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Dupilumab in paediatric Netherton syndrome: Can we do better?

Dear Editor,

The treatment of Netherton syndrome (NS) is currently debated, as no genetic therapy was yet established for its causative SPINK5 gene mutation, manifesting with various degrees of congenital erythroderma, scaling and pruritus, vastly influencing patient's quality of life (QoL).^{1,2} Among innovative therapeutic approaches, dupilumab stands out as compromise of safety and efficacy, on the basis of its immunomodulating effects and its encouraging outcomes on pruritus and eczema of severe atopic dermatitis.^{1,3}

Herein, we report a series of male NS paediatric patients (age: 4, 10, 14 years; body weight: 20–25, 39, 55 kg), diagnosed genetically after clinical suspect arose from observation of generalized erythroderma (EASI 68, 60, 64), characteristic bamboo brittle hair (trichorrhexis invaginata) and ichthyosis linearis circumflexa (ILC; [Figure 1](#)). Overall, intense pruritus (NRS 9) and low QoL (DLQI 28, 22, 26) were registered. Also, short stature and elevated serum Ig-E levels were observed.

Dupilumab was administered for respectively, 24, 12 and 4 months subcutaneously, starting from an initial dose of 160 mg (20 kg-adjusted dose) and 400 mg (39 and 55 kg patients), followed by 80–99 mg biweekly (20–25 kg-adjusted dose) and 200 mg biweekly (39 and

55 kg patients). After only 2 months of therapy, pruritus decreased considerably (NRS 3, 4, 4), attaining very good outcomes with ongoing therapy (NRS 0, 3, 3). Also, desquamation and ILC improved significantly, while only moderate effects (10–22%) were recorded on eczema (EASI 56, 54, 50) and DLQI (8, 14, 22) ([Figure 2](#)). School-going patients reported especially high impact of severe eczema on life quality and self-perception.

In addition to first-line topical emollients, the growing understanding of NS pathophysiology recently led to administration of biological therapies.² Dupilumab's widely documented safety profile encourages its use, especially in paediatrics. Dupilumab binds IL-4Ra inducing IL-4 and IL-3 signalling inhibition, with documented benefits on chronic pruritus, which is mediated, inter alia, by the latter.³ Conversely in NS, dupilumab's effects on erythema are debated: in our series only moderate effects were obtained on erythema (10–22%), leading to scarce DLQI improvement in school-going patients, despite good results on pruritus, desquamation and ILC. Özkaya et al. even described worsening of ILC during dupilumab therapy, possibly resulting from decreased camouflage effect provided by fading erythema.¹

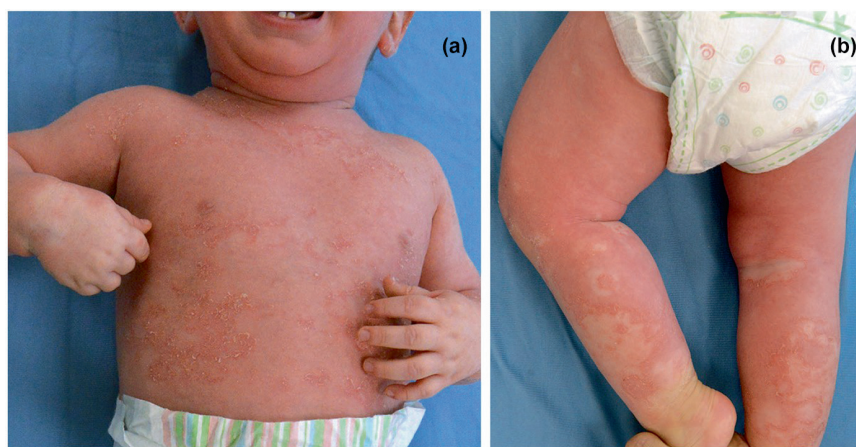


FIGURE 1 Clinical presentation of Netherton syndrome with generalized pruritus, ichthyosis linearis circumflexa (ILC) and erythroderma (EASI 68) of the anterior trunk (a) and posterior legs (b).

