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CASE SERIES

Successful Treatment of Pityriasis Rubra Pilaris with Risankizumab in Children

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ABSTRACT

Pityriasis rubra pilaris (PRP) is a rare inflammatory skin disease that affects men and women of all ages, including children. PRP is characterized by follicular and palmoplantar hyperkeratosis and salmon-colored scaling plaques. The exact pathogenesis of PRP is still unknown; most PRP cases are acquired, but some cases may show a familial occurrence, often associated with a mutation in the CARD14 gene. Due to the rarity of PRP, treatment recommendations are based mainly on case reports, small case series and expert opinions and still represent a major therapeutic challenge, especially in children. A growing number of reports on treatment with biologicals, particularly anti-TNFα, has been published. However, an involvement of the IL-23/Th17 axis in both psoriasis and PRP pathogenesis may suggest that this pathway may be a potential therapeutic target. Here, we present three pediatric patients with PRP successfully treated with risankizumab. All patients exhibited a severe course of PRP and lack of response to conventional therapy, including acitretin, cyclosporine and phototherapy. A single dose of 75 mg risankizumab resulted in almost complete clearance of skin lesions in case 1 and 2 at week 4. In patient 3, clear skin was achieved after the second administration of risankizumab (150 mg). All patients continue the treatment with risankizumab, and no adverse effects have been reported up to the present time. Our study demonstrates that risankizumab, an IL-23 blocker, shows good efficacy and safety among pediatric patients with PRP.

Keywords: Pityriasis rubra piliaris; PRP; Risankizumab; IL-23 blocker

Antonina Osin was under 18 years of age at the time of publication and participated in this study with permissions from their parent.

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Key Summary Points

Why carry out this study?

Pityriasis rubra pilaris (PRP) is a rare inflammatory skin disease that represents a major therapeutic challenge, especially in children and adolescents. Due to rarity of PRP, treatment recommendations are based mainly on case reports, small case series and expert opinions, and no treatment option is approved in this indication

There is a great need for new and safe therapeutic options in PRP, including the treatment of the pediatric population

The aim of our study was to evaluate the efficacy and safety of risankizumab in the treatment of PRP in three pediatric patients

What was learned from the study?

Risankizumab seems to be a safe and effective treatment of PRP in children

Rapid improvement of the skin condition can be observed after even the first dose of risankizumab

Placebo-controlled, double-blind, multicenter studies should be performed to prove the effectiveness and safety we observed

INTRODUCTION

Pityriasis rubra pilaris (PRP) is a rare inflammatory skin disease that affects men and women of all ages and races. It has a bimodal age distribution with two common peaks in first and fifth decades of life [1]. The classical clinical manifestation of PRP is characterized by follicular and palmoplantar hyperkeratosis and salmon-colored scaling plaques. "Nappes claires," which are islands of non-affected skin, are commonly observed in this disorder [2]. Initially, PRP was classified info five types, based on the clinical features, age of onset and prognosis [3]. Subsequently, an association of PRP with HIV infection was found, and the sixth PRP subtype has been distinguished [4]. PRP types III–V affect children and account for about 40% of all PRP cases, among which circumscribed juvenile type IV PRP is most commonly seen [5].

The exact pathogenesis of PRP is still unknown. Most PRP cases are acquired, but there have also been reports of a familial PRP occurrence, which is often associated with a mutation in the CARD14 gene. Those cases demonstrated autosomal-dominant inheritance with early age of onset, incomplete penetrance and variable expression. Familial PRP mostly belongs to the type V and account for about 5% of all PRP cases [6]. Due to the rarity of PRP, treatment recommendations are based mainly on case reports, small case series and expert opinions and still represent a major therapeutic challenge, especially in children. Retinoids, methotrexate, cyclosporine and phototherapy are most widely used in adults and juvenile [7]. Recently, a growing number of reports on PRP treatment with biologicals, particularly anti-TNFα, has been published [8]. However, a pathogenic role of the IL-23/Th17 axis was implicated in both psoriasis and PRP, suggesting that this pathway may be a potential therapeutic target for anti-PRP drugs [9]. Here, we present three pediatric patients with PRP successfully treated with risankizumab, an IL-23p19 blocker. The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from the patients and their parents for participation in the study and publication of the article, including publication of clinical photographs.

