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Psoriasis patients' characteristics associated with high PASI response to tildrakizumab: an international dual center study

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Abstract. – OBJECTIVE: Heterogeneous real-world evidence can complement the more strictly regulated clinical trial data. A benefit of this is the wide range of backgrounds, comorbidities and characteristics that can give additional insights into treatments. Observational, retrospective studies can help to fill in the mosaic that makes up a treatments landscape. Tildrakizumab, an interleukin 23p19 inhibitor, is approved for the treatment of plaque psoriasis and has been shown to be a safe and efficacious therapy in clinical trials and emerging real-world evidence. We aimed at confirming the efficacy of tildrakizumab in patients with plaque psoriasis in a dual center setting and identifying patients' characteristics leading to better treatment response.

PATIENTS AND METHODS: Patients with moderate to severe plaque psoriasis, eligible for systemic biological treatment, and treated with tildrakizumab were included in the study and the routine clinical parameters – Psoriasis Area and Severity Index (PASI), Dermatology Life Quality Index (DLQI), and safety – were retrospectively analyzed.

RESULTS: The combined cohorts included 89 patients, of which 64% were naïve to biologic therapies. At the time of analysis efficacy assessment was available for 39 patients after 12 months of treatment, 73 patients after 36 weeks, 79 patients after 16 weeks and 82 patients after 4 weeks. PASI and DLQI decreased significantly over time, with 52/73 (71.2%) patients achieving PASI 100 after 36 weeks. No severe side-effects were recorded in association with tildrakizumab.

CONCLUSIONS: We confirmed the safety and efficacy of tildrakizumab in a real-world clinical setting. A higher proportion of patients naïve to biologics achieved a greater PASI response than patients who had previously been treated with biologics. The same was true for older patients and patients with a shorter history of disease.

Key Words:
IL-23, Psoriasis, Real-world, Tildrakizumab, Treatment, Early intervention.

Introduction

Psoriasis is a common autoimmune mediated, systemic inflammatory disease that manifests mainly on the skin, but can also affect the joints, and other organs[1]. The etiological factors of the most prevalent form, the plaque type psoriasis, have been elucidated over the last decade revealing a complex interplay between different parts of the innate and adaptive immunity system, leading to dysregulation of keratinocyte proliferation. Such mechanisms result in chronic, scaly, erythematous lesions called plaques[2,3]. One of the key cytokines involved in the pathogenesis and pathophysiology of psoriasis is IL-23 that has been shown to promote pathogenic Th17 cell differentiation, which in turn, through the production of IL-17, drive the inflammatory process[4]. Clinical studies[5,6] have demonstrated that inhibition of IL-23 by administration of tildrakizumab, a humanized, IgG1 κ monoclonal antibody specifically targeting IL 23-p19, provides sustained disease control over 5 years, with a reassuring safety profile. Emerging real-world evidence over the last two years has further confirmed the efficacy and safety of tildrakizumab in heterogeneous clinical practice settings[7,8]. To confirm the efficacy and safety of tildrakizumab in a clinical practice setting and to further identify factors leading to improved

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treatment response, we retrospectively analyzed 89 psoriasis patients treated with tildrakizumab in two centers over 12 months.

Patients and Methods

Patients with moderate to severe plaque psoriasis (body surface area involvement ≥10%, Physician Global Assessment (PGA) score ≥3 and Psoriasis Area Severity Index (PASI) score ≥ 12) at baseline, eligible for systemic therapy, and administered 100 mg tildrakizumab at weeks 0 and 4 and then every 12 weeks, by subcutaneous injection, were included into the study. According to current clinical practice, this treatment was performed as recommended by local regulation (Ilumetri, EMA). The patients were referred to the Dermatology Departments of the Policlinico San Martino Hospital, IRCCS, Genoa, Italy, and of the University Hospital Zurich (USZ), Zurich, Switzerland, between March 2020 and November 2021.

Patients were assessed at baseline, and at weeks 4, 12 and 24 and 52, by a clinical visit and recordings of PASI, and Dermatology Life Quality Index (DLQI). All patients signed an informed consent form to the use of clinical data for publication.

Statistical Analysis

Data were summarized by descriptive analysis. Means, median and standard deviations (SDs) were calculated for continuous variables, while absolute values and frequency (percentage) were calculated for categorical variables. Comparison of mean values was performed by a *t*-test. The Wilcoxon Signed-Rank test was used to compare repeated measurements in each group, and the Mann-Whitney U test compared mean data between groups. Results were considered significant when $p<0.05$. All analyses were performed with SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA).

Results

A cohort of 89 patients, treated with tildrakizumab for plaque psoriasis, was enrolled. The demographic and clinical features and comorbidities at baseline are reported in Table I. The overall mean PASI score was 11.6 ± 5.3 at baseline (n=87). The populations from the two centers showed different baseline PASI scores: 12.8 ± 5.4 for patients of the Italian center (n=61), and 8.7 ± 3.5 for the Swiss center (n=26) ($p<0.001$). Genital psoriasis was present in two patients, and palmoplantar disease in three subjects. The overall mean PASI score was 5.8 ± 4.2 at week 4 (n=83), 2.1 ± 2.5 at week 16 (n=82), 1.1 ± 2.1 at week 36 (n=75), and 0.9 ± 1.7 at week 52 (n=39).

