. At week 28, improvements were observed in DASS-21 subscales [depression (– 2.6, 95% CI – 2.0 to – 1.0), anxiety (– 2.3, 95% CI – 2.0 to – 1.0), and stress (– 3.4, 95% CI – 4.0 to – 2.0)], accompanied by marked PASI reduction (– 13.7, 95% CI – 12.8 to – 10.1). DLQI, ESS, and WHO-5 scores also improved. Adverse events were generally mild or moderate, with no unexpected safety signals.

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Conclusion: In this real-world IA, tildrakizumab was observed to improve the psychological well-being of patients, reflected by a reduction in all items of the DASS-21 scale and, in parallel, confirmed its effectiveness in managing physical symptoms of psoriasis, establishing its role in the holistic management of psoriasis.

PLAIN LANGUAGE SUMMARY

Psoriasis is a lifelong inflammatory skin disease that affects both physical and emotional well-being. Tildrakizumab is a newer biological treatment that targets inflammation causing the disease. Little is known on whether treating the skin improves mental health. This study looked at how tildrakizumab works in everyday clinical practice among adults in Italy who have moderate-to-severe plaque psoriasis and how effective treatment of the skin can also impact on the mental health of patients. A total of 115 adults were enrolled and treated with tildrakizumab for up to 28 weeks. Dermatologists and patients evaluated changes in skin symptoms, quality of life, and psychological health. Several standardized tools were used, including the Psoriasis Area and Severity Index to measure disease severity, and questionnaires to assess depression, anxiety, stress, and psychological well-being. After 28 weeks of treatment, most patients experienced clear improvements. Skin symptoms and affected areas were greatly reduced, and many participants reported feeling less depressed, anxious, and stressed. Their overall sense of psychological well-being and quality of life also improved. The treatment was generally well tolerated, with most side effects being mild or moderate and no unexpected safety signals reported. Overall, this real-world study supports the use of tildrakizumab as an effective and safe treatment for psoriasis. In addition to reducing physical symptoms, it appears to help patients feel better emotionally, highlighting its value in improving both the skin and the overall quality of life of people living with psoriasis.

Keywords: Biologics; QoL; IL-23 inhibitor; Depression; Anxiety; Stress; Questionnaire

Key Summary Points

Why carry out this study?

Psoriasis is a chronic inflammatory disease with significant psychological and physical burden, yet real-world data on mental health outcomes with IL-23 inhibitors remain limited.

Evidence on whether effective skin clearance with tildrakizumab translates into meaningful improvements in psychological well-being in routine clinical practice is scarce.

Study question/hypothesis: Does treatment with tildrakizumab in real-world Italian clinical practice improve psychological well-being, clinical severity, and quality-of-life outcomes in adults with moderate-to-severe plaque psoriasis?

What was learned from the study?

After 28 weeks of treatment, tildrakizumab was associated with significant improvements in psoriasis severity (mean PASI reduction of −13.7) and clinically meaningful reductions in depression, anxiety, and stress as measured by DASS-21, together with improved DLQI and WHO-5 scores.

The study demonstrates that effective psoriasis control with tildrakizumab can lead to improvements in psychological well-being approaching levels seen in non-clinical populations, supporting a holistic benefit beyond skin clearance.

These findings reinforce the value of tildrakizumab as a safe, well-tolerated, and effective biologic treatment in real-world clinical settings, supporting its role in the comprehensive management of moderate-to-severe plaque psoriasis.

INTRODUCTION

Psoriasis is a chronic, immune-mediated skin disease that affects approximately 2–3% of the population worldwide, and up to 8–11% in Northern Europe [1]. In addition to physical discomfort, psoriasis causes psychological distress [2]. Patients often report feelings of stigma, social isolation, and low self-esteem, which can contribute to comorbid depression, anxiety, and stress [3], with as many as 20% of individuals with psoriasis experiencing depressive symptoms [4]. Severe disease is associated with poorer quality of life (QoL), and younger age at diagnosis is associated with increased risk for depression, anxiety, stress, and impaired QoL [5].

Treatments for managing moderate-to-severe psoriasis have significantly evolved in recent years, particularly with the availability of biologic therapies targeting key inflammatory pathways, such as tumor necrosis factor alpha (TNFα), interleukin (IL)-17, and IL-23 [6]. These treatments are not only effective in achieving skin clearance but also improve patients' QoL [7].

Biologic therapies, particularly IL-23 and IL-17 inhibitors, play an important role in alleviating the psychological distress experienced by patients with moderate-to-severe psoriasis. Guselkumab has shown to improve anxiety and depression in patients with moderate-to-severe psoriasis [8]. Few studies have been undertaken in Italy to evaluate the benefits of biologic therapies on the well-being of patients with psoriasis using questionnaires specific for mental health outcomes. In the SUPREME study, the Dermatology Life Quality Index (DLQI) questionnaire allowed for recording high levels of minimal disease activity in patients treated with secukinumab [9]. A post hoc analysis of the SUPREME study showed that secukinumab was associated with improvements in anxiety and depression, assessed using the Hospital Anxiety and Depression Scale [10] in patients with psoriasis [11].

In the randomized controlled trials reSURFACE 1 and 2, tildrakizumab achieved significantly higher proportions of patients reaching DLQI scores of 0 or 1 than placebo and etanercept, alongside improvements in Psoriasis Area and Severity Index (PASI) and Physician Global Assessment (PGA) responses [12].

