Dermatology Practical & Conceptual

Psoriasis with Leg Involvement as the New Difficult-To-Treat Area: A Cohort Study of Patients Treated With Risankizumab

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ABSTRACT

Introduction: Historically, difficult-to-treat areas in psoriasis included face, scalp, folds, genitalia, nails, and palmoplantar region. Recent studies have found that lower limbs behave like a "new" difficult-to-treat area as they can be the only site of residual disease even in patients undergoing biologic therapies.

Objectives: We aimed to evaluate whether legs had different response rates and response times to treatment with a new biologic drug, risankizumab, compared to other body sites.

Methods: We conducted a real-life, observational, retrospective, multicenter study including patients affected by moderate-to-severe psoriasis with leg involvement and undergoing biological therapy with risankizumab for more than 16 weeks. The Psoriasis Area Severity Index (PASI) and Leg-PASI were collected at T0 and at weeks 16, 28, 40, 52, 64, and 76. Statistical analysis using Student's t test and linear regression analysis were performed.

Results: A total of 124 patients were included. The difference between the improvement percentage compared to baseline was statistically significant at weeks 16 and 28, demonstrating that Leg-PASI improved less than PASI. From the linear regression it was deduced that the slope is statistically less steep for Leg-PASI than for overall PASI, confirming that this site responds more slowly to the therapy.

Conclusions: Leg response to risankizumab appears to differ significantly from other body sites in the first weeks of treatment, even if after 28 weeks, statistical significance is lost. Our preliminary finding suggests that risankizumab can be considered an effective treatment for leg psoriasis but with longer response times than other areas, demonstrating the relative nature of resistance to treatment of this district.

Introduction

Psoriasis is a chronic inflammatory disease that can affect any part of the body [1]. Some of these are traditionally considered difficult-to-treat areas; in the pre-biological therapy era, the application of topical products was extremely challenging, because of the delicacy of some areas, such as genitals, the functionality in everyday life of other ones, such as the hands and feet, and because of the aesthetic impairment, such as the face. Indeed, the anatomical sites historically considered as "difficult-to-treat" list the face, scalp, folds, genitalia, nails, and palmoplantar region [2]. However, with the revolutionary introduction of biotechnological therapies, complete or nearly complete clearance of disease has been achieved even in the these sites [3]. Nevertheless, what has emerged from recent studies is the evidence that the lower limbs also behave like a "new" difficult-to-treat area as they can be the only site of residual disease even in patients undergoing biologic therapies [4,5]. It is important to remember that each site of the body involved has a different impact on the patient's quality of life; understanding which ones are less responsive to treatments and what consequences they can have in everyday life can therefore be very useful to the clinicians in guiding therapeutic choices and providing adequate patient counselling. Based on the recent scientific literature, which has identified the legs as a new difficult-to-treat area, the aim of this study was to examine whether legs had different response rates and response times to psoriatic-specific treatment compared to other body sites in a group of psoriatic patients from different Italian centers who participated in this investigation.

Objective

Some data have already been reported regarding the use of biological drugs in psoriatic patients with leg involvement [6]. Based on this consideration and on the already proven efficacy of this recent, promising drug, we retrospectively reviewed psoriatic patients treated with risankizumab to evaluate the site-specific response.

Methods

We conducted a real-life, observational, retrospective, multicenter study, with nine centers in Emilia-Romagna (Italy) specialized in the treatment of psoriasis participating in the investigation. Patients affected by moderate to severe psoriasis with involvement of the legs and undergoing biological therapy with risankizumab for more than 16 weeks were selected. Of each patient, demographic data, the duration and type of psoriasis, the diagnosis of psoriatic arthritis, and the anatomical site of disease involvement were evaluated. Moreover, all previous traditional and biological therapies, the duration of each treatment, and concomitant medications were collected.

The Psoriasis Area Severity Index (PASI) and Leg-PASI were collected at T0 and at weeks 16, 28, 40, 52, 64, and 76, if available, for each patient included in the study. The body area corresponding to the leg was defined as the skin below the knee, except for the sole and the toenails. According to Lund and Browder estimation method [7], the aforementioned body surface corresponds to 17.5% of the total body surface area. Therefore, Leg-PASI was obtained by considering the degree of redness (R), scaling (S), and thickness (T) of the leg area, multiplied by the area estimation coefficient (A_L) and by the 0.175 coefficient, in accordance with the original PASI definition [8].

All the data were extracted from the patient records of each participating hospital. Statistical descriptive analysis was then performed using Student t-test in order to compare PASI and Leg-PASI improvements at each time point. Linear regression analysis and a non-linear regression model (cubic polynomial) were also calculated to analyze the trend of the

PASI and Leg-PASI over time. A *P* value less than 0.05 was considered significant. Statistical analysis was performed using Prism software (Prism 6.0, GraphPad Software, Inc., CA).

