Dermatology Practical & Conceptual

# Brodalumab Efficacy in Psoriasis Patients with Inadequate Response to IL-23 or IL-12/23 Inhibitors: Multicenter Italian Retrospective Analysis - IL PSO (Italian Landscape Psoriasis)

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ABSTRACT

**Introduction:** The use of brodalumab in patients with psoriasis who have failed other biologic drugs is an underexplored topic.

**Objectives:** To evaluate the safety and the efficacy of brodalumab in a subgroup of psoriasis patients who already failed anti-IL23 or anti-IL12/23 treatment.

**Methods:** Using the Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI), we retrospectively evaluated a cohort of 23 patients with psoriasis who underwent a change in therapy with brodalumab exclusively following primary or secondary therapeutic failure of anti-IL-23 or anti-12/23 drugs.

**Results:** The mean PASI decreased significantly following the introduction of brodalumab after four weeks of treatment, continuing to decrease at 16 and 36 weeks, reaching the nadir at 52 weeks (baseline PASI baseline: 14.6 ± 9.2 vs. 52 weeks PASI: 1.1 ± 1.8; $P<0.001$). Sixty-three point six percent of patients reached PASI 100 just after 16 weeks. The same trend of improvement was also observed for the DLQI. The adverse effects observed in our study population were generally mild.

**Conclusions:** Our results are in line with the current literature and suggest that patients who have failed therapy with IL-23 or IL-12/23 inhibitors may benefit from switching to brodalumab, which could be considered a good choice for patients who need a rapid resolution of the inflammatory skin condition.

## Introduction

The recent worldwide deployment of anti-interleukin (IL)-17 and anti-IL-23 drugs has revolutionized the treatment paradigm of psoriatic disease, allowing a dramatic improvement in the rate of achievement and maintenance of clinical remission [1, 2].

However, regardless of psoriasis forms and the disease domains involved, a variable percentage of patients still experience primary therapeutic failure, incomplete response, or progressive loss of treatment efficacy (secondary therapeutic failure). In this context, switching treatments among different mechanisms of action has been explored in previous studies conducted on psoriatic patients [3-5].

However, criteria providing a clear clinical rationale for such transitions are lacking, and no clear guidance is provided by international guidelines to date.

Considering that most patients treated with anti-IL drugs have previously experienced failure of at least one traditional DMARDs and in some cases even one or more biologics, the most obvious and widely used strategy to manage this difficult subgroup of patients is to attempt an interclass switch from an anti-IL-23 to an anti-IL-17 and vice versa. Brodalumab is the only monoclonal antibody directed toward the IL-17 receptor A. Because of this peculiar mechanism of action, brodalumab could block IL-17A, IL-17F, IL-17A/F, and IL-17E isotypes, providing deeper cytokine inhibition and faster anti-inflammatory activity than other drugs of the same class [6].

Results from the AMAGINE 1-2-3 randomized controlled trials (RCTs) showed that 51% of patients achieved complete skin clearance (PASI 100) after 52 weeks of treatment. Efficacy was sustained over a long period, with more than half of patients maintaining PASI 100 and more than 75% of patients maintaining almost clear skin (PASI 90) up to 120 weeks [7-9].

## Objectives

We performed a real-life retrospective study to evaluate the safety and the efficacy of brodalumab in a subgroup of psoriasis patients who already failed anti-IL23 or anti-IL12/23 treatment.

## Patients and Methods

We retrospectively evaluated over a follow-up period of 52 weeks a cohort of 23 psoriasis patients who underwent a medical switch to brodalumab exclusively following primary or secondary therapeutic failure of anti-IL-23 or anti-12/23 drugs. Patients who transitioned for adverse effects or because of any reason other than anti-IL23 or anti-12/23 failure were excluded from the study. Clinical and quality-of-life parameters collected at baseline (start of brodalumab treatment) and at four predefined timepoints (4, 16, 36, 52 weeks of continuous brodalumab treatment) were included for the purposes of this study. The following parameters were used for statistical comparisons: Psoriasi Area and Severity Index (PASI), Dermatology Life Quality Index (DLQI), presence/absence of active psoriatic arthritis, presence/absence of adverse events. Data were summarized by means of descriptive analysis. Means and standard deviations (SDs) were

calculated for continuous variables, while absolute values and frequency (%) were calculated for categorical variables. A *t*-test or analysis of variance was performed to compare mean values, while a paired t-test compared mean values at different timepoints. The chi-squared test was used to compare frequencies. The statistical significance was defined as $P<0.05$. All analyses were performed with IBM SPSS Statistics for Windows, Version 26.0.