Recently, a small Italian study included patients ($N = 30$) treated with 100 or 200 mg of tildrakizumab for at least 28 weeks. DLQI and World Health Organization–Five Well-Being Index (WHO-5) scores analysis revealed improvement in QoL in both groups [13].

The Depression Anxiety Stress Scale (DASS-21) is recognized as a valuable and reliable tool for measuring the psychological impact of psoriasis [14]. It was first developed as a 42-item questionnaire [15], then shortened to 21 items for faster administration [16]. It is easy to use, provides a comprehensive assessment, and is adaptable to various cultural and clinical settings [17]. This scale has been used in several therapeutic areas, such as cancer and diabetes [18, 19]. However, studies that adopt this validated tool in the context of psoriasis are limited [20, 21].

The present multicenter, prospective, observational study was designed to investigate changes in psychological well-*B*eing of moderate-to-severe p*L*aque psoriasis patients treated with tildrakiz*U*mab in clinical practic*E* in Italy (the "BLUE" study). Here, we report the 28-week interim analysis (IA) of the study, focusing on changes in the DASS-21 depression, anxiety, and stress subscales, as well as other relevant outcomes that assess the well-being and QoL, alongside selected measures for the physical assessment of the disease. Further assessments of the physical and functional burden of the disease will be reported in the final analysis of the complete study.

METHODS

Study Design, Setting, and Patient Population

The BLUE study is a multicenter, prospective, observational study enrolling 331 patients with moderate-to-severe plaque psoriasis (diagnosed at least 24 weeks before enrollment) across 28 public hospitals in Italy. All patients started treatment with tildrakizumab at enrollment (enrollment phase between May 2023 and July

2024) as per clinical practice and independently of their participation in this study. Tildrakizumab was administered subcutaneously according to the approved Summary of Product Characteristics [22], at 100 mg or 200 mg doses at weeks 0 and 4, and then every 12 weeks thereafter. Dosage selection was at the discretion of the treating physicians. Patients were asked to attend visits after 28 and 52 weeks. The study required participants to complete questionnaires through a smartphone or tablet application. Adult male or female patients (≥ 18 years) naïve to treatment with biologics or who had failed previous treatment with a biologic were included. Exclusion criteria included pregnancy or breastfeeding and inability or unwillingness to follow study procedures. This interim analysis (IA) was designed to provide a preliminary descriptive analysis of patient characteristics and some of the study endpoints at the 28-week follow-up. The IA was foreseen for patients enrolled by December 2023 who had reached week 28 of observation or who had discontinued the study early by June 2024.

This study followed Guidelines for Good Pharmacoepidemiology Practices of the International Society for Pharmacoepidemiology (ISPE 2016), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, the ethical principles laid down in the Declaration of Helsinki, and the Italian AIFA Guidelines for the classification and management of observational studies on drugs. Ethical approval was obtained from the independent ethics committee at each study site. All patients provided written informed consent prior to enrollment.

Assessments

Patients attended baseline and follow-up visits at week 28 and are scheduled to attend the 52-week follow-up visit as part of the full study. The primary outcome measure for the full study is the change in DASS-21 subscale scores from baseline to week 52 [15]. The DASS-21 is a self-administered questionnaire consisting of a set of three subscales measuring depression, anxiety, and stress (Supplementary Table 1). Scores for each subscale were calculated by summing the scores for the different items. Recommended cutoff values for the three subscales are shown in Supplementary Table 2.

For this IA, all outcomes were considered secondary outcomes of the full study. Changes in DASS-21 scores were evaluated from baseline to week 28. Further assessments, performed at baseline and week 28, included the DLQI, (Supplementary Table 3) [23]; the European Social Survey (ESS) Items, to gauge happiness and social well-being in a two-item questionnaire of the European Social Service (Supplementary Table 4); the WHO-5, a concise measure of subjective psychological well-being (Supplementary Table 5) [24]; the PASI [25]; the PGA, assessing severity of the three primary signs of the disease: erythema, scaling, and plaque elevation [26]; the Itch Numeric Rating Scale (Itch NRS) [27]; the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire [28]; and the Medical Outcomes Study Sleep Scale (MOS-Sleep) [29].

In the present IA, we present outcomes that assess the well-being and QoL (DASS-21, DLQI, ESS, WHO-5), in addition to PASI. Additional assessments of the physical and functional burden of the disease (PGA, Itch NRS, FACIT-F, and MOS-Sleep) will be reported in the final analysis upon completion of the study.

Safety Analysis

Treatment-emergent adverse events (TEAEs) were collected during follow-up visits and coded using the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs may also be detected when reported by the patient during or between visits, or through physical examination, laboratory tests, or other assessments.

Statistical Analysis

Continuous data were summarized by mean and standard deviation (SD), while categorical data were presented by absolute and relative frequencies (*n* and %). Baseline psychological status was assessed using total and subscale DASS-21 scores (depression, anxiety,

