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ORIGINAL RESEARCH

Rapid Efficacy of riSankizumab in pretibial psoriasis invOLVEment: RESOLVE

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Abstract

Background: Despite extraordinary improvements in the management of psoriasis in recent times, some areas of the body, such as the pretibial area, still show an unsatisfactory response and a more significant impact on patient quality of life. This multicentre study focuses on psoriasis affecting sensitive areas (particularly the pretibial area), its impact on quality of life and the therapeutic response to risankizumab.

Methods: This multicentre prospective observational study recruited patients with moderate-to-severe psoriasis with pretibial area involvement. All patients underwent treatment with risankizumab (150 mg every 3 weeks), and efficacy was assessed after 24 weeks.

Results: The study included 128 patients with a mean age of 51 years, suffering from moderate-to-severe psoriasis with involvement of the pretibial area with median total Psoriasis Area Severity Index score of 17.05 and Dermatology Life Quality Index of 16.27. The group was further divided into two sub-groups: the 'mother patch' group, in whom the very first psoriatic plaque appeared in the pretibial region (45 patients), and the 'non-mother patch' group, in whom the psoriatic lesion in the pretibial region was present but not as the first manifestation (83 patients). In order to better assess the involvement of psoriasis in the pretibial area, the pretibial plaque lesion severity index was also calculated at baseline in all patients: extent 2.75, erythema 2.64, infiltration 2.45 and desquamation 2.38. All participants in this study showed a good therapeutic response, with a reduction in all scores.

Conclusions: The pretibial area is becoming an object of therapeutic interest due to some resistance to clearance and the consequent impairment of patient quality of life. This study showed that risankizumab can give favourable therapeutic results not only in patients with moderate-to-severe psoriasis with involvement of the difficult-to-treat areas but particularly in patients with recalcitrant plaques in the pretibial area.

Keywords: psoriasis, difficult-to-treat-areas, IL-23 inhibitors, pretibial.

Citation

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Introduction

Psoriasis is a chronic inflammatory skin disease with multifactorial aetiology, whose chronic relapsing course requires a constant adjustment of treatment and personalization to address changes in each patient over the course of a lifetime.[1]

The severity of the disease is related not only to the extent of erythematous scaling patches on the skin surface but also to the involvement of specific body areas, which might be resistant to treatment and/or have a greater impact on patient quality of life (QoL).[2] Areas recognized as 'difficult-to-treat' currently include the scalp, face, nails, genitals, hands and feet.[3] Recently, the anterior lower leg (pretibial area) has attracted particular interest due to its poor response to treatment and stigma as an exposed visible region of the body.[4] Indeed, scores used to assess clinical severity, such as Psoriasis Area Severity Index (PASI), have shown less significant improvements after therapy in this area than in others.[4]

To further evaluate such preliminary experiences, a prospective multicentre study was designed to enrol all consecutive patients with psoriasis with pretibial area involvement who were candidates for systemic therapy. The study aimed to evaluate the efficacy of risankizumab in improving psoriatic lesions especially at this site, with the hypothesis that it could provide the same success in the pretibial area.

Patients and methods

Design and protocol

Patients with moderate-to-severe psoriasis receiving risankizumab therapy were enrolled in this observational, prospective, multicentre study. Dermatological clinics from seven university hospitals participated in the study. Ethical approval was obtained from the local competent Committee of the designated Coordinator Centre Polo Pontino Sapienza University (Protocol N. 0243678/2021 of 15/12/2021). This study was conducted in accordance with the principles of the Declaration of Helsinki. All patients in this manuscript gave written informed consent to the publication of their case details.

The primary objective of the study was to evaluate the efficacy of risankizumab. Therefore, the total PASI, Dermatology Life Quality Index (DLQI) and visual analogue scale (VAS) pruritus data were collected at the beginning (T0) and after 24 weeks (T24) of therapy. In particular, the reduction from baseline of the PASI value was assessed with responses of 90% and 100% (PASI90 and PASI100).