## Results

The mean age of the patients enrolled was 56.7 ± 13.9 years. Only 4/23 (17.4%) patients were normal weight, while the remaining were overweight or obese (mean BMI= 28.8 ± 5.9). The mean PASI at baseline was 14.4 ± 9.1, and 100% of participants had at least one difficult-to-treat area involved. Almost 13% (3/23) of patients had been diagnosed with oligoarticular psoriatic arthritis (PsA) yet were in complete and stable remission at the time of brodalumab prescription. Baseline demographic characteristics were summarized in Table 1.

**Table 1. Clinical and Demographic Characteristics of our Population at Baseline Visit.**

| Demography | N=23 |
|---|---|
| Male, N (%) | 18 (78.3%) |
| Age (years), mean ± SD | 56.7 (± 13.9) |
| Disease duration (years), mean ± SD | 20.4 (± 9.7) |
| BMI, mean ± SD | 28.8 (± 5.9) |
| Obese, N (%) | 7 (30.4%) |
| Overweight, N (%) | 19 (82.6%) |
| Normal weight, N (%) | 4 (17.4%) |
| Diabetes, N (%) | 2 (2.9%) |
| Hypertension, N (%) | 10 (43.5%) |
| Hyperlipidemia, N (%) | 8 (34.8%) |
| Thyroid disease, N (%) | 1 (4.3%) |
| Cardiopathy, N (%) | 3 (13.0%) |
| Other, N (%) | 3 (13.0%) |
| PsA, N (%) | 3 (13.0%) |
| ≥ 1 Difficult-to-treat areas, N (%) | 23 (100%) |
| PASI baseline, mean ± SD | 14.4 (± 9.1) |
| Naïve for systemic therapies, N (%) | 0 |

All patients involved in the study (N=23) had previously received unsuccessful treatment with traditional DMARDs and were receiving, at the time of enrollment, one of the following anti-IL-23 or 12/23 inhibitors–guselkumab, tildrakizumab, risankizumab, or ustekinumab–as their first biological treatment. Most participants (14, 60.8%) were on anti-IL23 treatment at the time of switching to brodalumab, while nine patients (39.1%) were on ustekinumab (anti-IL12/23). Previous biological treatments used by the study population are summarized in Table 2.

The mean PASI decreased significantly after the introduction of brodalumab as early as week 4 of treatment, from a mean value of 14.6 ± 9.2 to 6.0 ± 7.1 ($P<0.001$). The trend of PASI improvement persisted during follow-up assessments performed at 16 and 36 weeks, reaching the nadir at 52 weeks (PASI: 1.1 ± 1.8; $P<0.001$) (Table 3, Figure 1). The percentages of patients who progressively achieved the PASI 75, 90, and 100 clinical responses on assessments performed at the scheduled timepoints are shown in Table 4 and depicted graphically in Figure 2. Mirroring the results obtained on disease severity, the DLQI also improved significantly in our study population, dropping to 1/3 of the baseline level after just four weeks of treatment with brodalumab (baseline: 16.9 ± 7.6 vs. 4 weeks: 5.1 ± 7.0; $P<0.001$) and reaching the lowest value after 52 weeks of treatment (1.8 ± 3.8; $P<0.001$). The trend of the DLQI across all assessments is summarized in Table 5 and graphically represented in Figure 3. Of note, two patients (8.7%)

**Table 2. Last Previous Biological Therapies.**

| Last previous biological therapy | N=23 | Reason for discontinuation |
|---|---|---|
| *Guselkumab* | 6 (26.1%) | primary inefficacy (1, 16.7%)<br>loss of efficacy (5, 83.3%) |
| *Risankizumab* | 3 (13.0%) | primary inefficacy (1, 33.3%)<br>loss of efficacy (1, 33.3%)<br>other (1, 33.3%) |
| *Tildrakizumab* | 5 (21.7%) | primary inefficacy (1, 20.0%)<br>loss of efficacy (4, 80.0%) |
| *Ustekinumab* | 9 (39.1%) | primary inefficacy (1, 11.1%)<br>loss of efficacy (7, 77.8%)<br>other (1, 11.1%) |

12/23 (52.2%) patients have taken more than one previous biologic drug.