CASE REPORTS

Case 1

A 7-year-old female with a 4-year history of PRP confirmed by histopathological examination was admitted to the Department of

Dermatology in Rzeszów because of exacerbation of her skin condition. Genetic testing identified the p.Leu124Pro mutation in one allele of the CARD14 gene. Her family history of psoriasis or PRP was negative. Based on the entire clinical presentation (Fig. 1), type V PRP was diagnosed. Prior treatments included cyclosporine (5 mg/kg/day for several months) and acitretin (0.7 mg/kg/day for 6 months) but did not show a noticeable therapeutic effect. Due to lack of efficacy of previous therapies, treatment with adalimumab (ADA) was initiated. Primarily, ADA was used in combination with acitretin. In the 7th week of combined therapy, retinoid treatment was discontinued because of an elevated serum cholesterol level (240 mg/dl). Treatment with ADA was continued at monthly subcutaneous doses of 40 mg, with primarily good response (disappearance of about 90% of all skin lesions), but subsequently, a gradual loss of efficacy was observed and anti-TNFα therapy was discontinued at week 106.

About 8 months after the last dose of ADA, the patient developed well-demarcated, scaly erythematous plaques on the cheeks (Fig. 1A) and upper and lower extremities (Fig. 1B). These skin lesions significantly affected the quality of life and daily functioning of the child. Total BSA was approximately 12%. Laboratory tests performed during hospitalization did not show any significant abnormalities. Due to severity of PRP in the past, rapid deterioration of the skin condition and the impact of the disease on patient's quality of life, therapy with risankizumab was started. The drug was administered subcutaneously at a dose of 75 mg according to a standard schedule (weeks 0, 4 and 12-weekly thereafter). Significant improvement was observed after the first dose of risankizumab. At week 4 the patient exhibited only post inflammatory hyper- and hypopigmentation on the face (Fig. 1C) and extremities and mild palmar lichenification (Fig. 1D). BSA rating was 0%. At week 40, a sustained therapeutic effect was observed, and no adverse effects have been

