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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. List of the targeting genes in the deep sequencing (human comprehensive cancer panel v2)

Switching biologics in severe pediatric psoriasis: a retrospective analysis

Biologics are an emerging therapeutic option for severe pediatric psoriasis.[1]

Their efficacy and safety are widely established for adults but not for children, in whom safety concerns are an issue.[2]

Etanercept, ustekinumab, and adalimumab are approved in Europe for the treatment of severe pediatric psoriasis, whereas only recently (2016) etanercept received FDA approval for this indication.[1,3–5] Reports outside the context of clinical trials are scarce.[6,7]

We aimed to report the safety, efficacy, and switching trends of biological treatments for severe pediatric psoriasis in a real-life setting.

We performed a retrospective analysis of all pediatric patients with severe psoriasis treated with biologics in the last 8 years.

Fourteen patients (7 male) were included. Chronic plaque psoriasis was the main presentation ($n = 13$), followed by erythrodermic disease associated with psoriatic arthritis ($n = 1$). (Fig. 1) Previous treatments included systemic conventional agents ($n = 19$) and phototherapy ($n = 4$). (Table 1).

Mean PASI at the beginning of the biological treatment was 19.6. Etanercept was the first biologic used in 10 patients and ustekinumab in four. Seven of the patients initially treated with etanercept were switched to adalimumab ($n = 4$), infliximab ($n = 1$), and ustekinumab ($n = 2$) because of secondary loss of response ($n = 6$) or lack of initial response ($n = 1$). The mean total treatment duration was 53.5 months (41.7 for the first and 25.6 months for the second biological agent). Except for one patient, a PASI 75 or higher response at week 12 was obtained for all first-line treatment episodes.

Reported adverse events (AEs) included mild-to-moderate infections ($n = 8$) and injection-site reactions ($n = 2$). Serious AEs were not observed. Temporary drug suspension was necessary in two patients undergoing elective surgery. No efficacy issues were observed when the treatment was restarted later after surgery. Two patients discontinued biologics because of sustained clinical stability after 38 and