**Table 3. Mean PASI by Visit.**

| Visit | Mean PASI (SD) | mPASI decrease | Paired t-test |
|---|---|---|---|
| Baseline (N=22) | 14.6 (± 9.2) | | |
| 4 weeks (N=22) | 6.0 (± 7.1) | -8.6 (± 6.0) | <0.001 |
| 16 weeks (N=22) | 2.6 (± 5.7) | -11.9 (±6.8) | <0.001 |
| 36 weeks (N=22) | 1.7 (± 3.4) | -12.9 (±6.9) | <0.001 |
| 1 year (N=21) | 1.1 (± 1.8) | -12.0 (± 6.0) | <0.001 |

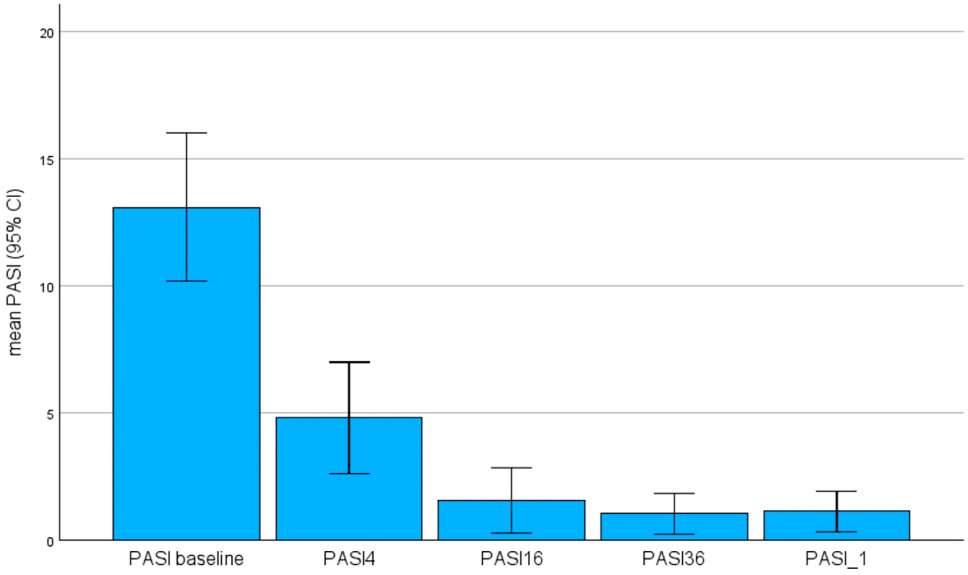


**Figure 1.** mPASI by Visit.

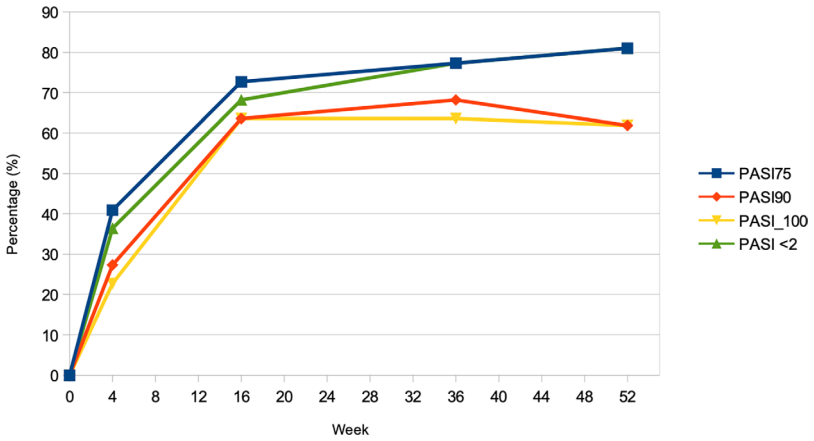


**Figure 2.** Relative PASI over One Year.

experienced a primary non-response to brodalumab treatment (median PASI at baseline: 9.3 vs median PASI at 16 weeks: 7.8; *P*= 0.3). Both subjects discontinued therapy after the assessment performed at 16 weeks of treatment and were further switched to a biologic of a different class. All three PsA patients maintained clinical remission; however, none of them underwent ultrasound assessment for subclinical disease detection. We found no significant difference in clinical response to brodalumab among the previous failed anti-IL23 or anti-IL12/23. None of patients included in the study experienced any major adverse effect, while 9/23 patients (39.1%) reported mild adverse events mainly related to an increased susceptibility to transient rhinopharyngeal infections and oral candidiasis. Furthermore, no significant depressive symptom was reported by patients enrolled during the scheduled follow-up period.

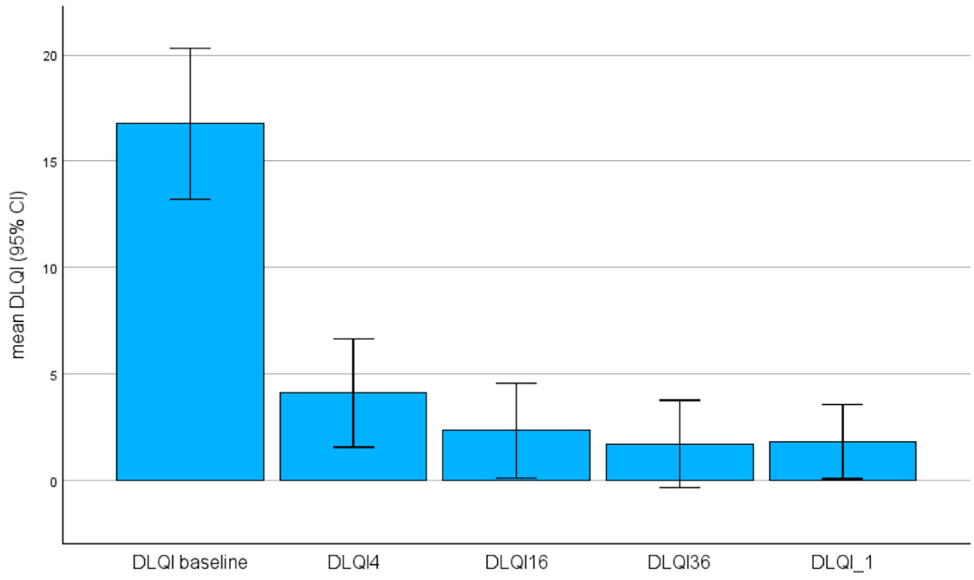