The second end-point was the assessment of therapeutic response in the specific body area, namely pretibial region. Hence, an additional PASI assessment was performed only for the pretibial area (lesional PASI), which included the main four PASI parameters (extent, erythema, infiltration and desquamation), with an associated score ranging from 0 to 4.

The drug was provided at the standard dosage approved in Italy for current clinical practice: risankizumab 150 mg sub-cutaneously week 0–4 and then every 12 weeks.

Study population

Inclusion criteria were age over 18 years, patients suffering from moderate-to-severe psoriasis (PASI >10) with involvement of the pretibial area; no therapeutic response to previous topical therapy, phototherapy or traditional systemic therapies; and being risankizumab naive (may have received other biological therapies that did not prove effective). However, all patients underwent a wash-out period of 2 weeks.

The presence of psoriasis in the pretibial area was the main inclusion criterion for the study. Patients were divided into two groups: the mother patch group, in whom the first manifestation of psoriasis was in the pretibial area, and the non-mother patch group, who had pretibial psoriatic plaque but this was not a lesion upon initial presentation. The data were collected anamnestically.

Exclusion criteria were age under 18 years; no involvement of the pretibial area; satisfactory therapeutic response to previous topical therapy, phototherapy or traditional systemic therapy; and former treatment with risankizumab.

Statistical analysis

The effectiveness of the biological therapy was assessed as the mean percentage of improvement on the PASI, DLQI and VAS pruritus scale; a parametric method based on the *t*-student test and the *p* value calculation was used to determine the statistical significance of the results obtained.

Results

A total of 128 patients (45 women and 83 men) with an average age of 51 years, with moderate-to-severe psoriasis presenting with involvement of the pretibial area were enrolled (Table 1). The patients had a heterogeneous history of psoriatic disease, ranging from a recent onset (3–4 years) to much longer periods (~50 years). The average history of psoriatic disease was therefore 19.73 years. The median duration of the disease was 18 years.

Table 1. Demographic characteristics of patients at baseline.

Sex	Men	83
	Women	45
	Total	128
Period of onset (average)	19.73 years	Min 3 years – Max 50 years
Disease duration period (median)	18 years	
Averaged scores at t=0	PASI	17.05
	DLQI	16.27
	VAS pruritus	6.08
Mother patch	Yes	45 (36%)
	No	83 (64%)
Lesional PASI T=0 (pretibial lesions)	Extension	2.75
	Erythema	2.64
	Infiltration	2.45
	Desquamation	2.45

The mean values of the scores evaluated at T0 were total PASI 17.05, DLQI 16.27 and VAS pruritus 6.08.

Amongst the patients enrolled in the study, 45 (36%) reported the first site of psoriasis onset being in the pretibial area and were included in the mother patch group, whilst the other 83 patients had psoriasis distributed in other regions of the body with subsequent pretibial localization and included in the no mother patch group. The four items that make up the PASI (extent, erythema, infiltration and desquamation) were evaluated for the pretibial area to try to best highlight the therapeutic response of risankizumab in this difficult-to-treat area. Thus, mean PASI values at T0 referred to pretibial plaques (lesional PASI) in the overall examined population were extension 2.75, erythema 2.64, infiltration 2.45 and desquamation 2.38.

As regards other difficult-to-treat areas, 45 (36%) patients had nail involvement, 42 (33.6%) had genital involvement, 46 (36.8%) had palm/plantar psoriasis, 70 (56%) had psoriasis of the scalp and 27 (21.6%) had face involvement. PASI values related to the evaluation of the complete clinical picture and those referred to the assessment of the pretibial plaque only were reported. For clarity, they are referred to as 'total PASI' and 'lesional PASI', respectively.

All patients enrolled in the study showed good therapeutic response. After 24 weeks of therapy with risankizumab (T24), the mean values of the scores were remarkably reduced: total PASI 1.08, DLQI 1.1 and VAS pruritus 0.49.

The average improvement in total PASI at T24 was of 93.14% compared with the average value at T0. Particularly, at 24 weeks of observation, 85 out of 128 (66.4%) patients achieved PASI90 and, of these, 71 (83.5%) achieved PASI100. Finally, at the end of the observational period (T24), the mean lesional PASI of the pretibial area was also significantly reduced: extension 0.28, erythema 0.27, infiltration 0.08 and desquamation 0.25.