and stress), summarized both as continuous measures and according to established severity categories (normal, mild, moderate, severe, and extremely severe). Given the single-arm, observational design of this study, treatment effects were evaluated by analyzing within-patient changes from baseline to week 28. Accordingly, paired *t* tests (for normally distributed values) or Wilcoxon signed rank test (for non-normally distributed values) were used for within-group comparisons (after checking for normality using the Shapiro–Wilk test). This approach was considered appropriate for evaluating treatment-associated changes in the absence of a control group. An interim analysis was planned as soon as 115 enrolled patients had reached the 28-week visit or had discontinued. Two analysis populations were defined: the full analysis set (FAS), which included all patients receiving ≥ 1 dose of tildrakizumab who underwent DASS-21 evaluations at baseline and week 28; and the safety set (SAF), which included all patients receiving ≥ 1 dose of tildrakizumab. Missing data were handled using an available-case approach. For the interim efficacy analysis, patients without a DASS-21 assessment at week 28 were excluded from efficacy analyses, and no imputation of missing outcome values was performed. Patients were included in each analysis based on available data, and missing values were reported as "missing" in descriptive summaries. For partially missing dates, prespecified rules were applied (the 15th day was imputed when the day was missing; 1st July when both day and month were missing). This approach was adopted to avoid introducing unverifiable assumptions and to reflect the real-world observational nature of the study. All efficacy objectives were evaluated on the FAS population for the IA, whereas all safety analyses were assessed on the SAF population. Descriptive statistics were used to summarize demographic and baseline characteristics and changes in each outcome measure at week 28. All statistical analyses were performed using SAS software, version 9.4 or later (SAS Institute, Inc., Cary, NC, USA).

Table 1 Demographic and clinical characteristics of the FAS population

Patient characteristics (*n* = 102)	***n*** **(%)**
Age, years (mean ± SD)	52.5 ± 16.0
Sex	
Male	62 (60.8)
Female	40 (39.2)
Marital status (married)	62 (60.8)
Living alone	18 (17.6)
BMI, kg/m^2 (mean ± SD)	27.2 ± 5.5
Medical history	
At least one medical condition	50 (49.0)
Vascular disorders	28 (27.5)
Metabolism and nutrition disorders	27 (26.5)
Cardiac disorders	8 (7.8)
Neoplasms	8 (7.8)
Psychiatric disorders	5 (4.9)
Infections and infestations	5 (4.9)
Others	26
Currently smoking	52 (51.0)
Regular alcohol consumption	10 (9.8)
Psoriasis history	
Disease duration (mean ± SD)	17.5 ± 11.9
Age at disease onset (mean ± SD)	34.3 ± 17.6
PASI	15.6 ± 10.2
Disease severity	
Moderate	47 (46.1)
Severe	55 (53.9)
Lesions in difficult-to-treat areas	87 (85.3)
Nails	38 (43.7)
Scalp	60 (69.0)
Face	34 (39.1)
Genitals	36 (41.4)

Table 1 continued

Patient characteristics ($n = 102$)	n (%)
Previous psoriasis treatments (non-biologic)	88 (86.3)
Acitretin	8 (9.1)
Cyclosporine	40 (45.5)
Dimethyl fumarate	2 (2.3)
Methotrexate	30 (34.1)
NB-UVB phototherapy	11 (12.5)
Other treatment	26 (29.5)
Previous biologics treatment	38 (37.3)
Anti-IL-12/23: ustekinumab	3 (7.9)
Anti-IL-17: brodalumab	2 (5.3)
Anti-IL-17: ixekizumab	4 (10.5)
Anti-IL-17: secukinumab	4 (10.5)
Anti TNF: infliximab	1 (2.6)
Anti-TNF: adalimumab	22 (57.9)
Anti-TNF: etanercept	11 (28.9)

Each patient could have more than one disease, past condition, or previous treatment

FAS full analysis set, *n* number, *PASI* Psoriasis Activity Severity Index, *SD* standard deviation

RESULTS

Patient Disposition and Baseline Characteristics

Baseline characteristics of the study FAS population are presented in Table 1. By the 28-week cutoff, of the 115 enrolled patients in the SAF population, 14 had discontinued tildrakizumab prematurely. Reasons for discontinuation were adverse events ($n = 9$), patient withdrawal ($n = 3$), lost to follow-up ($n = 1$), and death ($n = 1$). The FAS population included 102 patients. Mean age was 52.5 ± 16 years, 60.8% were male and 39.2% were female, and mean disease duration was 17.5 ± 11.9 years. Baseline PASI was 15.6 ± 10.2, and the majority of patients had severe disease (53.9%), with 85.3% having lesions in high impact areas. Approximately half (49%) of patients had comorbidities, mainly vascular (27.5%), and metabolic and nutritional disorders (26.5%). At baseline visit, only 5 (4.9%) patients were diagnosed with psychiatric disorders (3 for depression, 1 for anxiety, and 1 for insomnia). Prior treatments for psoriasis included non-biologics (86.3%) and biologics (37.3%), primarily anti-TNF agents like adalimumab (57.9%).

Tildrakizumab Exposure

The majority of patients were started on the approved 100 mg dose (73.5%), and the remaining 26.5% received 200 mg. Seven patients (6.9%) changed their treatment dose by week 28, increasing from 100 to 200 mg.

Depression, Anxiety, and Stress: DASS-21 Scores

Changes in depression, anxiety, and stress levels were evaluated through the DASS-21 questionnaire, from baseline to week 28. By week 28, there was a clinically meaningful significant decrease in mean depression (– 2.6, 95% CI – 2.0 to – 1.0), anxiety (– 2.3, 95% CI – 2.0 to – 1.0), and stress (– 3.4, 95% CI – 4.0 to – 2.0) DASS-21 subscale scores (Fig. 1a), with a reduction of 43–57% from baseline levels.