**Figure 3.** Mean DLQI by Visit.

## Discussion

A critical question in the clinical management of psoriasis, and particularly in the case of therapeutic failure of a biologic drug, is whether it is more appropriate to use a drug of the same class or to switch to another class. Some real-world evidence has shown that failure of a specific cytokine-directed treatment does not preclude the use of biologics from other classes or from the same class, making this an interesting research topic regarding the long-term management of psoriasis [10-12].

Unfortunately, to date there is a lack of biomarkers to guide treatment changes. Therefore, intra- or interclass switching in the treatment of psoriasis is currently based on the dermatologist's experience, the severity of the disease, the skin areas involved, and the patient's comorbidities. In this context, real-world data supporting the availability and the rate of efficacy and safety of these treatment changes are highly needed. A recent study showed brodalumab to be one of the biologic drugs with lowest anti-drug-antibody (ADAs) formation rates. This finding supports this biologic agent as a suitable drug for patients who have experienced therapeutic failures potentially due to the presence of ADAs [13]. A recent trial on psoriatic patients experiencing a failure of ustekinumab showed a favorable and earlier effect of brodalumab as compared to guselkumab, thus providing important information to help physicians in the choice of therapy for this subgroup of patients [14].

Recently, Papp et al. conducted an open-label study on a large cohort of patients with psoriasis that demonstrated how brodalumab can be useful in patients who do not respond to TNF-α, IL-12/23, or IL-17 inhibitors. These authors found a PASI 100 response in 40.3% of patients after 16 weeks of treatment with brodalumab and in 45.5% of patients after 26 weeks [15].