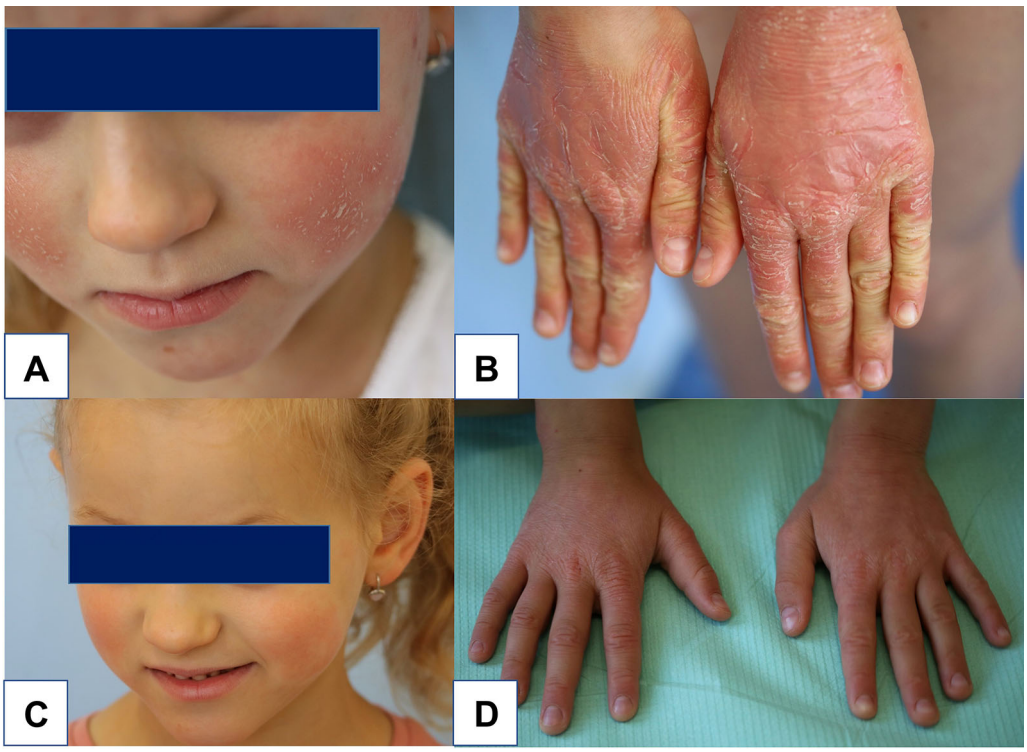

Fig. 1 Well-demarcated, scaly erythematous plaques on cheeks (**A**) and on the dorsal surfaces of the hands (**B**). The skin lesions had almost completely disappeared after 4 weeks of risankizumab therapy (**C**, **D**)

reported. Currently, the patient remains in complete remission after being weeks on the treatment.

Case 2

A 5-year-old girl with severe PRP was admitted to intensify systemic treatment. The diagnosis of PRP was confirmed by histopathological examination in the 4th year of the patient's life, and the genetic testing identified the p.Lys118Pro mutation in the one allele of the CARD14 gene. The patient's family history was positive; her grandfather and her father's cousin both suffered from psoriasis. As in the first case, atypical juvenile type V PRP was identified. Systemic treatment modalities attempted at that point included acitretin (0.7 mg/kg/day for 16 months) with initially good response and secondary loss of effectiveness and UVB 311 nm phototherapy (7 exposures) without any improvement. On admission, the patient exhibited widespread scaly, erythematous plaques with islands of non-affected skin on the upper and lower extremities and single well-demarcated plaques on the trunk. Erythematous lesions on the chin, cheeks and ears were also observed; BSA was 55% (Fig. 2A). Laboratory investigations showed no significant abnormalities. Due to the severity of PRP and lack of effectiveness of the applied at that point therapies, risankizumab was started knowing the good treatment effect of the previous patient. Risankizumab was administered subcutaneously at a dose of 75 mg according to a standard schedule (weeks 0 and 4 and 12-weekly thereafter). Exactly as in the first case, a great improvement was observed after the first dose of risankizumab. At week 4, a complete clearance of skin lesions was observed (BSA = 0%) (Fig. 2B). At week 28, a durable therapeutic effect was noticed, and no adverse effects have been reported so far.

Case 3

A 17-year-old female with severe form of PRP was re-admitted to our department because of lack of effectiveness of the hitherto used therapies to modify systemic treatment (Fig. 3). The patient's history of widespread skin lesions dates back to the age of 4 when plaque psoriasis was diagnosed. The diagnosis of psoriasis was then revised based on the clinical features and histopathological findings of the patient at the age of 16, and PRP was finally diagnosed (Fig. 4). No mutations of CARD14 gene were revealed, although her mother and grandmother presented skin lesions characteristic for plaque psoriasis. In the past the patient was treated with phototherapy UVB 311 nm (for 6 months), methotrexate (15 mg/week for 3 years), acitretin (for 3 months, at the maximum dose of 35 mg/day), etanercept followed by etanercept in combination with methotrexate (for 3 months) and cyclosporine A (5 mg/kg/day for 3 months), without any clinical improvement or even with deterioration of the skin condition.

Upon admission, the patient demonstrated diffuse, scaly salmon-erythematous lesions on the trunk and extremities (Fig. 3A). Lesions of similar morphology were also present on the scalp, neck and forehead (BSA = 75%) (Fig. 3B). Laboratory tests did not show any significant abnormalities. As in previous cases, risankizumab therapy was started. The drug was administered subcutaneously at a dose of 150 mg according to a standard regimen (weeks 0 and 4 and 12-weekly thereafter). At week 8, the patient exhibited almost clear skin (Fig. 3C and D). At week 16, only subtle erythematosus papules and plaques on the upper limbs were observed (BSA = 4%), and slightly higher disease severity also persisted at week 28 (BSA = 5.5%). To date, no adverse effects have been reported by the patient.

