Acrodermatitis Continua of Hallopeau Treated Successfully with Ustekinumab and Acitretin after Failure of Tumour Necrosis Factor Blockade and Anakinra

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Introduction

Acrodermatitis continua of Hallopeau (ACH) is a rare and disabling variant of pustular psoriasis which is characterized by the presence of periungual and subungual sterile pustules, paronychia, onychodystrophy and osteolysis of the distal phalanx of the fingers and toes and atrophic skin changes. This is a difficult-to-treat condition, with no treatment guidelines [1].

Case Report

A 53-year-old Caucasian male patient was referred to our department for typical pustular lesions of ACH affecting the 10 hand nails (fig. 1). He was an active smoker (20 cigarettes/day) with chronic bronchitis. He had no personal or family history of psoriasis. The eruption had begun 1 year earlier. Full blood count was within the normal range, and there was no biological inflammatory syndrome. He had been unsuccessfully treated with topical agents, acitretin (between 25 and 35 mg/day for 10 months), TL-01 UVB phototherapy (90 sessions), methotrexate (22.5 mg once a week for 3 months), ciclosporin-A (3, then 4 mg/kg/day, which induced hypertension and an impairment of renal function), adalimumab 40 mg s.c. every other week (4 months), etanercept 50 mg s.c. twice a week associated with acitretin (35 mg/day; 8 weeks), infliximab (5 mg/kg) associated with methotrexate 10 mg/week (3 months). Because he had elevated plasma levels of interleukin (IL)-1β (117 pg/ml; normal range 0–20 pg/ml, Quantikine ELISA kit, R&D Systems, Minneapolis, Minn., USA), he received anakinra 100 mg s.c. daily for 7 weeks with no clinical improvement. Aside ciclosporin-A, which permitted partial remission but was withdrawn for toxicity, all other treatments failed, and a major impairment of the patient’s quality of life was recorded. Ustekinumab 45 mg (1 injection at week 0 and week 4, then every 12 weeks) was then introduced (according to body weight: 84 kg). There was a rapid significant improvement within 4 weeks after the first injection, but lesions remained incompletely controlled thereafter: there was no more pustular lesion of the fingertips and periungual folds, but the patient still pre-
Presented flares of pustules of the nail beds. This led us to double the doses of ustekinumab (90 mg for 12 weeks) which increased the interval between flares. However, 1 year after initiation of ustekinumab, he still had paronychia and occasional pustular lesions of the nail beds (fig. 2). Acitretin (progressively increased up to 30 mg a day) was added, which induced complete control of the lesions and nail regrowth (fig. 3). Plasma IL-1β was controlled at the normal level (<4 pg/ml).

**Discussion**

ACH is considered as a variant of pustular psoriasis. On account of its low prevalence, there are no guidelines to manage this pathology. Topical treatments (topical steroids, calcipotriol, topical tacrolimus) are classically prescribed as first-line therapy; systemic treatments such as acitretin, methotrexate or ciclosporin can be efficient in some cases [1].

Several case reports or short series report some benefits of biological agents. Though anti-tumour necrosis factor (TNF) can induce palmoplantar pustular psoriasis (PPPP), it has been proven efficient for ACH. The results of 33 treatments with anti-TNF in 23 ACH patients have been reported so far [2–7]. In responsive patients, clearance of lesions was reported to occur more rapidly than in psoriasis vulgaris. Anti-TNF as a monotherapy was reported to induce or maintain remission in 16 cases (infliximab: 4; etanercept: 5; adalimumab: 7); of note, in 2 patients treated with infliximab, there was a rapid loss of efficacy (within 3 months) after an initial clearance of the lesions (1 case in monotherapy; 1 case in association with methotrexate 10 mg/week). In 7 cases, clearance was obtained upon combination to a variety of systemic treatments (methotrexate, acitretin or ciclosporin). Treatment was unsuccessful in 3 cases with infliximab, in 6 cases with etanercept and in 1 case with adalimumab. In 7 reported patients, a second-line anti-TNF treatment was efficient after failure or loss of efficacy of another anti-TNF. At last, Lutz and Lipsker [8] reported the case of a patient whose ACH was refractory to the 3 available anti-TNF treatments.