Baseline DASS-21 scores indicated on average mild symptoms (see Supplementary Table 2 for cutoff values) across the depression (mean 5.0 ± 4.5), anxiety (mean 4.2 ± 3.8), and stress subscales (mean 7.9 ± 4.8) in the cohort overall, although 24–30% patients exhibited moderate, severe, or extremely severe severity categories in the three subscales (Fig. 1b). A high proportion of these patients shifted toward mild or normal categories by week 28 (77.4% for depression, 84% for anxiety, 87.1% for stress) with only 6–11% patients exhibiting moderate, severe, or extremely severe severity categories in the three subscales (Fig. 1b). Stratified subanalysis by previous biologic exposure also revealed similar improvements in DASS-21 scores from baseline to 28 weeks in patients

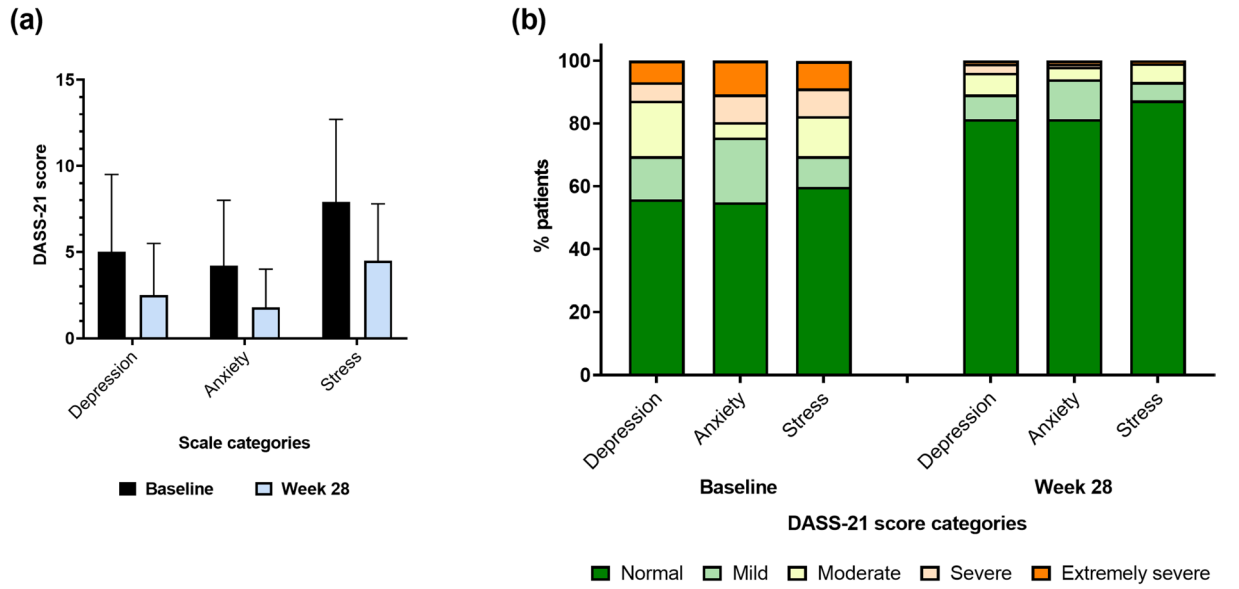

Fig. 1 Depression, anxiety, and stress (DASS-21) questionnaire. **a** DASS-21 subscales scores at baseline and week 28; **b** DASS-21 severity category distribution at baseline and week 28. Data presented as mean and standard deviation for **a** or frequencies (absolute number of patients) for **b**

that were naïve (from 5.4 ± 4.9 to 2.6 ± 3.2) and not biologic naïve (from 4.4 ± 3.9 to 2.3 ± 2.6).

Other Assessments of Well-Being and Quality of Life: DLQI, ESS, and WHO-5

A high proportion of patients (66 out of 69, 95.7%) shifted from moderate-to-extremely large impact on daily life to small/no impact (Fig. 2a), with mean DLQI scores improving substantially from baseline to week 28 (10.1 ± 7.1 at baseline vs 1.2 ± 1.9 at week 28) (Fig. 2b). The WHO-5 well-being index showed a meaningful increase, from 50.9 ± 23.9 at baseline to 66.0 ± 18.4 at week 28 (Fig. 2c).

Physical Assessment of Disease Severity: PASI and PGA

By week 28, mean PASI showed a marked reduction (from 15.6 ± 10.2 to 1.8 ± 2.6, Fig. 3a), with the majority of patients achieving PASI ≤ 3 (from 3.9% at baseline to 77.5% at week 28), and over half of the patients achieving PASI ≤ 1 (from 1% to 52.9%, Fig. 3b). Sub-analysis by prior biologic treatment also revealed similar improvements (from baseline to 28 weeks) in patients that were naïve (from 16.02 ± 10.1 to 1.5 ± 2.4) or not biologic naïve (14.8 ± 10.5 to 2.4 ± 2.9).

Patients who achieved PASI ≤ 3 at week 28 had more pronounced improvements in depression and stress scores compared with those who had PASI > 3 (Table 2).

The distribution of patients by PGA index of their whole body at baseline and week 28 is summarized in Table 3. The matched PGA index shift is shown in Fig. 3c. Overall, there was a net improvement in PGA, with 77 out of 79 (97.5%) moderate-to-severe patients improving to a clear-to-mild PGA index. Similar trends are also observed when considering specific areas of lesions, including the scalp, face, nail, palmoplantar, and genital areas (data not shown).