Patient's Experience (Case 3)

Psoriasis has been in my family for generations. Both my mother and my grandmother and aunt have it. At the age of 4, lesions began to appear on my skin, which were also diagnosed as psoriasis by doctors. I do not know what treatment was taken, but my mother decided to consult a private dermatologist, thus forgoing state treatment for many years. Until I was about 12 years old, I was treated only with ointments—

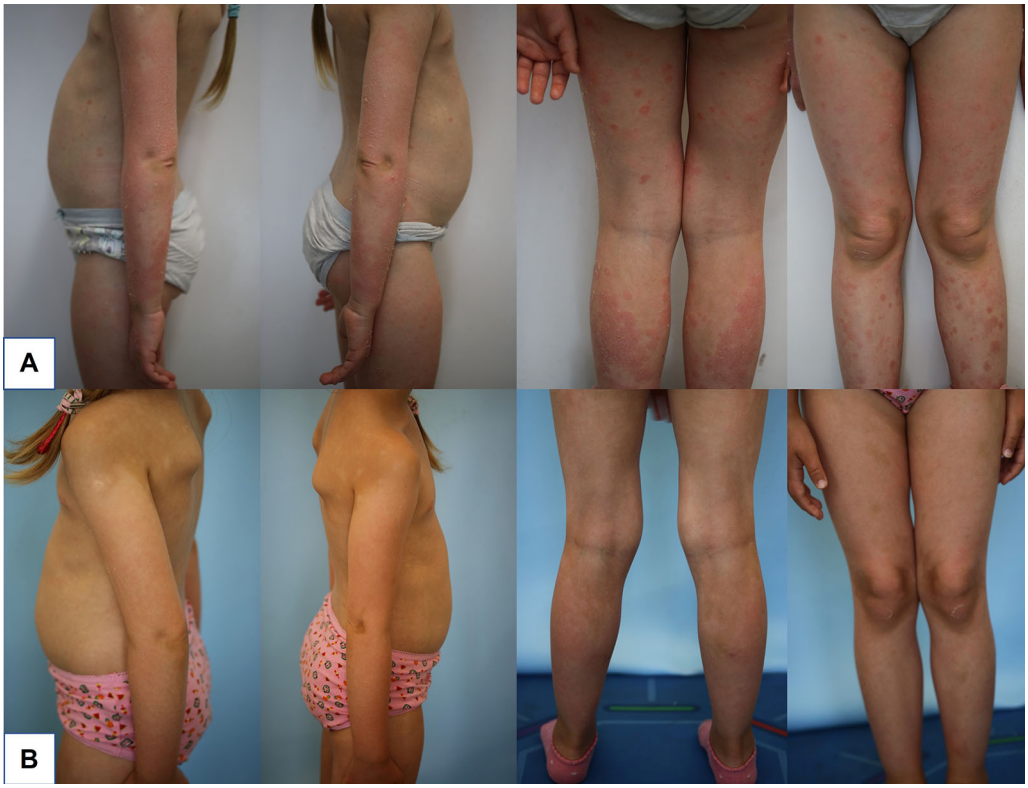

Fig. 2 Widespread scaly, erythematous plaques with islands of non-affected skin on upper and lower extremities and single well-demarcated plaques on the trunk (**A**, **B**). The skin lesions had almost completely disappeared after 4 weeks of risankizumab therapy (**C**, **D**)

from simple petroleum jelly to tar ointments to steroid ointments. Intensive sunbathing of the lesions was also recommended, which during the vacations actually gave improvement for a few weeks, but after about 2–3 months the skin condition was even worse—new lesions appeared, and the old ones became redder and more flaky. For 8 years of treatment there was practically no improvement, and in fact it got worse and worse—at the very beginning the lesions appeared only on the body and head, then occupying the face, hands, nails and feet. After moving to another city, the new doctor decided to undertake a different treatment and, in addition to ointments, introduced methotrexate in a dose of 15 mg per day. Initially, a minor improvement was seen—the lesions faded and shrank a bit, but this did not last long, and after a few months to a year, there was no trace of improvement. In the meantime, phototherapy was used, which also had no effect. During this time, the disease began to cause more and more discomfort in my life—the flaky skin left behind a kind of "dust" that not only covered my clothes, but was found in huge amounts in the house, resulting in the need for thorough vacuuming for the family. Heavy ointments ruined clothes incredibly, and the fear of new lesions appearing prevented me from at least wearing makeup. In addition, the disease caused me a sense of shame, caused my distancing from my peers, who did not understand its nature more than once and feared contagion.