To further assess drug effectiveness on the pretibial skin by mean of percentage improvement in PASI value at T24, patients in the mother patch group (group A) and patients in the non-mother patch group (group B) were assessed separately. The average PASI improvement percentage in group A was 93.56% (SD 8.55) and 95.88% in group B (SD 6.38). The values were plotted on a box plot to highlight and possibly cancel outlier values of the dependent variable (Figure 1). The difference between the values examined in the two groups was statistically significant (p=0.043).

The same procedure was applied to assess the regional PASI improvement in the two independent groups of patients: group C (mother patch) and group D (non-mother patch). The lesional PASI response at T24 in group C was 96.36 (SD 5.62), whilst in group D it was 98.14 (SD 4.92). Values were plotted on a box plot to highlight and possibly cancel out outlier values of the dependent variable (Figure 2). The difference between the values examined in the two groups was statistically significant (p=0.033).

Finally, another variable examined was disease duration and its effect on therapeutic response. Therefore, the sample was divided into two groups with a cut-off of 5 years: patients with a history of psoriasis of less than 5 years (group E) and patients with a disease duration of more than 5 years (group F). The mean percentage improvement in PASI at T24 was 89.94% (SD 10.98) and 93.59% (SD 9.81) in groups E and F, respectively (Figure 3). In this case, the difference between the two groups was statistically significant (p=0.03).

Patient QoL was evaluated by considering the number of patients achieving lowest DLQI at week 24. Generally, 85 (68%) patients achieved a DLQI in the range of 0–1 with risankizumab treatment. The sample was then divided into two groups to estimate the mean percentage improvement in DLQI at T24 between the mother patch (group G) and non-mother patch (group H) groups. The mean improvement in DLQI was 98.66%

Figure 1. Total PASI improvement in patients with mother patch (group A) and non-mother patch (group B) psoriasis.