57 (64%) patients were naïve to biologic drugs, and the last therapy before tildrakizumab (data are available for 70 cases) had been methotrexate (n=29; 41%), cyclosporin A (n=10, 14%), adalimumab (n=7, 10%), dimethyl fumarate (n=6; 9%), acitretin (n=4, 6%), phototherapy (n=4; 6%), ustekinumab (n=3; 4%), etanercept (n=2; 2%), ixekizumab (n=2; 2%) and secukinumab (n=2; 2%).

According to the PASI score reduction, a progressive improvement of psoriasis was observed through the observation period (Figure 1). PASI 100 was reached by 11/82 (13.4%) patients after 4 weeks, 34/79 (43%) after 16 weeks, 52/73 (71%) after 36 weeks and 27/39 (69%) after 1 year. No difference in mean PASI score was present between the two centers starting from week 4 and through the whole observation period.

The group of patients who had PASI 100 after 36 weeks of treatment with tildrakizumab had a significantly shorter history of plaque psoriasis in comparison with the patients who did not reach PASI 100 at 36 weeks (16.5 ± 15 years *vs.* 26.8 ± 13 years, $p=0.007$). In addition, the mean age at psoriasis onset of patients reaching PASI 100 at 36 weeks of treatment was significantly

Table I. Primer sequences.

Demographic and clinical features	n = 89, mean ± SD or n (%)
Age (years)	53.0 ± 15.5
Age at psoriasis onset (years)	32.7 ± 17.0
Age at tildrakizumab onset (years)	52.4 ± 15.5
Weight (kg)	78.2 ± 14.9
BMI (kg/m^2)	26.7 ± 4.5
Gender:	
• Male	53 (59.6%)
• Female	36 (40.4%)
Comorbidities:	
• Obesity	18 (20.2%)
• Diabetes	8 (9.0%)
• Hyperlipidemia	17 (19.1%)
• Hypertension	27 (30.3%)
Mean PASI	11.6 ± 5.3 (n = 87)
Mean DLQI	14.8 ± 4.7 (n = 62)

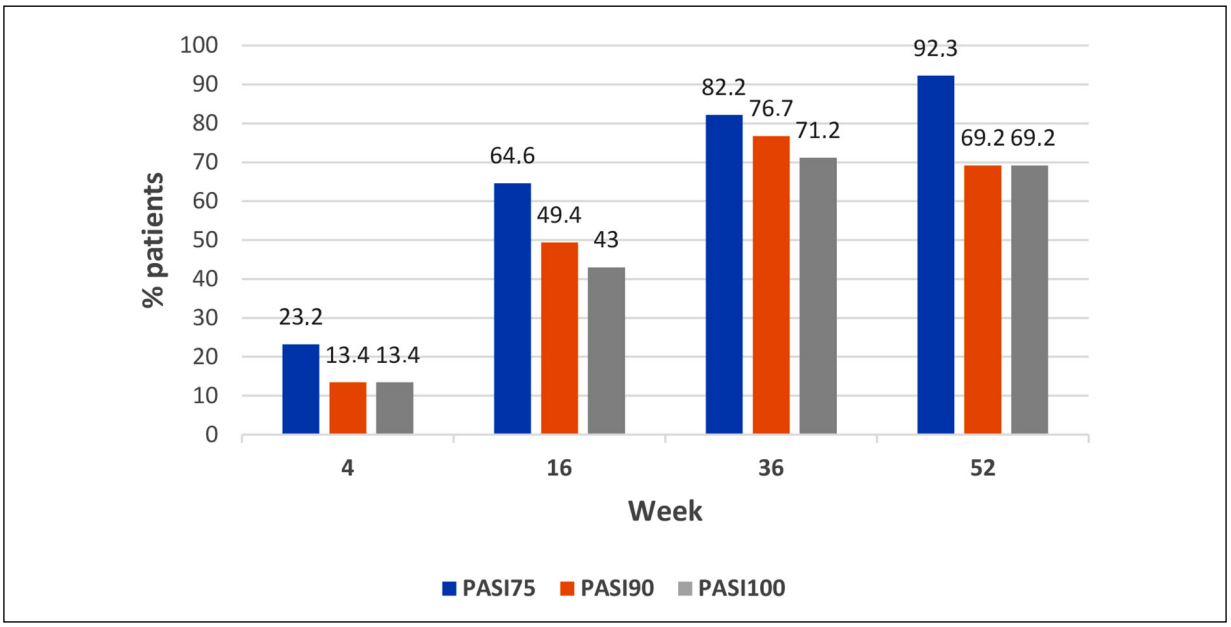

Figure 1. Psoriasis Area and Severity Index improvement at study time points.

higher than the age of patients who showed a lower PASI score (37 ± 17 years *vs.* 25 ± 14 years, p=0.004). Finally, after 36 weeks, PASI 90 and PASI 100 were obtained by a significantly higher proportion of patients who were naïve to biologics than those who were not naïve (84% *vs.* 53%, p=0.018 and 77% *vs.* 47%, p=0.033, respectively; Table II).