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FIGURE 2 After 2 years of dupilumab therapy, pruritus and desquamation improved significantly, while only moderate effects were recorded on eczema (EASI 56): (a) anterior trunk (a) and posterior legs (b) are displayed.

Notably, NS exhibits prevalently IL-17-dominant profile with induction of T-helper-17/IL-23 pathway genes, explaining the marked cutaneous improvement in NS patients treated with IL-17A antibody secukinumab. Indeed, remarkable reduction in ichthyosis area and severity index, DLQI and pruritus were recently reported, especially in erythrodermic patients.^{4,5}

Advances in paediatric NS treatment highlight the need to administer patient-tailored therapy, addressing concrete patients' needs. Indeed, erythema and scaling still represent relevant issues in NS, strongly influencing adolescents' self-perception and causing social and psychological consequences and deserve to be carefully addressed.

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KEYWORDS

atopic dermatitis, dupilumab, genodermatosis, Netherton, quality of life

CONFLICT OF INTEREST STATEMENT

The authors have no relevant financial or non-financial interests to disclose.

ETHICS STATEMENT

This study was performed in line with the principles of the Declaration of Helsinki.

CONSENT TO PARTICIPATE AND PUBLICATION

Written informed consent was obtained for the participation and publication of the present case and of relative documentation, including photographic documentation.

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Reply to: ‘Melanoma diagnosis at a specialist dermatology practice without the use of photographic surveillance’

Brown et al.’s¹ study of primary melanomas diagnosed at a private dermatology practice by full skin examination with dermoscopy, but without total body photography (TBP) or sequential digital dermoscopic imaging (SDDI), reported a ratio of in situ to invasive melanoma of 4.6:1, which the authors infer is higher than previous studies utilising TBP/SDDI.

When assessing the quality of melanoma screening, the benign to malignant ratio of excised lesions, which was not reported by Brown et al.,¹ is more important than the ratio of in situ to invasive disease as it provides more accurate assessment of screening effectiveness. A melanoma screening quality framework is needed, which includes who to screen (targeted screening), how to screen (which methodologies) and how it should be evaluated.

We do not advocate for general population skin cancer screening, nor the use of melanoma surveillance photography in low-risk patients. In Brown’s study, only 14% of patients had melanoma risk factors extracted and among these, only 25% met our high-risk criteria.² This patient cohort is not comparable with those of Guitera et al, where photographic surveillance was used for detection of subsequent primary melanomas.² Prospective, controlled studies are required to accurately assess melanoma surveillance photography in

reducing unnecessary biopsies and enhancing early detection. We look forward to results of the IMAGE trial of high-risk patients, in which a reduction in benign biopsies is a primary objective.³

We are concerned by the biopsy practices in Brown’s study, with over half of invasive melanomas diagnosed by shave procedures and 4.3% with deep margin transection.¹ Compared with elliptical excision, shave procedures are more likely to transect the tumour base and reduce capacity to accurately assess tumour depth for prognostication, staging and treatment planning.^{4,5} The Australian Cancer Council Guidelines recommend complete excision with 2 mm margin for suspicious pigmented lesions.⁴

The high rates of in situ melanoma in Brown’s report may be partly attributed to overdiagnosis. In Brown’s study, histopathological results were obtained from a single pathology provider.¹ A study by Elmore and colleagues demonstrated that pathologists’ diagnoses within the spectrum from moderately dysplastic naevi to early-stage invasive melanoma are neither reproducible nor very accurate.⁶ The higher rates of lentigo maligna in Queensland may also contribute to the reported high ratio of in situ to invasive disease.

We disagree that targeted screening with the use of photographic surveillance for high-risk patients is ‘dangerous’ and ‘risks patient safety.’¹ This demonstrates a misunderstanding of photographic monitoring. Monitoring