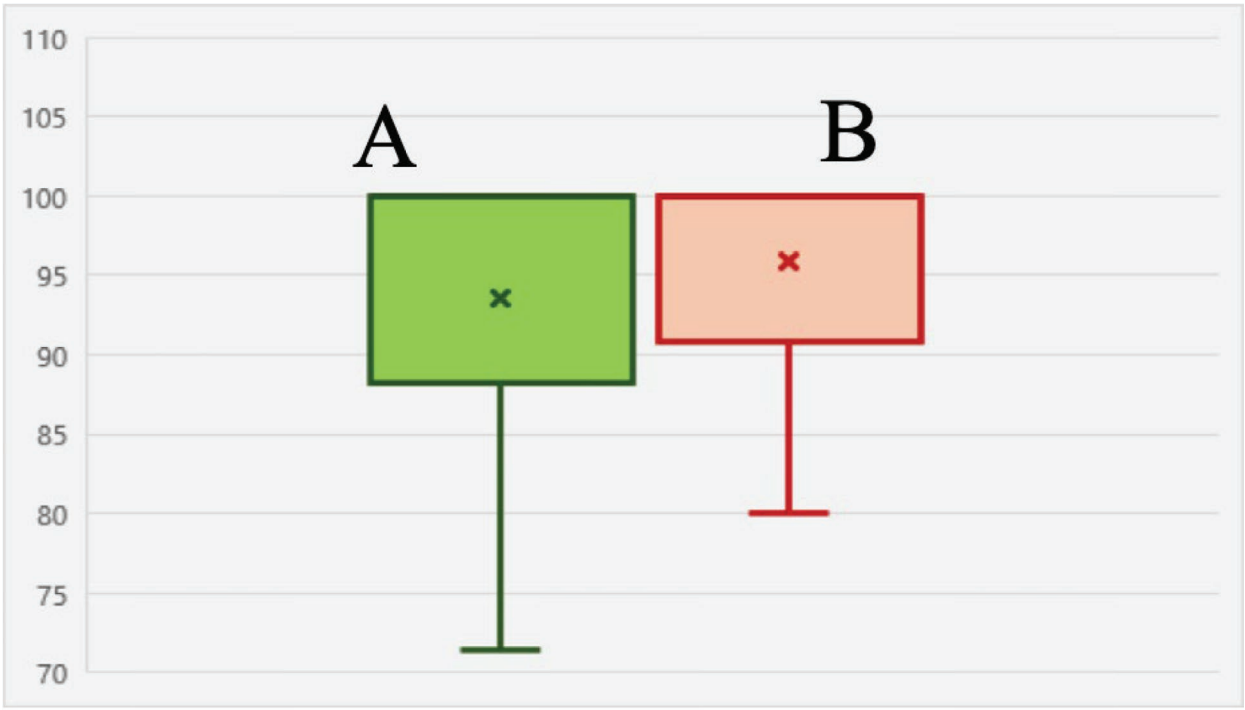


Figure 2. Lesional PASI improvement in patients with mother patch (group C) and