Safety Measures

All 115 enrolled patients were included in the safety analysis. Tildrakizumab was well tolerated over 28 weeks, and 15 patients (13%) experienced at least one TEAE, totaling 17 events. Of these, 3 events (2.6%) were mild, 7 events (5.2%) were moderate, and 7 events (6.1%)

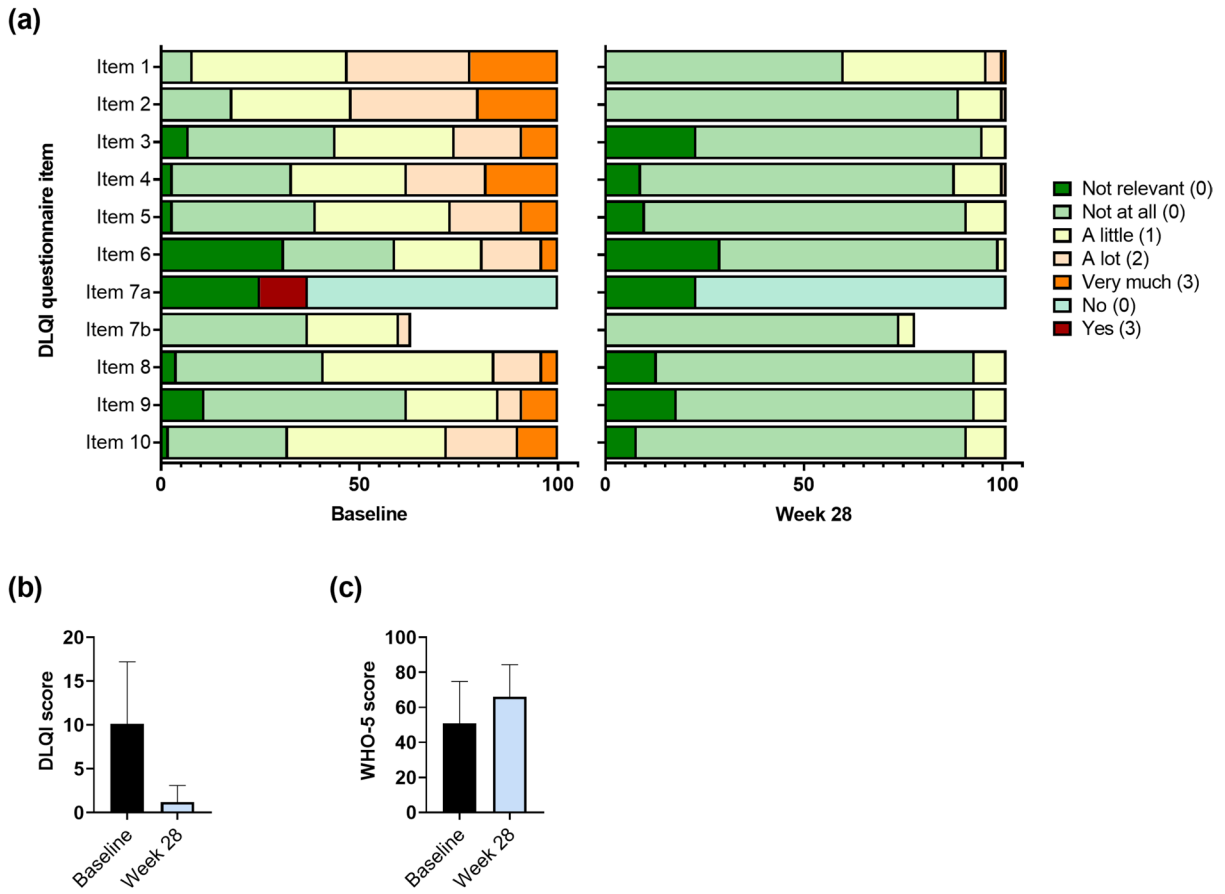

Fig. 2 Well-being and quality of life assessments. **a** Dermatology Life Quality Index (DLQI) distribution of patients by item at each timepoint; **b** DLQI scores at baseline and week 28; **c** World Health Organization-Five Well-Being Index (WHO-5) scores at baseline and week 28. Data presented as frequencies (absolute number of patients) for **a** or mean and standard deviation for **b** and **c**

were severe (Table 4). Serious adverse events (SAEs) occurred in 4 patients (3.5%), including cardiac disorders ($n = 2$), chronic obstructive pulmonary disease ($n = 1$), and drug ineffectiveness ($n = 1$). One SAE resulted in death due to myocardial infarction in a patient with known cardiovascular comorbidities; this event was not considered related to tildrakizumab by the investigator. Overall, 10 TEAEs in 8 patients (7.0%) were judged to be related to treatment, most commonly general disorders and administration site conditions, including drug ineffectiveness (3.5%), peripheral edema (1.7%), and treatment failure (0.9%). Additional treatment-related events included arthralgia, COPD, and psoriasis (each 0.9%). No TEAEs led to temporary treatment interruption; however, 10 patients (8.7%) permanently discontinued tildrakizumab because of adverse events, and 9 patients (7.8%) discontinued the study. No clinically relevant laboratory abnormalities or vital sign changes suggestive of drug toxicity were observed. No new or unexpected safety signals emerged, and the safety findings were consistent with the established safety profile of tildrakizumab (Table 4).