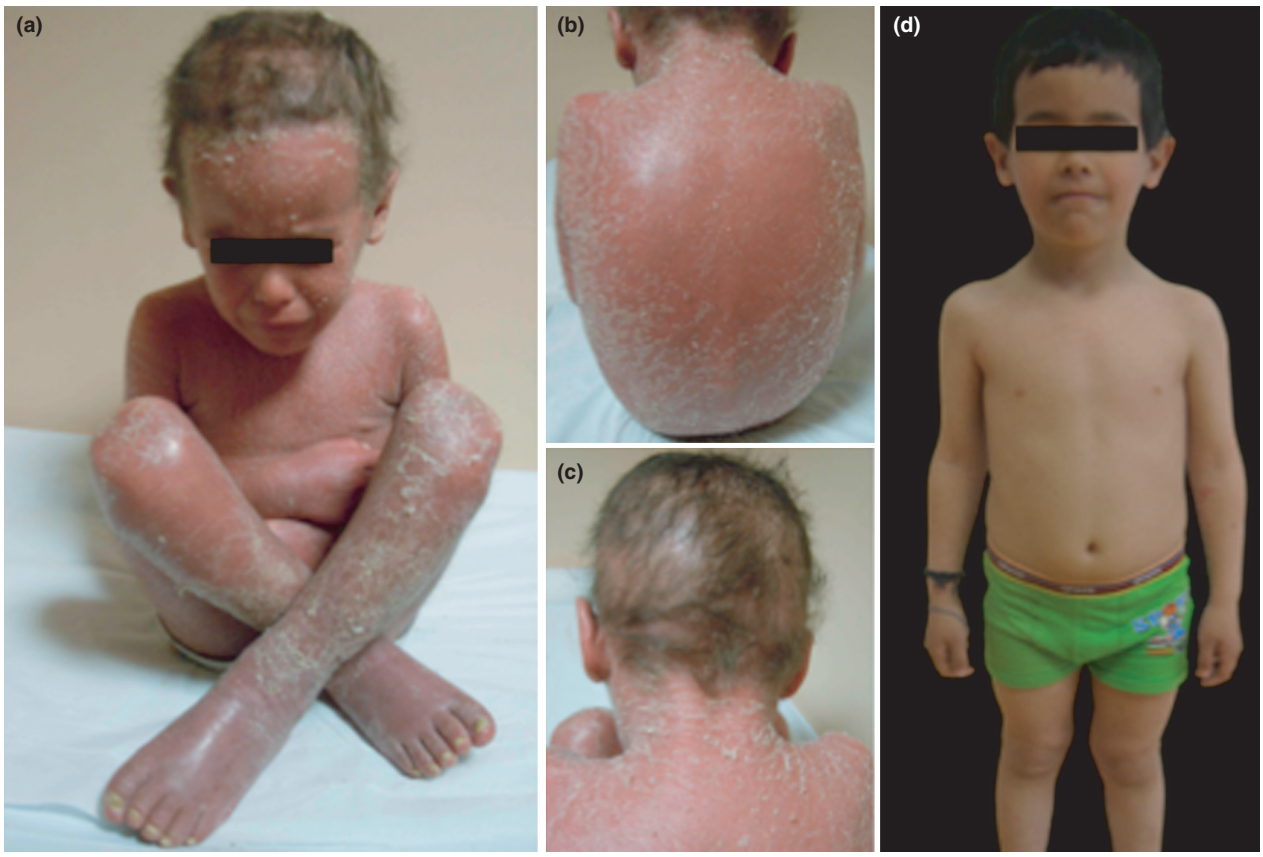

Figure 1 (a–c) Patient presenting with erythrodermic arthropathic psoriasis at the beginning of therapy with etanercept. (d) PASI 90 response after 24 weeks of etanercept treatment, associated with remission of joint symptoms and marked improvement of quality of life

75 months of therapy and remain controlled off treatment. The remaining 12 patients are stable under treatment (PASI < 3).

Biologics are effective for severe pediatric psoriasis. Based on clinical trials, the overall safety data seems overlapping with the existing evidence for adults.[1,3–7] Most short-term AEs are mild-to-moderate infections, which have not been unequivocally linked to biological treatments since they are common in otherwise healthy children.[5,6] Concerning long-term AEs, Paller *et al.* reported no safety concerns in 69 children treated with etanercept for 5 years.[5] Additionally, safety data from studies of pediatric inflammatory bowel disease and juvenile arthritis treated with biologics is reassuring, demonstrating a favorable long-term safety profile that overlaps with Paller *et al*[5] and our findings.[8,9]

Remarkably, our study showed an unexpected high number of biological switches (50%) because of efficacy issues, which differs from the previous long-term efficacy data available.[5] We hypothesized that greater adaptive immune system competency in young age may underlie the high rate of gradual loss of efficacy observed. Additionally, in our study all switchers were initially treated with etanercept. In contrast, none of the patients treated with first-line ustekinumab needed switching, suggesting a longer drug survival for ustekinumab, as is established for adults.[10] For now, no head-to-head comparisons between different biologics are available for pediatric psoriasis, but these may prove useful in the future.

Since children with severe psoriasis have a potential lifetime of treatment ahead of them, the negative impacts of biological switching concerning costs and cumulative life-course impairment are especially relevant in pediatric age.

We acknowledge the limitations of our small sample-sized study with data retrospectively collected from registries. However, it represents one of the largest real-life series with longest follow-up periods of pediatric psoriasis treated with biologics. Additionally it provides unique switching and efficacy data in this population, revealing a surprisingly high switching rate. Further larger studies are warranted to clarify our findings.

Table 1 Detailed patient information including demographic data, disease, and treatment characterization

Gender	Age at diagnosis	Age at start of therapy	Psoriasis presentation	PASI (before starting biological therapy)	Previous treatments (except topical)	Biological treatment, 1st and 2nd line	Associated therapies	Duration	≥PASI75 response 12 weeks therapy	Adverse events	Biological therapy suspension and discontinuation
Male	6 m.o.	4 y.o.	Erythrodermic Psoriatic arthritis	Erythrodermic	Cyclosporine Acitretin	1st Etanercept 2nd Adalimumab	None	1st 65 months 2nd 12 months	1st yes 2nd yes	Injection site reaction	–
Female	5 y.o.	11 y.o.	Chronic plaque psoriasis Palmoplantar psoriasis	26	Cyclosporine Phototherapy Acitretin	1st Etanercept 2nd Ustekinumab	Methotrexate	1st 35 months 2nd 17 months	1st yes 2nd no	Upper respiratory infection	–
Female	6 y.o.	10 y.o.	Chronic plaque psoriasis	17	Cyclosporine Phototherapy	1st Etanercept 2nd Adalimumab	None	1st 37 months 2nd 38 months	1st yes 2nd yes	Injection site reaction	Stopped biological therapy because of maintained clinical stability
Female	6 y.o.	9 y.o.	Chronic plaque psoriasis	17	Cyclosporine Phototherapy	1st Ustekinumab	None	1st 58 months	1st yes	None	Bariatric surgery
Female	7 y.o.	10 y.o.	Chronic plaque psoriasis	12	Cyclosporine	1st Etanercept	None	1st 38 months	1st yes	None	Stopped biological therapy because of maintained clinical stability
Male	7 y.o.	8 y.o.	Chronic plaque psoriasis	12	Cyclosporine Acitretin	1st Etanercept 2nd Adalimumab	Methotrexate	1st 29 months 2nd 11 months	1st yes 2nd yes	None	Urological surgery
Male	8 y.o.	15 y.o.	Chronic plaque psoriasis	11	Cyclosporine Acitretin	1st Etanercept	None	1st 23 months	1st yes	Upper respiratory infection	–
Male	8 y.o.	14 y.o.	Chronic plaque psoriasis	16	Methotrexate	1st Ustekinumab	None	1st 15 months	1st yes	None	–
Female	9 y.o.	10 y.o.	Chronic plaque psoriasis	13	Cyclosporine	1st Etanercept 2nd Ustekinumab	None	1st 5 months 2nd 57 months	1st no 2nd no	Dental abscess	–
Male	9 y.o.	10 y.o.	Chronic plaque psoriasis	9	Cyclosporine Acitretin	1st Etanercept 2nd Adalimumab	Methotrexate	1st 77 months 2nd 12 months	1st yes 2nd yes	Upper respiratory infection	–
Female	9 y.o.	13 y.o.	Chronic plaque psoriasis	20	Methotrexate	1st Etanercept 2nd Infliximab	Methotrexate	1st 15 months 2nd 32 months	1st yes 2nd yes	None	–
Male	10 y.o.	12 y.o.	Chronic plaque psoriasis	23	Cyclosporine Phototherapy	1st Ustekinumab	None	1st 50 months	1st yes	Urinary Tract Infection Upper respiratory infection	–
Female	10 y.o.	11 y.o.	Chronic plaque psoriasis	11	Cyclosporine	1st Etanercept	None	1st 90 months	1st yes	Conjutivitis	–
Male	15 y.o.	15 y.o.	Chronic plaque psoriasis	16	Methotrexate	1st Ustekinumab	None	1st 47 months	1st yes	Upper respiratory infection	–