Shortly before my 16th birthday, the doctor who was treating me at the time, unable to offer us any new treatments, recommended that my mother contact Prof. Adam Reich in Rzeszow. I was referred for hospitalization at the Dermatology Clinic in Rzeszow, where I first stayed, if I remember correctly, for a week. During this time I was given various tests, continued to

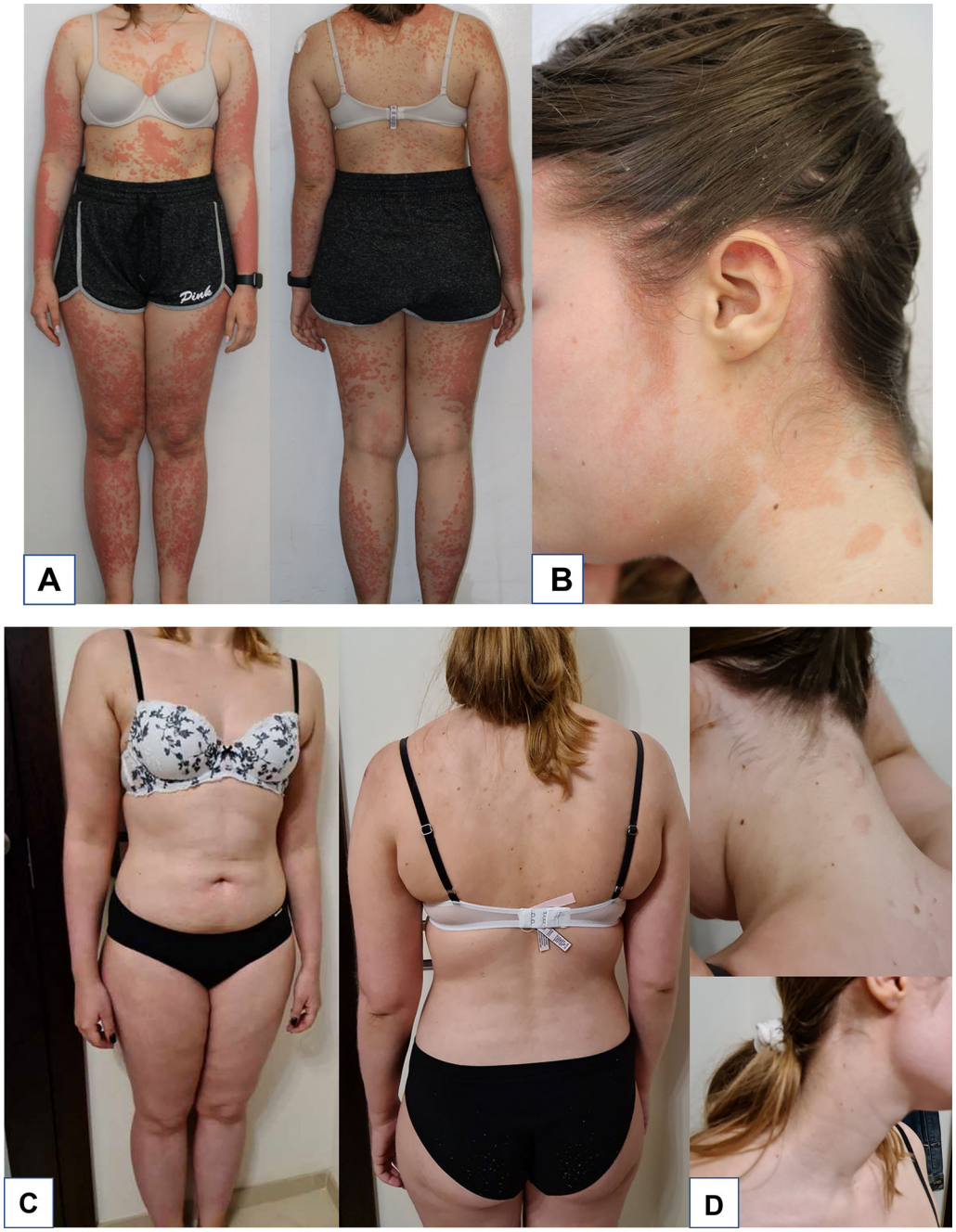

Fig. 3 Diffuse, scaly salmon-erythematous lesions on the trunk and extremities (**A**). Lesions of similar morphology were also present on the scalp, neck and forehead (**B**). At week 8, only subtle erythematosus papules and plaques on upper limbs were observed (**C**, **D**)

receive ointments and received another referral. Between October 2021 and June 2022, further medications were applied, including biological treatment, this one to match something that would help. However, as with the ointments used before, they had a temporary improvement effect, and the body would "get used" to the drugs and the changes would reappear.