DISCUSSION

This interim analysis of a prospective, real-world observational study in Italy reveals that tildrakizumab therapy for moderate-to-severe plaque psoriasis significantly reduces

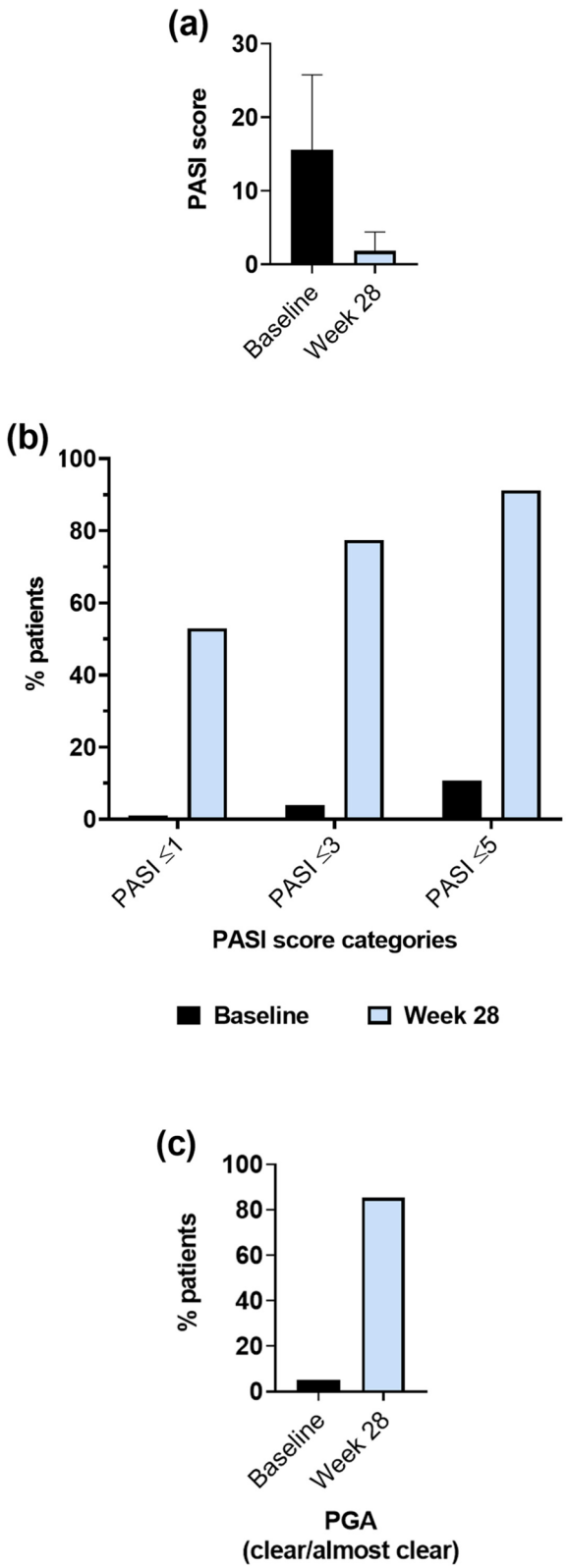

Fig. 3 Physical assessment of disease severity. **a** Psoriasis Activity Severity Index (PASI) scores; **b** PASI score categories; **c** Physician's Global Assessment (PGA) index (whole body) shifts from baseline to week 28. Data presented as mean and standard deviation for **a** or frequencies (absolute number of patients) for **b** and **c**

patient-reported symptoms of depression, anxiety, and stress after 28 weeks. Improvements in DASS-21 subscale scores (depression, anxiety, and stress) were paralleled by robust improvements in physical disease severity scores (PASI and PGA), as well as other psychological and well-being scores (DLQI and WHO-5). These findings support and extend results from previous studies highlighting the broad impact of tildrakizumab on key patient-centered outcomes in routine clinical care of patients with plaque psoriasis [12, 30–41].

To our knowledge, this is the first study evaluating the use of a biologic for moderate-to-severe plaque psoriasis that adopts changes in DASS-21 questionnaire subscale scores as a primary endpoint. We observe that after 28 weeks of treatment with tildrakizumab, depression, anxiety, and stress scores of patients with psoriasis reached levels comparable to the non-clinical population [42]. Specifically, mean DASS-21 scores in our population at week 28 vs. the non-clinical population in Henry and Crawford 2005 were 2.5 vs. 2.8 for depression, 1.8 vs. 1.9 for anxiety, and 4.5 vs. 4.7 for stress [42].

Although the DASS-21 is indeed recognized as a valuable and reliable tool for measuring the psychological impact of psoriasis [43, 44], many patients will also have overlapping symptoms (i.e., depression and anxiety) which was not assessed in the present study. In addition, only 5 patients (4.9%) reported psychiatric disorders at baseline (reflecting prior clinical diagnoses), while 24–30% of patients were identified as having moderate-to-severe symptoms as measured using the DASS-21. This discrepancy likely reflects underdiagnosis in routine care and the difference between medical history (capturing only established disorders) and sensitive self-report scales such as the DASS-21, which detect subclinical and situational distress.

Table 2 Association between PASI (≤ 3 and > 3) at week 28 and each DASS-21-scale score-change from baseline to week 28

	PASI ≤ 3	PASI > 3
DASS-21 subscales	*N* = 79	*N* = 23
Depression score-change		
Mean (SD)	− 2.8 (4.5)	− 2.0 (6.0)
95% CI	− 3.00; − 1.00	− 4.54; 0.63
Anxiety score-change		
Mean (SD)	− 2.1 (3.6)	− 3.1 (5.0)
95% CI	− 2.00; − 1.00	− 4.00; 0.00
Stress score-change		
Mean (SD)	− 3.4 (5.0)	− 3.3 (5.0)
95% CI	− 5.00; − 2.00	− 5.46; − 1.15

CI confidence interval, *DASS-21* Depression, Anxiety, Stress Scale 21, *PASI* Psoriasis Area and Severity Index, *SD* standard deviation

Table 3 Whole-body PGA index distribution

PGA index	Baseline	Week 28
Clear	1 (0.99)	47 (46.08)
Almost clear	4 (3.96)	40 (39.22)
Mild	17 (16.83)	13 (12.75)
Moderate	59 (58.42)	2 (1.96)
Severe	20 (19.80)	0
Total	101 (99.02)	102 (100.00)

Data reported as *n* (%)

PGA Physician Global Assessment, *n* number

One important study is the TRIBUTE study, an international, multicenter, phase IV, open-label trial that assessed the efficacy and real-world impact of tildrakizumab in patients with moderate-to-severe psoriasis. It demonstrated significant improvements in skin symptoms, patient-reported outcomes such as pruritus, pain, and sleep, and QoL scores (DLQI and Skindex-16) after 24 weeks of treatment [36].