m.o., months old; y.o., years old; PASI, Psoriasis Area and Severity Index

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Clinical and radiological improvement in idiopathic calcinosis cutis with topical 25% sodium metabisulfite

A 10-year-old boy had multiple painful ulcers present linearly over his left leg for the last 3 years. There was history of intermittent pus discharge from the ulcers which used to improve with oral antibiotics, but the ulcers never healed completely. There were no other local or systemic complaints. Past history was significant for blunt trauma on the left leg because of a fall from height 1 year before the onset of skin ulcers. On examination, there were multiple shallow round-to-oval, 1-3 cm sized ulcers in a linear distribution over the left leg, extending from the medial aspect of knee up to the ankle. Scars of healed ulcers were present in the intervening skin. Chalky-white material was present on floor of some of the ulcers (Fig 1a). Rest of the cutaneous and systemic examination was unremarkable. Skin biopsy from edge of one of the ulcers showed fragmented basophilic calcium deposits in the deep dermis with surrounding infiltrate of histiocytes and lymphocytes (Fig 2). Special stains and tissue cultures were negative for

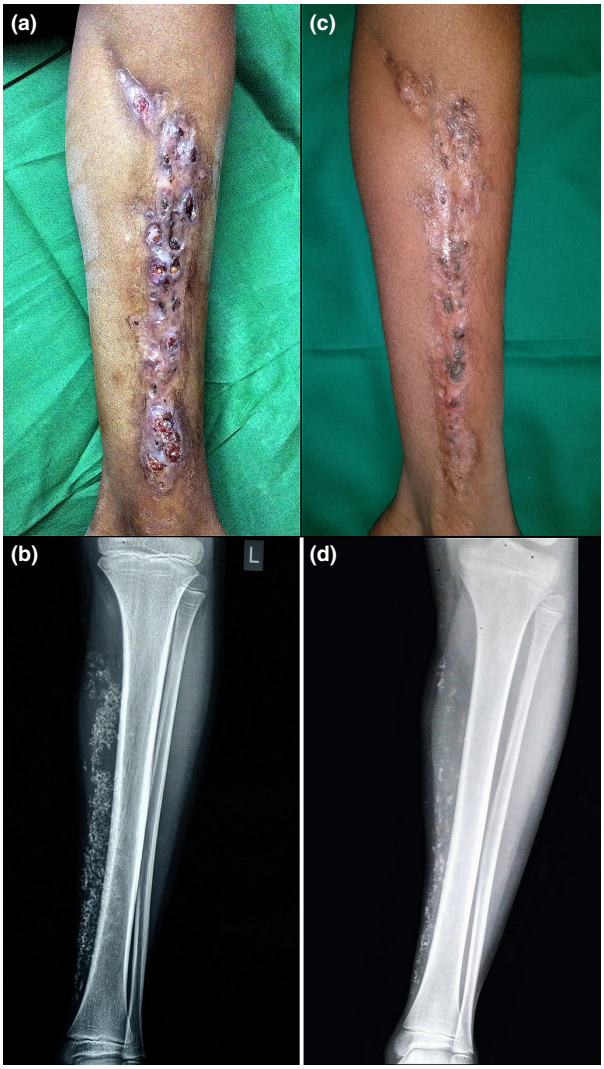

Figure 1 (a) Multiple shallow ulcers present linearly on the left leg (b) X-Ray left leg (antero-posterior view) showing soft tissue calcification (c) Significant clinical improvement after 3 months of treatment with topical 25% sodium metabisulfite d) Marked reduction in soft tissue calcification after 3 months