Doctors at the clinic had doubts about the correctness of the diagnosis, so in the meantime

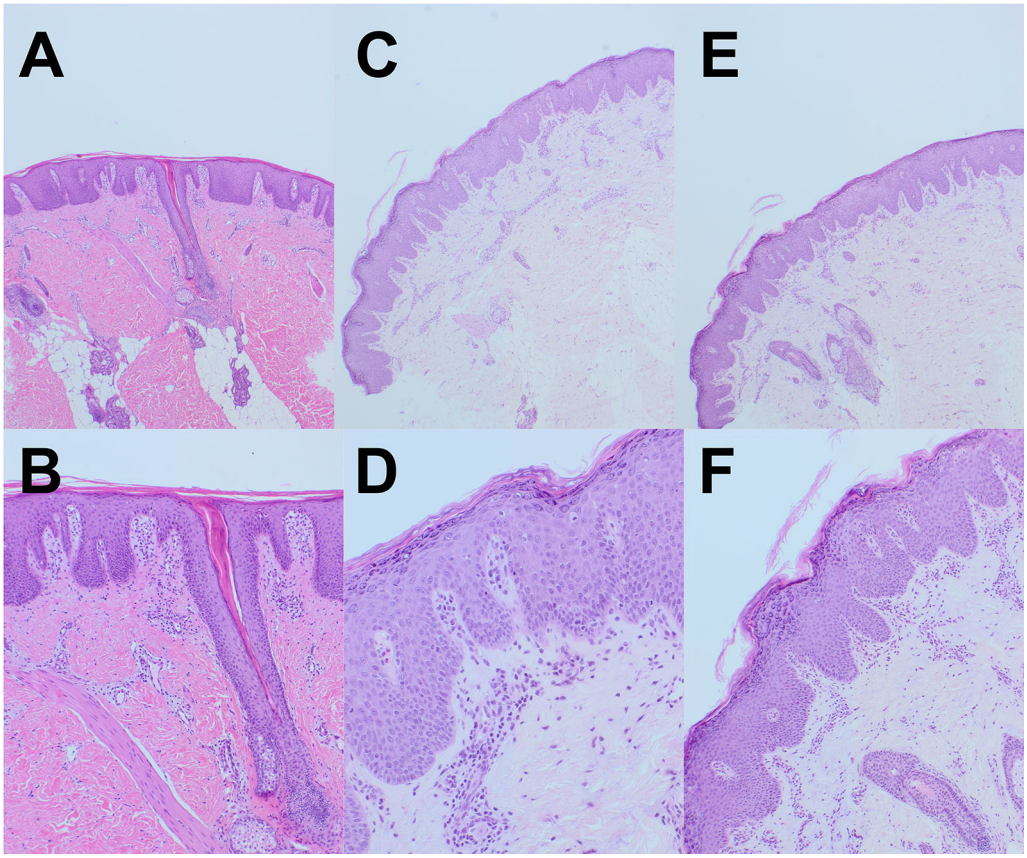

Fig. 4 Histological features of skin lesions of described patients were rather similar: regular acanthosis of the epidermis with thickening of the stratum granulosum and hyperkeratosis and focal parakeratosis, particularly severe around the follicular orifices, can be seen within the epidermis. In the dermis, sparse lympho-histiocytic inflammatory infiltrates around the blood vessels of the superficial plexus. A keratinous plug can be seen at the follicular orifice. **A** and **B** Patients 1; **C** and **D** patient 2; **E** and **F** patient 3 (H&E staining, original magnification: × 40 – **A**, **C**, **E**; × 100 – **B**, **D**, **F**)

a biopsy was performed, which showed that I did not actually have psoriasis, but pityriasis rubra pilaris. From March 2022 to June 2022, I was treated with cyclosporine, unfortunately without any effect, but my doctor—Dr. Marta Kolt-Kaminska—during my June hospitalization decided to implement treatment with risankizumab. To my joy, not only did my skin condition improve, but what is more, it lasted until September 2022. In addition, this is probably the first drug to which my body did not react negatively. Only at the end of September did a few small pimples reappear, which first disappeared, then reappeared again, and so on until November. Currently, that is, in December 2022, the lesions have returned to a small extent on the upper and lower limbs, but this is by far the best condition of my skin that I have observed in the last 13 years, and the comfort of my life has increased significantly.