non-mother patch (group D) psoriasis.

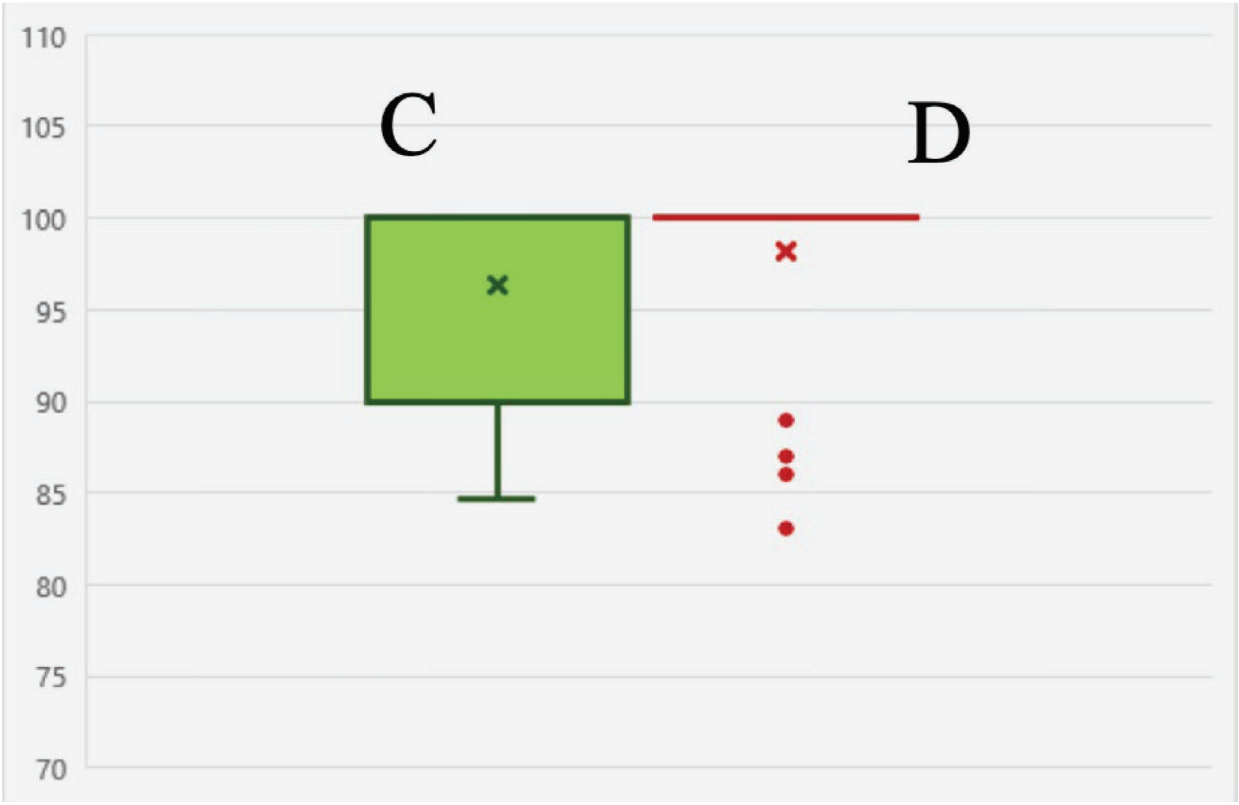
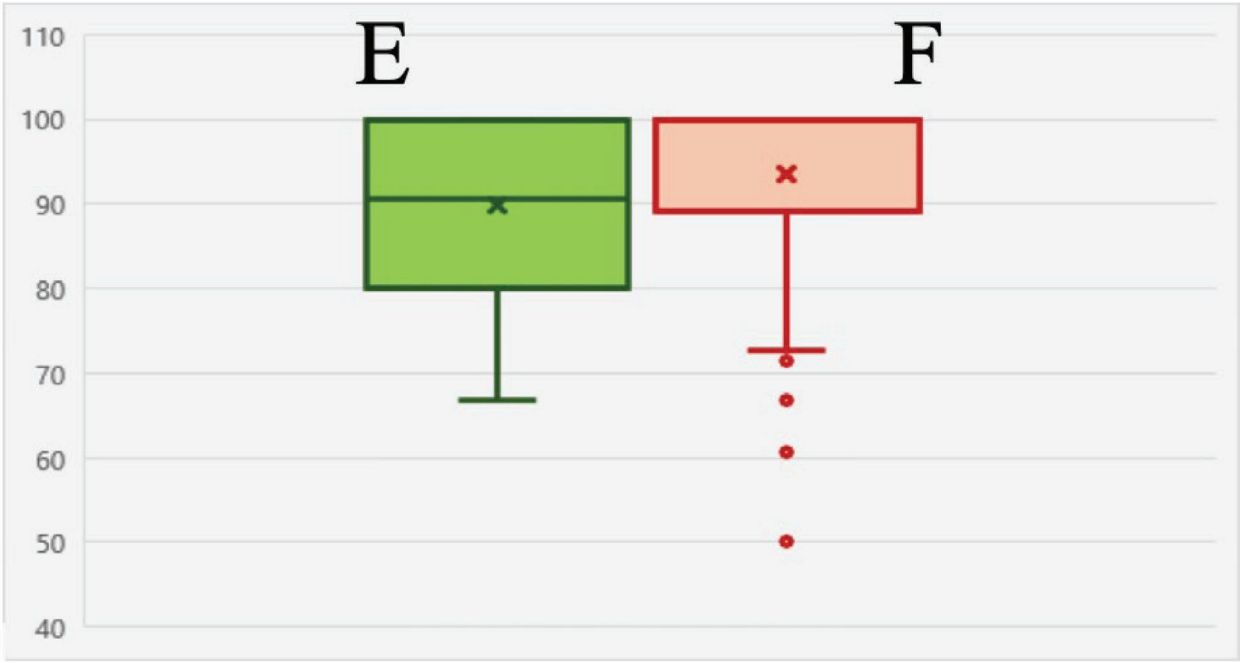


