Standard dose of Ustekinumab for childhood-onset deficiency of interleukin–36 receptor antagonist

We read with interest the letter from *Bonekamp et al*[1] reporting two children with severe deficiency of interleukin-36 receptor antagonist (DITRA) treated with high dose of Ustekinumab. DITRA, an autosomal recessive disease caused by mutations of *IL36RN*, is characterised by generalised pustular psoriasis and systemic inflammation.[2] We report here a paediatric case successfully treated with standard dose of Ustekinumab, a monoclonal antibody against the p40 subunit of interleukin (IL)-12/IL-23.

We reported in 2015 a boy born from consanguineous Tunisian parents who presented at 1 month of life with diffuse inflammatory pustular psoriasis and erythrodermic extension.[3] At the age of 2 months, he was referred to us with fever, irritability, severe failure to thrive and recurrent diarrhoea; he had slight microcephaly and triangular chin. Oesophageal and gastrointestinal endoscopy showed minimal gastric ulcers, normal macroscopic colonic aspect but focal inflammatory infiltrates (predominant lymphocytes) in gastric body specimens. Leucocyte/neutrophil/platelet counts were markedly increased during flares, conversely with normal erythrocyte sedimentation/C-reactive protein rates. Cytokine profile secretion was unexpected, with high tumour necrosis factor (TNF)-α secretion in blood and high IL-1β secretion in cerebrospinal fluid (normal IL-1β, IL-6 rates in blood; normal TNF-α, IL-6 rates in cerebrospinal fluid). Cutaneous biopsy was consistent with the diagnosis of pustular psoriasis and homozygous L27P mutation in *IL36RN* gene was detected. Topical corticosteroids and acitretin were inefficient. We started treatment with Anakinra, at doses up to 6 mg/kg, which initially induced complete response on fever.[3 4] A partial cutaneous response was observed but Anakinra quickly failed to control skin rashes (figure 1A). Moreover, he presented recurrent bacterial skin infections, without biological signs of primary immunodeficiency. In addition, his general condition did not globally improve with time and he still presented severe weight and growth retardation. We decided to stop Anakinra and we started Etanercept during 3 months (0.8 mg/kg/week) without any efficacy. After parental consent, Ustekinumab, on monotherapy, was started at 4.5 years old at a dose of 0.75 mg/kg every 3 months (after second induction dose at week 4). A quick complete response was initially observed and sustained at a 15-month follow-up; his rash completely vanished, he never had fever again and he recovered normal growth velocity (figures 1B, C and 2). We maintained a standard dose until now, with an excellent tolerance, and a 12-month discontinuation of topical steroids.

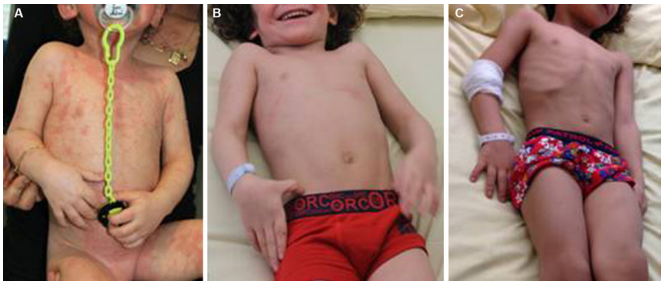

Figure 1 Cutaneous evolution under Anakinra and Ustekinumab. (A) New flare of generalised psoriasis under treatment with Anakinra (January 2012). (B) Clinical picture after 6-month treatment with Ustekinumab (January 2017). (C) Clinical picture after 12-month treatment with Ustekinumab (October 2017).