DISCUSSION

PRP, especially its severe forms, significantly affects the quality of life and psycho-social wellbeing of children and their parents. However, the lack of treatment recommendations for this disease forces the search for new therapeutic options, often used off-label, especially in children. In our patients we chose risankizumab because of the observed excellent effects

in the treatment of plaque psoriasis in adults, reports of similar pathogenesis of PRP and psoriasis and, above all, a good safety profile. Risankizumab is a humanized monoclonal IgG1 antibody targeted against the p19 subunit of IL-23, which results in the inhibition of IL-23 signaling and subsequent decrease in synthesis of proinflammatory cytokines such as IL-17. It has been tested as therapy for several immune and inflammatory conditions, being most widely used in plaque psoriasis [10]. It has been shown to be well tolerated and efficacious in patients with moderate-to-severe plaque psoriasis and is approved for the treatment of this disease in over 70 countries, including the USA, Canada, Japan and European countries [11–16]. The long-term safety analysis included data from 17 completed or ongoing clinical trials of risankizumab for moderate-to-severe psoriasis and indicated the favorable safety profile of this drug in adults [17].

Importantly, the crucial role of the IL-23 axis in PRP pathogenesis has been emphasized recently [9]. So far, only a few cases of risankizumab therapy in patients with PRP have been reported. In seven patients treated with risankizumab, a positive response to treatment was observed [18–22]. However, in two other patients no satisfactory effect was obtained. One was a 72-year-old man with severe type I PRP who had also previously failed to respond to other systemic therapies such as retinoids, methotrexate, prednisolone and infliximab. The second patient who did not respond positively to rizankizumab treatment was a 62-year-old man with a very short, 6-week history of PRP and initial very high disease activity [20, 23]. Moreover, several cases successfully treated with other IL-23 inhibitors, such as guselkumab or tildrakizumab, have also been published [24–29].

To the best of our knowledge, no data on treatment with interleukin 23 inhibitors in children with PRP have been published to date. Thus far, ten cases of biological treatment in pediatric patients with PRP have been described, of which five involved etanercept, two ustekinumab, one secukinumab and one efalizumab. All of these patients responded positively to this treatment. One patient, a 17-year-old boy previously treated with oral corticosteroids, phototherapy, acitretin and cyclosporine, did not respond to etanercept therapy but achieved disease remission with adalimumab [30–39]. Here, we have demonstrated a good efficacy and safety profile of risankizumab among pediatric patients with PRP. Of note, patients 1 and 2 were positive for CARD14 gene mutation; despite this, they achieved complete PRP resolution after a single dose of risankizumab. Particularly patient 1 is interesting, as the girl was refractory to adalimumab, another biological agent, but responded perfectly to risankizumab. The third patient differs from the two other children as she was CARD14 mutation negative and had been treated with a number of other systemic agents in the past. Despite poor response to previous therapies, she improved significantly when she received risankizumab, although residual skin lesions were present. However, as a result of the treatment we used, all our patients obtained clean or almost clean skin and returned to normal life activities and relationships, which could not be achieved with traditional treatment methods.

CONCLUSION

Risankizumab seems to be a safe and effective treatment option for PRP in children. Rapid improvement of the skin condition can be observed after even the first dose of this drug. Nonetheless, placebo-controlled, double-blind, multicenter studies should be performed to prove the effectiveness and safety we observed.

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pictures: Ewa Kaznowska. Supervision: Adam Reich.

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Authorship All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

Compliance with Ethics Guidelines The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from the patient and her parents for participation in the study and publication of the article, including publication of clinical photographs. We thank the patient for her involvement.

Data Availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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