Figure 3. Duration of psoriasis: less than 15 years (group E) and over 15 years (group F).



(SD 3.24) and 95.86% (SD 7.57) in groups G and H, respectively (Figure 4), and the difference between the two groups was statistically significant (p=0.009).

Discussion

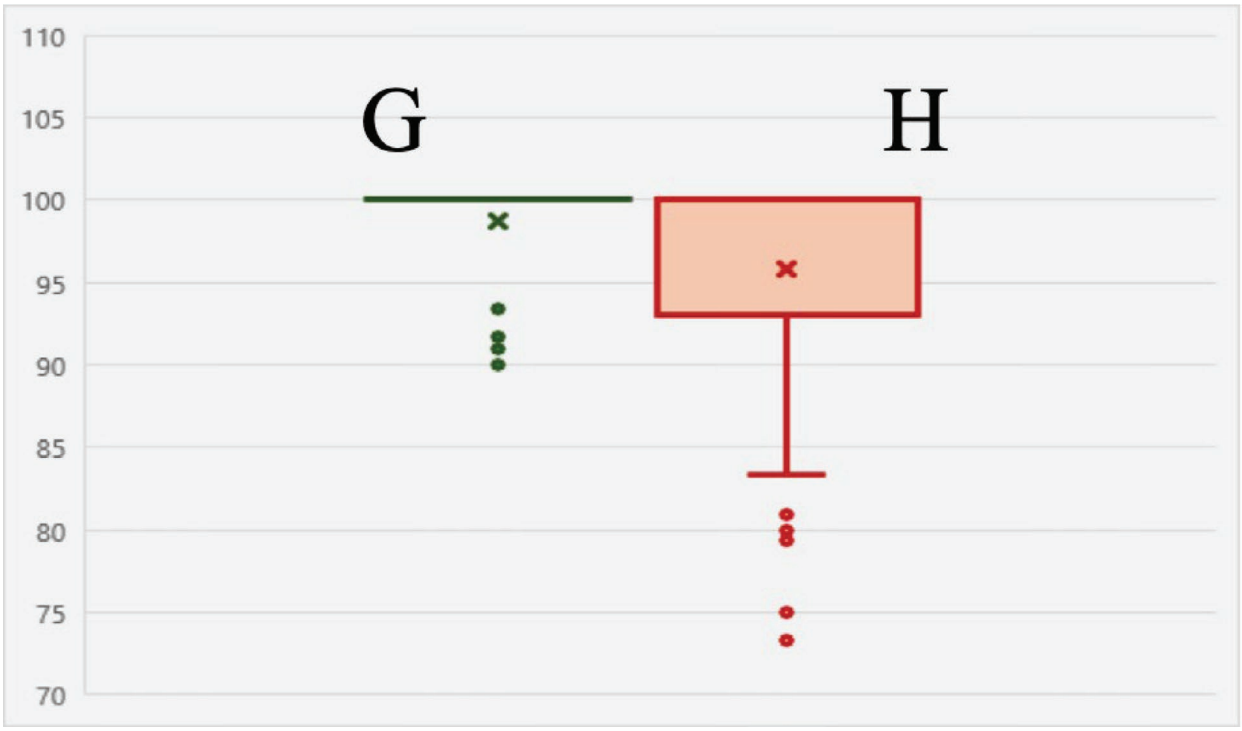
In addition to the significant improvements in the treatment of psoriasis due to the introduction of biologic drugs in terms of therapeutic efficacy, some anatomical sites still show poor and unsatisfactory results. As a result, the medical community is making an additional effort to develop strategies to better cope with conditions that differ from patient to patient and even in the same patients across the lifespan.

For example, amongst the areas currently considered difficult to treat, the lower legs are not included, although actual clinical practice suggests a sub-optimal response of these areas to local and systemic treatment. To argue whether this condition represents an effective unmet need in psoriasis treatment landscape, 128 patients with moderate-to-severe psoriasis presenting with psoriatic plaques in the pretibial area were prospectively studied, and their response to treatment was analysed. The drug risankizumab was chosen because it has demonstrated a long-lasting efficacy in the treatment of psoriasis, regardless of the involvement of other areas defined as difficult to treat.[5] Moreover, anti-IL-23 drugs are showing very promising results in the control and eventual reduction of memory T cells in psoriasis plaques, which are considered the main source of the auto-inflammatory loop in chronic lesions.[6]

In general, the lower extremities are considered a clinically difficult site as response to therapy is often minimal or completely absent, particularly in patients with additional stasis due to chronic venous insufficiency.[7,8] Furthermore, a differential diagnosis is sometimes necessary, through incisional skin biopsies to discriminate psoriasis from other possible conditions such as chronic eczema or stasis dermatitis.[7]

A sub-analysis of the randomized, controlled trial of adalimumab conducted by Armstrong et al. put in evidence an improvement in lower limb PASI of 73.9% at 16 weeks compared with values recorded in other difficult-to-treat sites such as the face and scalp, where PASI improved by more than 80%.[9] In an Italian retrospective study, which analysed data from 240 patients, 41 patients showed an unsatisfactory response after ~2 years of biological therapy, and 53.6% of them had lower extremity involvement, preceded in frequency only by nail involvement.[10] A further study, which compared the effectiveness of biologic therapy in different body areas of psoriatic disease, showed that the head, neck and lower limbs were less likely to have faster PASI responses than the trunk and upper extremities.[11] In addition, in a comparative study of the real-life efficacy of different classes of biologics, Megna et al. found that lower limbs, along with the scalp and palmoplantar area showed less PASI improvement at