Preliminary results of the POSITIVE study show that treatment with tildrakizumab was associated with increased psychological well-being of patients, assessed using the WHO-5 questionnaire [45]. Specifically, mean WHO-5 scores at baseline were 53.9, similar to our baseline WHO-5 score of 50.9. Putting these values in context, mean WHO-5 score for the general population, in patients with type 2 diabetes and among female patients with breast cancer are 63.9, 60.3, and 52.2, respectively [46–48]. After 28 weeks of treatment, the POSITIVE study recorded an increase in the WHO-5 score in patients treated with tildrakizumab, reaching a mean of 67.3, which was similar to the mean value in our study of 66.0 and the score of the general population. The only other study that evaluated depression, anxiety, or stress in patients treated with tildrakizumab was a recent small study by Trovato et al., where the tools used were DLQI and WHO-5 questionnaires [13].

WHO-5 provides a good general overview of mental health aspects [24], and DLQI directly evaluates how the disease affects daily life [23]. However, they may not fully capture the emotional burden and social stigma of psoriasis. The DLQI, while widely used to assess the impact of psoriasis on QoL, has several limitations. It captures a limited range of patient-relevant domains, as it is based on only 10 items, and some questions combine multiple issues, complicating interpretation. In addition, items may be irrelevant for certain patients, leading to "not relevant" responses that can underestimate disease severity and quality-of-life impact, highlighting the need for supplementary assessments [45].

Several mechanisms may explain the association between skin clearance and psychological benefit. Psoriasis-related disfigurement and associated stigmatization are known risk factors for depression, anxiety, and perceived stress [3, 49]. Achieving skin clearance or near-clearance (e.g., PASI ≤ 3) may therefore reduce the social and emotional toll of psoriasis, thus alleviating depressive and anxious symptoms [8, 11, 50]. Moreover, research indicates that the relationship between psoriasis and mood disorders such as depression and anxiety is bidirectional: higher levels of depression have been shown to predict

Table 4 TEAEs registered in the safety population ($n = 115$)

TEAEs	Patients *n* (%)	Events
Total	15 (13.0)	17
Mild	3 (2.6)	3
Moderate	6 (5.2)	7
Severe	7 (6.1)	7
Serious	4 (3.5)	4
Cardiac disorder	2 (1.7)	2
Drug ineffective	1 (0.9)	1
COPD	1 (0.9)	1
Related to treatment	8 (7.0)	10
General disorders and administration site conditions	7 (6.1)	7
Drug ineffective	4 (3.5)	4
Edema peripheral	2 (1.7)	2
Treatment failure	1 (0.9)	1
Arthralgia	1 (0.9)	1
COPD	1 (0.9)	1
Psoriasis	1 (0.9)	1
Leading to study drug temporarily discontinued	0	0
Leading to study drug permanently discontinued	10 (8.7)	11
Leading to study discontinuation	9 (7.8)	9
Fatal (myocardial infarction)	1 (0.9)	1

COPD chronic obstructive pulmonary disease, *n* number, *TEAE* treatment emergent adverse event

poorer clinical outcomes and lower efficacy in psoriasis treatment [51]. This suggests that not only does effective management of psoriasis lead to improved emotional well-being but also that addressing psychological comorbidities can enhance treatment responses. Supporting this idea, Timis et al. demonstrated that improvements in PASI scores significantly correlated with reductions in depression and anxiety, whereas changes in DLQI showed no such association [52]. This finding reinforces the limitations of relying solely on DLQI to assess QoL and highlights the importance of incorporating broader psychosocial measures. Moreover, the authors concluded that biologic therapies not only reduce disease severity but also effectively alleviate depression and anxiety symptoms in patients with psoriasis.

Our preliminary results revealed that patients with the greatest PASI improvements also showed larger reductions in DASS-21 depression and stress scores (independent of prior biologic exposure), indicating a correlation between dermatological improvement and psychological benefit [53]. This finding highlights the clinical relevance of achieving

rigorous control of skin lesions, potentially reinforcing the concept that the extent of dermatologic improvement can translate into a tangible psychosocial benefit [54, 55]. A similar relationship was observed for DLQI (data not shown), indicating that improvements in skin-related QoL and psychological well-being often track in parallel [54, 55]. While this observation is clinically useful and highlights the importance of holistic care for both patients and physicians, it is important to note that improving PASI scores does not automatically lead to improved mental health for every patient since psychological distress can persist independent of skin severity.

Study Limitations

The main limitations of this study include the absence of a direct comparator arm. In this regard, improvements in DASS-21 scores should be interpreted with caution because, without a placebo or active comparator, we cannot exclude contributions from placebo effects, natural disease variability, or other external influences. Furthermore, given the observational design and that this is strictly an IA, we did not adjust DASS-21 outcome results for potential confounder variables such as baseline psychiatric disorders and antidepressant use, socioeconomic status, or previous biologic use. Adjusted and multivariable analyses including additional covariates are planned in the final 52-week analysis. Although observational studies do lack the strict randomization of clinical trials, they reflect the complexities of routine practice and a broader patient population, including those with multiple comorbidities or prior biologic therapy failures. These patients may be underrepresented in controlled trials.