**Table 4. Percentage of Patients with PASI Score Reduction of 75, 90, and 100, by Visit.**

| PASI 75 | | |
|---|---|---|
| **Visit** | **N** | **%** |
| *4 weeks* | 9/22 | 40.9 |
| *16 weeks* | 16/22 | 72.7 |
| *36 weeks* | 17/22 | 77.3 |
| *1 year* | 17/21 | 81.0 |
| **PASI 90** | | |
| **Visit** | **N** | **%** |
| *4 weeks* | 6/22 | 27.3 |
| *16 weeks* | 14/22 | 63.6 |
| *36 weeks* | 15/22 | 68.2 |
| *1 year* | 13/21 | 61.9 |
| **PASI 100** | | |
| **Visit** | **N** | **%** |
| *4 weeks* | 5/22 | 22.7 |
| *16 weeks* | 14/22 | 63.6 |
| *36 weeks* | 14/22 | 63.6 |
| *1 year* | 13/21 | 61.9 |
| **PASI <2** | | |
| **Visit** | **N** | **%** |
| *4 weeks* | 8/22 | 36.4 |
| *16 weeks* | 15/22 | 68.2 |
| *36 weeks* | 17/22 | 77.3 |
| *1 year* | 17/21 | 81.0 |

As shown in Table 4, the percentage of our patients who achieved PASI 100 just after 16 weeks of treatment was 63.6%, a significantly higher proportion compared to the results obtained by Papp et al.

**Table 5. Mean DLQI by Visit.**

| Visit | MeanDLQI (SD) | mDLQI decrease | Paired t-test |
|---|---|---|---|
| *Baseline (N=22)* | 16.9 (± 7.6) | | |
| *4 weeks (N=22)* | 5.1 (± 7.0) | -11.9 (± 9.2) | <0.001 |
| *16 weeks (N=22)* | 2.9 (± 5.5) | -14.0 (± 8.4) | <0.001 |
| *36 weeks (N=22)* | 2.6 (± 5.9) | -14.4 (± 8.6) | <0.001 |
| *1 year (N=21)* | 1.8 (± 3.8) | -15.0 (± 8.2) | <0.001 |

Additional data on brodalumab efficacy after anti-IL 23 failure are lacking. In this context, our real-life 52-week retrospective study demonstrates good efficacy, speed of action, and safety of brodalumab in psoriasis patients with previous exposure to IL-23 and 12/23 inhibitors with performances similar or superior to those shown in RCTs. The excellent results obtained in our group of patients unresponsive to IL-23 inhibitors could be explained by a more extensive suppressive effect exerted by this drug on the Th-17 pathway. Interestingly, this feature was not associated in our study population with a higher incidence of infectious events or the occurrence of inflammatory bowel disease.

### Limitations of the study

The main limitations of our study include its retrospective design and the relatively small number of patients involved. However, it should be noted that IL-23 inhibitors have very high response rates and a consequently limited number of treatment failures. Another limitation of our study was the inability to demonstrate whether main clinical and anamnestic variables could influence the therapeutic performance of brodalumab. Despite the implementation of a Cox regression model, the small sample size, and high remission rate achieved in patients (only two primary failures) probably precluded us from identifying any variable that could affect the key endpoint of the study.

## Conclusions

In conclusion, our results suggest that patients who had previously failed therapy with IL-23 or IL12/23 blockers may respond to medical switch to another class of biologics. In particular, brodalumab could be considered a good choice for this group of difficult-to-treat patients because, burdened by several therapeutic failures, they could be considered high-need of an effective and fast-acting drug which also shows a very low immunogenicity risk. However, more data are needed to further explore the possibility of switching therapy among different classes of biologics for the treatment of psoriasis.

**Ethics Approval:** Institutional review board approval was exempted for this study as its procedure did not deviate from good routine clinical practice. The study was conducted in accordance with the Helsinki Declaration of 1964 and its later amendments.

**Consent to Participate:** All patients gave written informed consent for the retrospective retrieval of anonymized data.

**Consent for Publication:** All patients gave written informed consent for the publication of anonymized data.

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