Figure 4. Distribution of DLQI improvement in patients with mother patch (group G) and without mother patch (group H) psoriasis.



week 12 in all classes, suggesting that the lower limbs are indeed a difficult-to-treat body region.[12]

In light of this recent scientific interest, the present study was designed to collect data from patients from different Italian regions and prospectively evaluate whether the pretibial area represents a treatment-hostile zone, choosing amongst the current therapeutic options of the Italian standard of care. The decision to use risankizumab, a monoclonal antibody against IL-23, was driven by its very easy schedule of treatment and optimal safety profile in patients with different comorbidities.[5]

From the statistical analyses performed, after 24 weeks of risankizumab treatment, in the 128 patients, the mean total PASI was reduced by 93.14%, the mean DLQI by 92.35% and the VAS pruritus reduced by 91.84% compared with T0 values. These results are in line with the overall expectation of risankizumab efficacy and long-term disease control.[5] To assess the specific impact on lower leg psoriasis, lesional PASI was considered and there was a 90% reduction in plaque extension, erythema and desquamation, whilst infiltration decreased by 96% from baseline measurements. The main findings at T24 were statistically significant, with overall improvement in PASI, DLQI and VAS pruritus. Furthermore, patients who did not report the pretibial area as the primary site of onset (non-mother patch) showed more significant improvement (groups A and C) compared with mother-patch patients, who had the first occurrence of psoriasis in the anterior lower leg (groups B and D). Conversely, the impact on patient QoL showed a higher average percentage improvement in DLQI after 24 weeks in patients with the mother patch (group G), confirming how this involvement of this anatomic site could impact patient QoL. Furthermore, evaluating the impact of disease duration, our data showed that the group of patients with a shorter disease history (group E) had a better improvement in clinical response with risankizumab than the group with a longer duration (group F), though not the difference was not statistically significant.

All this information further supports the idea that the pretibial area represents a specific site of chronic activation in psoriasis, a disease niche difficult to treat, compared with other sites. Such recalcitrant areas could be crucial in the overarching maintenance of inflammation in patients with psoriasis.[6] Chronic plaques show a high percentage of $CD8^+$ expressing resident memory T (T_{RM}) cell markers.[12] Thus, selective inhibition of T_{RM} cells by anti-IL-23 drugs would lead to a significant reduction in inflammation.[13] Notably, T cells infiltrate the epidermis, transform into T_{RM} cells and establish a memory of the disease, maintaining their inflammatory capacity for up to 6 years after treatment initiation, thus being able to reactivate the disease even after years of therapeutic

success.[12,13] Therefore, strategies to inhibit long-term T_{RM} cells as well as very early interventions, before 'mother-patch' grounding, are warranted. A recent report suggests changing the injection site from the abdomen to the lower legs to improve such recalcitrant psoriatic lesions.[14]

Conclusion

The lower legs can be considered a difficult-to-treat area, deserving peculiar attention, given their certain resistance even to biological therapy.[2,11,14–16] However, only a few scientific papers on this topic exist to date. In light of these results, it could be supposed that risankizumab works when these anatomical districts are involved, probably due to its unique mechanism of action on long-term T_{RM} cell control.

The results obtained encourage us to continue clinical monitoring of enrolled patients until at least 104 weeks. Additionally, early treatment of patients with moderate-to-severe psoriasis and skin areas refractory to conventional therapies could be a therapeutic strategy to be considered, especially in patients with a long history of the disease.

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Data availability statement: The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials upon request.