Furthermore, patients who discontinued early may differ systematically from patients who completed, potentially introducing bias in our results. Nonetheless, the low overall dropout rate and consistent improvements in multiple patient-reported outcomes strengthen the validity of the findings. Another limitation of this study is that the present IA is only based on 28-week data and a proportion of the cohort are yet to complete follow-up, potentially introducing uncertainty and the risk of premature conclusions. The final 52-week analysis with the complete cohort may yield additional insights.

CONCLUSION

This 28-week interim data suggest that tildrakizumab provides clinically important improvements not only in psoriatic skin lesions but also in psychological well-being and QoL parameters in real-world clinical practice. These effects have significant implications for patient management, particularly given the notable psychosocial burden of psoriasis [56]. Longer-term analyses (including the adjusting for potential confounding variables) from this study, including the 52-week data, will help clarify the durability of these benefits.

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Declarations

Conflict of Interest. Emanuele Trovato has nothing to disclose; Claudio Bonifati has received support for consulting fees, honoraria, and support for attending meetings from AbbVie, Lilly, Janssen-Cilag, Novartis, and Amgen; Simone Ribero has received research grants, travel support, and consultancy fees from AbbVie, Almirall, Leo Pharma, Johnson & Johnson, L'Oréal, Sanofi, Sandoz, UCB, Eli Lilly, Novartis, and Bristol Myers Squibb; Massimiliano Scalvenzi has nothing to disclose; Alessandra Narcisi has served on advisory boards and has received honoraria for lectures and research grants from Almirall, AbbVie, Leo Pharma, Celgene, Eli Lilly, Janssen, Novartis, Sanofi Genzyme, Amgen, and Boehringer Ingelheim; Aldo Cuccia has nothing to disclose; Vincenzo Panasiti has nothing to disclose; Antonio Giovanni Richetta has nothing to disclose; Gianluca Pagnanelli has no financial disclosures regarding the study; Ketty Peris has received support for consulting fees and honoraria from AbbVie, Almirall, Biogen, Celgene, Janssen, Galderma, Novartis, Lilly, Pierre Fabre, Sandoz, Sanofi, and Sun Pharma; Franco Rongioletti has nothing to disclose; Francesca Satolli has nothing to disclose; Federico Bardazzi has been a consultant, adviser, and clinical study investigator for Eli Lilly, AbbVie, Novartis, Leo Pharma, Sandoz, Bristol Myers Squibb, Abiogen Pharma, Celgene, and Janssen; Alessandro Borghi has nothing to disclose; Carlo Carrera has served as a board participant or speaker for AbbVie, Lilly, Janssen, Novartis, Celgene, Almirall, and Leo Pharma; Marco Galluzzo declares to have acted as speaker and/or consultant for AbbVie, Almirall, Eli Lilly, Johnson & Johnson, LEO Pharma, Novartis, and Sanofi, outside the submitted work; Claudia Lasagni declares a conflict of interest with AbbVie, Novartis, Lilly, and Almirall; Giovanna Moretti has nothing to disclose; Marco Romanelli has nothing to disclose; Emanuele Cozzani has acted as a speaker for AbbVie, Almirall, Eli Lilly, and Novartis; Claudio Guarneri has been a scientific consultant, speaker, and/or clinical study investigator for AbbVie, Celgene, Janssen, Eli Lilly, Novartis, Pfizer, Sanofi, Almirall, and Leo Pharma; Marina Venturini has served as advisory board member and/or consultant and has received fees and speaker's honoraria and/or has participated in clinical trials for AbbVie, Almirall, Amgen, Bristol Myers Squibb, Boehringer Ingelheim, Eli Lilly, Galderma, Janssen, Leo Pharma, Novartis, Pierre Fabre, and UCB Pharma; Maria Rita Bongiorno has nothing to disclose; Francesca Prignano has served as advisory board member and consultant and has received fees and speaker's honoraria or has participated in clinical trials for AbbVie, Almirall, Leo Pharma, Eli Lilly, Janssen, Novartis, Biogen, Sanofi Genzyme, UCB, and Boehringer Ingelheim; Vito Di Lernia has served as consultant and/or member of Data Safety Monitoring Boards or advisory boards and/or has received speaker honoraria from AbbVie, Amgen, Eli Lilly, Janssen, and Novartis; Franca Taviti has nothing to disclose; Severino Persechino has nothing to disclose; Rocco De Pasquale has nothing to disclose; Fabrizio Colonna has received fees from Almirall for conference and scientific consultancy; Marina Talamonti declares to have acted as speaker and/or consultant for AbbVie, Almirall, Eli Lilly, Johnson & Johnson, LEO Pharma, Novartis, and Sanofi; Antonio Costanzo has served as advisory board member and consultant and has received fees and speaker's honoraria or participated in clinical trials for AbbVie, Almirall, Biogen, LEO Pharma, Lilly, Janssen, Novartis, Pfizer, Sanofi Genzyme, and UCB Pharma.

Ethical Approval. This study followed Guidelines for Good Pharmacoepidemiology

Practices of the International Society for Pharmacoepidemiology (ISPE 2016), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, the ethical principles laid down in the Declaration of Helsinki, and the Italian AIFA Guidelines for the classification and management of observational studies on drugs. Ethical approval was obtained from the independent ethics committee at each study site. All patients provided written informed consent prior to enrollment.

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