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THERAPEUTIC HOTLINE: SHORT PAPER

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Effectiveness of dupilumab for the treatment of nummular eczema phenotype of atopic dermatitis in adults

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Abstract

Nummular eczema (NE) is currently considered as one of the clinical phenotypes of atopic dermatitis (AD) of the adult. In this multicentre study, 30 adult patients (age ≥ 18 years) affected with nummular-like AD were treated with dupilumab, a monoclonal antibody against the receptor for interleukin(IL)-4 and IL-13. The evaluation of the results after 16 weeks of treatment showed a significant improvement of the disease, as demonstrated by reduction in Eczema Area Severity Score (EASI), visual analogue score (VAS) of pruritus, and Dermatology Life Quality Index (DLQI) scores. Conjunctivitis in one patient was the only side effect. In conclusion, dupilumab seems to be an effective and safe treatment in NE phenotype of AD of the adult.

KEYWORDS

adult atopic dermatitis, dupilumab, nummular eczema, phenotype

Nummular eczema (NE) is a chronic, inflammatory skin disease characterized by round or oval plaques that can affect all skin areas, both sexes, and of all age groups (Bonamonte, Foti, Vestita, Ranieri, & Angelini, 2012). NE may be the expression of different conditions, such as atopic dermatitis (AD), contact dermatitis, and dry skin (Bonamonte et al., 2012; Silvestre Salvador, Romero-Pérez, & Encabo-Duràn, 2017). Furthermore, it has been also reported as an adverse reaction to anti–tumor necrosis alpha agents or to interferon/ribavirin, after mastectomy, or in association with some infections (Bonamonte et al., 2012). Recently, NE was mainly described as a relatively frequent clinical phenotype of AD in adults, a disease characterized by clinical heterogeneity, especially when it directly starts in adulthood (adult-onset AD) (Megna, 2017). Indeed, in addition to NE, other atypical phenotypes are described in these patients, such as prurigo nodularis, seborrheic dermatitis-like dermatitis, or psoriasiform dermatitis (Silvestre Salvador et al., 2017). AD of adulthood is a chronic skin disease that often requires long-term treatment with systemic immunosuppressive drugs, such as cyclosporine A (CsA) (Calzavara Pinton et al., 2018). NE phenotype of AD seems to be particularly resistant to these treatments (Hello, Aubert, Bernier, Neel, & Barbarot, 2016). Recently, dupilumab, a fully human monoclonal IgG antibody against the alpha subunit receptor for interleukin (IL)-4 and IL-13, was introduced for the treatment of adult AD resistant to the treatment with conventional drugs (Fabbrocini, Napolitano, Megna, Balato, & Patruno, 2018). Furthermore, effectiveness of dupilumab has been reported also in atypical cases of adult AD, such as in the prurigo nodularis phenotype (Napolitano et al., 2019).

A multicenter, retrospective study was performed on adult (≥18 years) patients affected with NE phenotype of AD and treated with dupilumab, in five Italian University Dermatology Units (Bari, Catanzaro, Milan, Naples, and Perugia). All patients started treatment between July 2018 and July 2019. The following data were recorded for each patient: (a) personal and demographic data, (b) past and current history of AD, (c) disease severity, (d) comorbidities, and (e) previous and current systemic treatments. Disease severity was evaluated at baseline (T0) and 16 weeks after the beginning of treatment (T1) with dupilumab using Eczema Area and Severity Index (EASI), visual analogue scale (VAS) for pruritus ranging from 0 to 10 (where "0" means "doesn't itch at all" and "10" means "itch is worse than ever"), and Dermatology Life Quality Index (DLQI) (Calzavara Pinton et al., 2018). Exclusion criteria were other skin or internal diseases, cognitive impairment preventing completion of DLQI, and the contemporary use of topical or systemic anti-inflammatory drugs with proven efficacy on AD.

The study was conducted following the principles of the Declaration of Helsinki. Unpaired Student's *t*-test was used to calculate statistical differences, p value <.05 was considered to be statistically significant. GraphPad Prism 4.0 was used for all statistical analyses (GraphPad Software Inc., La Jolla, California).