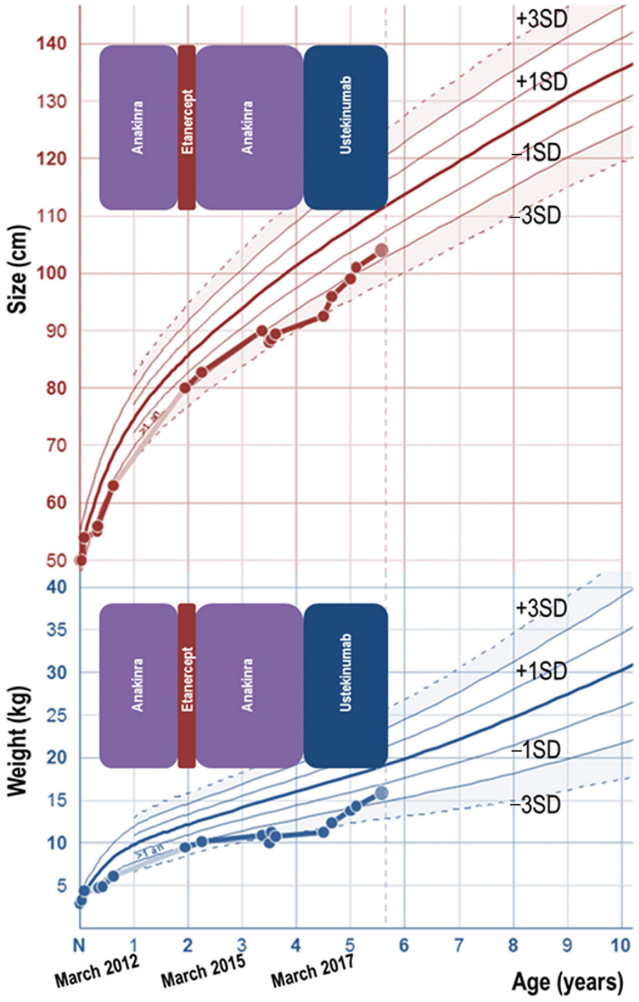

Figure 2 Our deficiency of interleukin-36 receptor antagonist patient weight and height curves under three types of biological treatments.

Our experience underlines the interest of the blockade of the IL-23/T helper cell 17 axis in patients with DITRA and standard dose of Ustekinumab, those regularly applied in treating non-monogenic psoriasis may be sufficient. DITRA and non-monogenic psoriasis may have pathophysiological features in common,[5] meaning that complex interactions between innate and adaptive immune systems may be involved.[6–10] Failure to thrive in DITRA children may be explained by exudative cutaneous protein loss, systemic inflammatory activity, gastrointestinal inflammatory involvement and/or the late repercussions of a lack of early maternal attachment.

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REFERENCES

1 Bonekamp N, Caorsi R, Viglizzo GM, *et al*. High-dose ustekinumab for severe childhood deficiency of interleukin-36 receptor antagonist (DITRA). *Ann Rheum Dis* 2018;77:1241–3.
2 Marrakchi S, Guigue P, Renshaw BR, *et al*. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. *N Engl J Med* 2011;365:620–8.
3 Rossi-Semerano L, Piram M, Chiaverini C, *et al*. First clinical description of an infant with interleukin-36-receptor antagonist deficiency successfully treated with anakinra. *Pediatrics* 2013;132:e1043–7.
4 Podlipnik S, Morgado-Carrasco D, Fustà-Novell X, *et al*. Dynamics of plasma cytokines in a patient with deficiency of interleukin-36 receptor antagonist successfully treated with Anakinra. *Br J Dermatol* 2017.
5 Kim J, Krueger JG. Highly effective new treatments for psoriasis target the IL-23/Type 17 T cell autoimmune axis. *Annu Rev Med* 2017;68:255–69.
6 Johnston A, Xing X, Wolterink L, *et al*. IL-1 and IL-36 are dominant cytokines in generalized pustular psoriasis. *J Allergy Clin Immunol* 2017;140:109–20.
7 Tortola L, Rosenwald E, Abel B, *et al*. Psoriasiform dermatitis is driven by IL-36-mediated DC-keratinocyte crosstalk. *J Clin Invest* 2012;122:3965–76.
8 Carrier Y, Ma HL, Ramon HE, *et al*. Inter-regulation of Th17 cytokines and the IL-36 cytokines in vitro and in vivo: implications in psoriasis pathogenesis. *J Invest Dermatol* 2011;131:2428–37.
9 Cua DJ, Tato CM. Innate IL-17-producing cells: the sentinels of the immune system. *Nat Rev Immunol* 2010;10:479–89.
10 Gaffen SL, Jain R, Garg AV, *et al*. The IL-23-IL-17 immune axis: from mechanisms to therapeutic testing. *Nat Rev Immunol* 2014;14:585–600.