Recent descriptions of auto-inflammatory syndromes secondary to deficiency...
of IL-1 family member receptor, namely DIRA (deficiency of the IL-1 receptor antagonist) and DITRA (deficiency of the IL-36 receptor antagonist) [9], provided a pathophysiological background to support the use of IL-1 blockade in cases of refractory pustular psoriasis. DIRA is a rare autosomal recessive auto-inflammatory disorder caused by homozygous mutation in the gene encoding for the IL-1 receptor antagonist, leading to systemic inflammation because of uncontrolled IL-1 signalling; it is characterized by perinatal onset of a pustular dermatitis similar to pustular psoriasis, skeletal involvement and elevated inflammatory markers. DITRA is a recently identified syndrome resulting from deficiency of the IL-36 receptor antagonist and characterized by sudden-onset, recurrent severe generalized pustular psoriasis. One case report describes the efficacy of anakinra (IL-1 receptor antagonist) in ACH [8], which provided quick improvement of lesions in the treated patient. Moreover, anakinra was recently successfully used in a case of DITRA syndrome in an infant [10] as well as in 3 cases [11, 12] of generalized pustular psoriasis, one of them carrying a mutation of the IL-36RN gene [12]. IL-36 RN mutations can be found in patients with generalized pustular psoriasis [10, 11] and in rare patients with ACH [12–15]. It has been hypothesized that such mutations could be associated with the response of generalized pustular psoriasis [12] or ACH [9] to anakinra [13, 14], but this has not been demonstrated [14, 16]. Indeed, IL-36RN gene mutations do not account for all cases of pustular psoriasis [13, 14, 17, 18]; moreover, the consequences of IL-36RA deficiency on the expression of pro-inflammatory cytokines are not fully known, and, although IL-36RA deficiency may induce increased production of IL-1, it has not been demonstrated that IL-1 blockade was the most relevant strategy in that context [16]. Tauber et al. [16] suggested that anakinra would account for partial benefit in pustular psoriasis, since it counteracts only one of the various inflammatory signalling pathways induced by IL-36, and they did not rule out a potential clinical interest of ‘targeted inhibition of one of several effector inflammatory cytokines such as (…) TNF or eventually IL-6, IL-8 or IL-23/Th17 axes’ [16]. Nevertheless, IL-36-targeted inhibition strategies would probably be more relevant [16, 17]. In our observation, in spite of an elevated IL-1β plasma level, anakinra was not effective, which confirms that the IL-1 signalling pathway does not play a primary role in all cases. It has been shown that expression of members of the IL-1 family can be increased in ex vivo skin culture by inflammatory stimuli such as IL-17 and TNF-α [19]. Therefore, in our patient, the elevated IL-1β plasma level could have been secondary to the skin condition; this would also explain the normalization of IL-1β plasma levels after clinical control under ustekinumab. It could also be partially due to heavy smoking [20].

Ustekinumab is a fully human monoclonal antibody that binds to the p40 subunit shared by IL-12 and IL-23 [21], thereby preventing subsequent pro-inflammatory effects. IL-23 induces development of Th17 cells and secretion of IL-17 [22]. IL-17 causes neutrophil influx and is involved in neutrophil-mediated inflammatory responses [23]; IL-17 mRNA levels (assessed by quantitative PCR) in lesional skin samples of psoriasis have been found to be higher in pustular psoriasis than in other clinical subtypes [24]; this may explain why ustekinumab has been successfully used once in generalized pustular psoriasis [24]; moreover, it has been shown that successful treatment of generalized pustular psoriasis by infliximab + acitretin was followed by a marked reduction of IL-12 and IL-23 expression in the skin (evaluated by immunohistochemistry) [25].

According to published data, efficacy of ustekinumab in the treatment of PPPP is inconsistent and somewhat contradictory. Morales-Múñera et al. [26] report the efficacy of ustekinumab (45 mg/injection) in 5 patients with otherwise refractory PPPP, whereas Bissonnette et al. [27] report no statistically significant difference at 16 weeks between PPPP patients receiving either ustekinumab (45 mg/injection; 10 patients) or placebo (10 patients). In the study of Bissonnette et al., expression of IL-17 and IL-12/IL-23 was quantified in lesional skin of patients with palmoplantar pustulosis or PPPP (pustular lesions) and in skin of healthy controls: an increased expression of IL-17 was found in palm pustular lesions compared to skin of healthy controls, whereas there was no increase in IL-12/IL-23 expression. This finding is consistent with the treatment’s failure in this study. Such a quantification of IL expression in lesional skin was not performed in the series of Morales-Múñera et al. [26], but it would be interesting to know if IL-12 and IL-12/IL-23 expression in skin lesions at baseline is different in responders and non-responders to ustekinumab and could be used as a response predictor.

Data are scant regarding the use of ustekinumab in the treatment of ACH since it was reported only once, without success [8]. In our case, ustekinumab was effective but complete resolution of the lesions required both higher doses than usually proposed in psoriasis vulgaris and association with acitretin.

Acitretin is a retinoid; it exerts its effects by binding to nuclear receptors, thereby enhancing or inhibiting target gene transcription. It participates to regulate epidermal proliferation, angiogenesis and inflammation. Several case reports and series illustrate the usefulness of acitretin in case of suboptimal results of biological therapy. In such situations, it can indeed enhance the clinical result without adding immunosuppressive effects [28]. This treatment was inefficient in our case in monotherapy. In conclusion, whether ACH is a subtype of psoriasis or a distinct entity is still a matter of debate. Although recent data highlight the potential usefulness of anakinra in various presentations of pustular psoriasis, the IL-1 signalling pathway does probably not account for all cases. Our case illustrates the potential usefulness of IL-12/IL-23 blockade, though achievement of a complete resolution required higher doses than usual and association with acitretin.

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