A total of 396 AD Caucasian adult patients (189 males and 207 females; mean age: 45.7 ± 17.9 years; range: 18–87 years) were treated with dupilumab. All patients suffered from severe AD (EASI≥24) and in them all CsA treatments had been inefficacious or contraindicated or not tolerated (two requirements mandatory in Italy for prescription of dupilumab). The mean therapy duration was of 35.7 ± 7.9 weeks. NE phenotype was observed in 30 of 396 (7.6%) cases; 7 of 30 (23.4%) had a mixed form, NE and flexural eczema. Other possible causes of NE have been excluded in all of them. Patients included were 18 males and 12 females with a mean age of 38.2 ± 16.1 years (range: 19–78 years). Twenty-four of them (80.0%) suffered from AD persisting from childhood, whereas in 6 of 30 (20.0%) adult-onset AD was diagnosed. The average age at symptom onset was 12.6 ± 8.6 years. The most common previous topical treatments were emollients (30/30; 100.0%) and topical corticosteroids (18/30; 60.0%), followed by topical calcineurin inhibitors (8/30; 26.7%). Regarding systemic treatments, a brief course of systemic corticosteroids was the most frequently prescribed (28/30; 93.3%), followed by CsA (22/30; 88.9%). CsA was not prescribed in 8 of 30 (26.7%) patients because of arterial hypertension. The main reason for the discontinuation of CsA was therapeutic ineffectiveness (14/30; 46.7%), after an average treatment time of 22.4 ± 6.1 weeks, followed by adverse events (8/22; 36.3%). All NE patients were treated with dupilumab administered in the standard dosing regimen (600 mg induction dose and 300 mg every 2 weeks thereafter). Evaluation of the results was made after 16 weeks of treatment. A significant improvement in EASI from baseline (T0) to week 16 (T1) (mean: 37.7 ± 12.95 at T0 vs 4.83 ± 3.82 at T1; $p < 0.001$), pruritus VAS score (mean: 8.4 ± 4.69 at T0 vs 1.23 ± 0.7 at T1; $p < 0.001$) values, and DLQI (mean: 18.6 ± 5.26 at T0 vs 4.03 ± 5.43 at T1; $p < 0.001$) was observed in all patients (Figure 1). No differences between patients with persistent AD since childhood and those with adult-onset AD were observed. Conjunctivitis was the only side effect recorded and was reported by one patient of the persistent AD group. No patient dropped out.

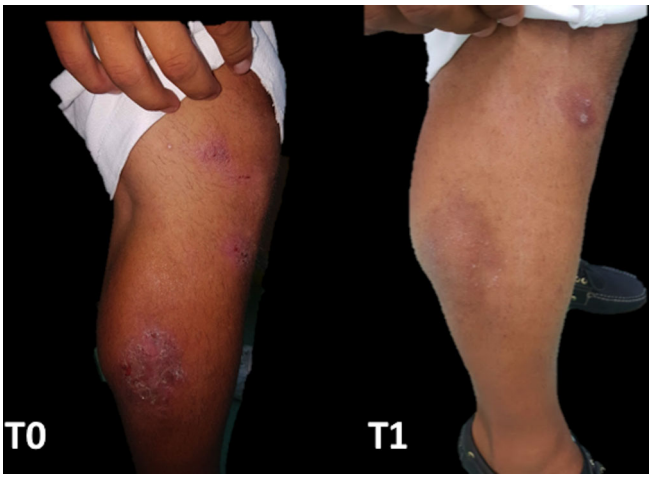

FIGURE 1 Nummular eczema phenotype of atopic dermatitis of the adult: before (T0) and after 16 weeks (T1) of treatment with dupilumab

Diagnosis of AD in adults is often challenging (Silvestre Salvador et al., 2017). Indeed, due to clinical heterogeneity, current diagnostic criteria are not able to detect the disease in many cases and specific diagnostic criteria for adults are lacking (Liu et al., 2016). Furthermore, no validated diagnostic biomarker is currently available (Bieber et al., 2017). Therefore, diagnosis is essentially clinical and clinician's experience is fundamental for differential diagnosis (Calzavara Pinton et al., 2018). In adults, AD more frequently affects face, neck, flexures of the limbs, and hands (Liu et al., 2016). However, NE and other atypical phenotypes may be observed (Silvestre Salvador et al., 2017). NE phenotype of AD seems to be particularly frequent in adult Asiatic patients: it was reported as clinical presentation in 413 of 2662 (15.5%) adult Chinese patients affected by AD (Liu et al., 2016). Our study seems to confirm these data. Indeed, NE phenotype accounted for 7.6% of 396 Caucasian patients with severe AD. Furthermore, different reports show that NE phenotype of DA may be resistant to the treatment with conventional drugs (Hello et al., 2016). In our experience, dupilumab was effective, as it significantly reduced skin symptoms improving quality of life in a series of 30 adult patients with severe NE phenotype of AD with an excellent safety profile. Therefore, dupilumab should be considered an effective and safe treatment in cases of NE phenotypes of AD resistant to traditional treatments.

CONFLICT OF INTEREST

C.P. acted as speaker and consultant for AbbVie, Novartis, Pfizer and Sanofi. L.S. acted as speaker and consultant for AbbVie, Almirall, Celgene, Lilly, Novartis and Sanofi. K.H. acted as speaker and consultant for AbbVie and Celgene. S.M.F acted as speaker for Novartis and AbbVie. G.F. acted as speaker and consultant for AbbVie and Leo Pharma. C.F. acted as a speaker for Sanofi. M.N. acted as speaker for Sanofi. The remaining authors declare no potential conflict of interest.

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