Results

We included a total of 124 patients, 74 of whom were male, with a mean age of 55 years old, a mean BMI of 28.6, and a mean disease duration of 21.27 years. Regarding the type of psoriasis, 120 (96.7%) patients presented a vulgar form, two inverse, six palmoplantar, five pustular, and two erythrodermic; none of the 124 presented a guttate form. Of the 124 patients, 121 (97,5%) had localization in typical sites: 12 in the folds, 17 palmoplantar, 19 in nails, 36 on the scalp, and 18 in the genital area. Of the total, 54 patients were not taking any home therapy, while 41 were on polypharmacotherapy. Only 22 patients were naive to biological therapy, while of those who had already undergone previous treatments, 11 had taken etanercept, 48 adalimumab, 13 infliximab, two certolizumab, 35 secukinumab, eight ixekizumab, 18 brodalumab, four guselkumab, two tildrakizumab, and seven apremilast, as reported in Table 1.

Table 1. Epidemiologic data about the study population, body sites involved and previous biologic therapies before administration of risankizumab.

Study Population	No. of Patients
Total	124
Males	72

Type of Psoriasis	No.	Body Sites Involved	No.
1: Vulgar	120	1: typical sites	121
2: Inverse	2	2: folds	12
3: Palmo-plantar	6	3: palmo-plantar	17
4: Pustular	5	4: nails	19
5: Guttate	0	5: scalp	36
6: Erythrodermic	2	6: genitals	18
Psoriatic arthritis	34		

Epidemiologic Data				
	Age	Weight (Kg)	BMI (Kg/m2)	Duration of PsO
Average	55.2016129	82.72072072	28.65911985	21.27118644
Minimum	20	50	19	1
Maximum	85	140	70	53

Therapies			
Previous Biologic Therapies	No.	Concomitant Therapies	No.
BIO naive	22	none	54
Average before risankizumab	1.61	polytherapy	41
Etanercept	11		
Adalimumab	48		
Infliximab	13		
Certolizumab	2		
Secukinumab	35		
Ixekizumab	8		
Brodalumab	18		
Guselkumab	4		
Tildrakizumab	2		
Risankizumab	19		
Apremilast	7		

BMI = body mass index; PsO = psoriasis.