Among the 3 patients with palmoplantar psoriasis, one attained PASI 100 by 4 weeks, one by 12 weeks, and one was lost to follow-up after 4 weeks. One patient with genital psoriasis attained PASI 100 by 4 weeks, and this result was maintained after 24 weeks. PASI of the second patient with genital psoriasis was not recorded.

Obese patients and patients with one or more comorbidities had similar PASI improvements as those who were not obese and had no comorbidities, respectively.

The DLQI score was ≥1 in all patients at baseline (n=62), while a score <1 was recorded in 4 (7%, n=60) patients at week 4, in 27 (48%, n=56) patients at week 16, in 36 (68%, n=53) patients at week 36, and in 22 (56%, n=39) patients at week 52.

Discussion

In this retrospective observational study of an unselected patients cohort, we confirmed the safety profile and efficacy profile of tildrakizumab, as previously shown by clinical trials[7]. Large randomized controlled clinical trials are an important tool to validate the efficacy and safety of drugs for registration. However, their strict inclusion and exclusion criteria rarely reflect the real-world clinical patient profile, which is why it is important to analyze the results from more heterogeneous patient populations[9].

The aim of the present analysis was to characterize patients achieving PASI 100 in real life.

Table II. Psoriasis Area and Severity Index improvement after 36 weeks of treatment in patients naïve to biologic drugs.

PASI	Naïve, n (%)	Not naïve, n (%)	*p*-value
PASI 75	49/56 (85.5%)	11/17 (64.7%)	0.064
PASI 90	47/56 (83.9%)	9/17 (52.9%)	0.018
PASI 100	43/56 (76.8%)	8/17 (45.5%)	0.033

PASI: Psoriasis Area and Severity Index.

We observed a progressive improvement of PASI, as expected. The proportion of patients achieving PASI 90 and PASI 100 by 4 weeks of treatment was nevertheless lower than previously observed in the Italian center alone (13% *vs*. 24%)[8]. We can explain this difference by the lower baseline PASI value of patients from the Swiss center, which may provide a lower percentage change in the short-term. PASI improvement was later obtained in the expected proportion of subjects.

As expected, patients who were naïve to biologic therapy showed a better PASI improvement after 24 weeks, as did patients with a shorter history of plaque type psoriasis. This supports the growing evidence for the early intervention hypothesis[10]. It has been speculated that early blockage of the IL-23/Th17 inflammatory *circulus vitiosus* may prevent the development of tissue-resident memory cells that could cause lesion relapse even after years of disease remission[11]. Thus, in addition to the efficacy of tildrakizumab previously demonstrated and confirmed in our patients, early intervention may have further lifelong benefits[12].

Interestingly, our analysis showed that older patients had a better PASI response than younger patients. While this may be due to the relatively small cohort and confounding factors, such as mismatching baseline characteristics between age groups (e.g., time since diagnosis or disease severity), earlier onset of psoriasis has been associated with more severe disease[13,14]. With the gradual increase in childhood psoriasis[15], further studies analyzing the most recent biologics in early onset psoriasis could lead to a better understanding of the disease[16].

Finally, although in a very limited number of patients, tildrakizumab seems to be very efficacious in difficult-to-treat areas such as palmoplantar and genital psoriasis, and in patients with comorbid conditions like in obese patients.

Conclusions

Real life data confirm that tildrakizumab appears to have a remarkable safety profile and good efficacy reflected by an improvement in quality of life of psoriasis patients. Tildrakizumab can be safely used in a wide range of psoriasis patients, and it should be considered for early intervention. Analysis of larger cohorts will allow a better characterization of psoriasis patients' profile for anti-IL23 treatment.

Conflicts of Interest

M. Burlando acted as a speaker and consultant for Abbvie, Janssen, Amgen, Novartis, Eli Lilly, UCB Pharma. A. Parodi served as consultant/investigator for AbbVie, Eli Lilly, Janssen-Cilag, Novartis and UCB Pharma. J-T Maul has served as advisor and/or received speaking fees and/or participated in clinical trials sponsored by AbbVie, Almirall, Amgen, BMS, Celgene, Eli Lilly, LEO Pharma, Janssen-Cilag, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi, UCB. Birkenmaier I is an employee of USZ/UZH and has served as Medical Advisor for Almirall.

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Availability of Data and Material

Data are available upon reasonable request to the corresponding author.

Authors' Contribution

Study conception and design: MB, JTM; Collection and interpretation of data: MB, JTM, AK, DS, IS; Manuscript editing: JTM, IB, MA, DS, IS, EC, AP; Approval to submit: All authors.

Ethics Approval

This is a real-world study, with treatment carried out according to the clinical practice, and no ethic committee approval is required according to the European regulation.

Informed Consent

All patients signed an informed consent to the use of clinical data for publication.

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