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References

1. Griffiths CEM, Armstrong AW, Gudjonsson JE, Barker JNWN. Psoriasis. *Lancet*. 2021;397(10281):1301–1315. https://doi.org/10.1016/S0140-6736(20)32549-6
2. Sojević Timotijević Z, Majcan P, Trajković G, et al. The impact of changes in psoriasis area and severity index by body region on quality of life in patients with psoriasis. *Acta Dermatovenerol Croat*. 2017;25(3):215–222.
3. Handa S. Newer trends in the management of psoriasis at difficult to treat locations: scalp, palmoplantar disease and nails. *Indian J Dermatol Venereol Leprol*. 2010;76(6):634–644. https://doi.org/10.4103/0378-6323.72455
4. Hjuler KF, Iversen L, Rasmussen MK, Kofoed K, Skov L, Zachariae C. Localization of treatment-resistant areas in patients with psoriasis on biologics. *Br J Dermatol*. 2019;181(2):332–337. https://doi.org/10.1111/bjd.17689
5. Mastorino L, Susca S, Megna M, et al. Risankizumab shows high efficacy and maintenance in improvement of response until week 52. *Dermatol Ther*. 2022;35(5):e15378. https://doi.org/10.1111/dth.15378
6. Fülle M, Metze D, Böer-Auer A, Osada N, Braun SA. Psoriasis on the leg: site-specific histopathological and immuno-histochemical features and diagnostic difficulties. *Acta Derm Venereol*. 2021;101(5):adv00453. https://doi.org/10.2340/00015555-3817
7. Armstrong AW, Villanueva Quintero DG, Echeverría CM, Gu Y, Karunaratne M, Reyes Servín O. Body region involvement and quality of life in psoriasis: analysis of a randomized controlled trial of adalimumab. *Am J Clin Dermatol*. 2016;17(6):691–699. https://doi.org/10.1007/s40257-016-0229-x
8. Campanati A, Moroncini G, Ganzetti G, et al. Adalimumab modulates angiogenesis in psoriatic skin. *Eur J Inflamm*. 2013;11(2):489–498. https://doi.org/10.1177/1721727X1301100218
9. Bardazzi F, Viviani F, Filippi F, Carpanese MA, Piraccini BM, Abbenante D. The legs: an underestimated difficult-to-treat area of psoriasis. *Dermatol Ther*. 2022;35(6):e15485. https://doi.org/10.1111/dth.15485
10. Yeh CP, Huang YW, Tsai TF. Comparison of the relative efficacy of different biologics in different body areas in patients with moderate to severe psoriasis receiving biologics and tofacitinib in phase 3 randomized controlled trials: a 15-year single-center experience. *Exp Rev Clin Pharmacol*. 2022;15(7):887–895. https://doi.org/10.1080/17512433.2022.2103538
11. Megna M, Cirillo T, Balato A, Balato N, Gallo L. Real-life effectiveness of biological drugs on psoriatic difficult-to-treat body regions: scalp, palmoplantar area and lower limbs. *J Eur Acad Dermatol Venereol*. 2019;33(1):e22–e23. https://doi.org/10.1111/jdv.15119
12. Cheuk S, Wikén M, Blomqvist L, et al. Epidermal Th22 and Tc17 cells form a localized disease memory in clinically healed psoriasis. *J Immunol*. 2014;192(7):3111–3120. https://doi.org/10.4049/jimmunol.1302313
13. Matos TR, O'Malley JT, Lowry EL, et al. Clinically resolved psoriatic lesions contain psoriasis-specific IL-17-producing αβ T cell clones. *J Clin Invest*. 2017;127(11):4031–4041. https://doi.org/10.1172/JCI93396
14. Katsuo K, Honda T, Kabashima K. Improvement of recalcitrant psoriatic lesions on the lower legs by changing the injection site of secukinumab from the abdomen to lower legs. *J Dermatol*. 2020;47(2):e54–e55. https://doi.org/10.1111/1346-8138.15159
15. Jeon C, Nakamura M. "Two-step phototherapy" for treatment-resistant psoriasis on the lower extremities. *J Am Acad Dermatol*. 2017;77(4):e101. https://doi.org/10.1016/j.jaad.2017.05.012
16. Bhatia ND, Vlahovic TC, Green LG, et al. Halobetasol 0.01% lotion in the treatment of moderate-to-severe plaque psoriasis of the lower extremities. *J Drugs Dermatol*. 2019;18(10):1029–1036