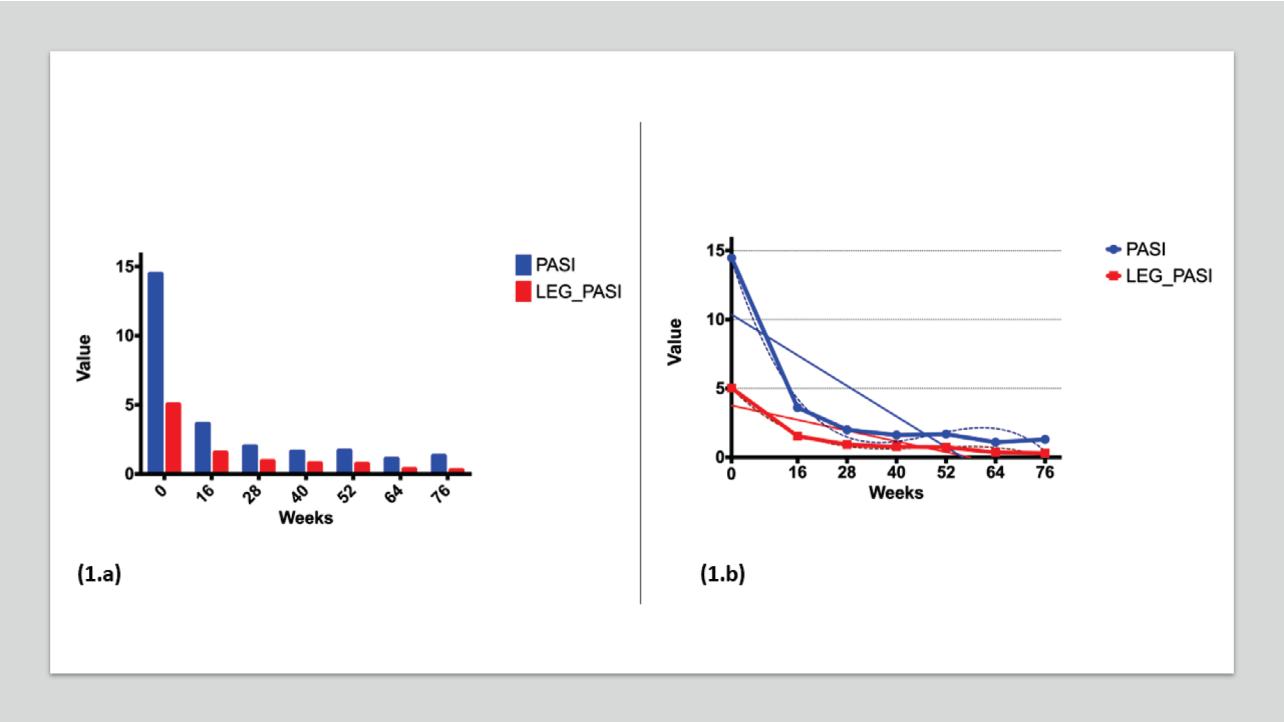

Figure 1. (A) The graphic shows the different trend of PASI and LEG_PASI over time from week 0 to week 76. (B) Linear regression shows that the difference between PASI and LEG_PASI is statistically significant only up to week 28.

The difference between the percentage of improvement compared to baseline of PASI and Leg-PASI was statistically significant at 16 and 28 weeks, demonstrating that Leg-PASI improved less than PASI at these time points (Figure 1A). From the linear regression it can be clearly deduced that the slope of the line is statistically less steep for Leg-PASI than for the overall PASI, confirming that this site responds more slowly to the therapy, as reported in Figure 1B.

Discussion

There is a new and growing scientific literature showing that lower limbs are frequently severely affected in psoriatic patients, representing one of the most difficult-to-treat regions even in patients undergoing biological treatments [9]. As early as 2019, Hjuler et al. [5] investigated in 146 psoriatic patients treated for >6 months with biologic agents the location of treatment-resistant disease; they found that the most common site of recalcitrant psoriasis was the anterior lower leg [49, 3%; 95% confidence interval (CI): 41.2–57.4]. Further common sites of recalcitrant psoriasis were the posterior lower leg (24.7%; 95% CI: 17.7–31.6), elbow (35.6%; 95% CI: 27.8–43.4), and the scalp (19.2%; 95% CI: 12.8–25.6%).

In 2022, Apalhao et al. [10], in a pooled analysis of CLEAR and CLARITY studies of secukinumab versus ustekinumab by body region, reported that the mean PASI scores decreased at a slower rate in the lower limbs compared with other body regions (head and neck, trunk, and upper limbs) in both treatment arms. Additionally, the time needed to achieve total clearance was shortest for the head and neck regions, followed by that for the trunk and upper limbs. In contrast, the mean time to achieve total clearance was the longest in the lower limbs, supporting the concept that lower limbs are difficult to treat and take longer to show a therapeutic response.

The same findings were also confirmed in 50 psoriatic patients included in a South Korean study [11]: the patients were treated with biologics for more than six months and exhibited a partial or good response (reaching a PASI of 1–5 after biologics treatment), and the most common biologics-resistant areas were the anterior lower leg (56.0%), followed by the knee (48.0%), and posterior lower leg (42.0%). In this study, the biologics included ustekinumab (n=16, 32.0%), secukinumab (n=14, 28.0%), guselkumab (n=12, 24.0%), ixekizumab (n=7, 14.0%), and adalimumab (n=1, 2.0%).

However, to date, the site-specific effectiveness of the new biologic drug risankizumab has not been investigated in a real-world setting.

Our retrospective multicenter study enrolled a cohort of 124 patients with several characteristics that are very

common in a real-life setting of specialized clinics for the care of complex psoriasis patients, represented by a high average age (55.2 years), bio-experienced status (82.3%), a high BMI (28.7), and a high number of comorbidities that require multiple concomitant medications (56.5%). The analysis of our cohort of patients demonstrated that legs improved significantly less than the rest of the body between weeks 16 and 28, and from the statistical linear regression showed that this site responded more slowly to the therapy.

Thus, this new biologic drug does not appear to differ significantly from previous ones with regard to site-specific response in the first few weeks of treatment. However, although the legs are confirmed to be a difficult-to-treat area, after 28 weeks, the statistical significance was lost, and the legs began to respond like the other body sites.

Limitations

The limitations of our study were its retrospective design and its multicenter nature.

Conclusions

Our preliminary finding suggests that risankizumab can be considered an effective drug in this body region, with longer response time than in other affected body areas, demonstrating the relative treatment resistance nature of this district. Overall, our findings highlight that the lower limbs can take longer to respond, but in patients undergoing risankizumab therapy, a further grade of response is possible even beyond six months. This finding, although preliminary and observed in a small cohort, may be of reassurance to patients.

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