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References

- Di Giovanna JJ, Kraemer KH. Shining a light on xeroderma pigmentosum. *J Invest Dermatol*. 2012; **132**:785–96.
- Jacyk WK. Xeroderma pigmentosum in black South Africans. *Int J Dermatol*. 1999; **38**:511–914.
- Austerlitz F, Kalaydjieva L, Heyer E. Detecting population growth, selection and inherited fertility from haplotypic data in humans. *Genetics* 2003; **165**:1579–986.
- Fassihi H, Sethi M, Fawcett H et al. Deep phenotyping of 89 xeroderma pigmentosum patients reveals unexpected heterogeneity dependent on the precise molecular defect. *Proc Natl Acad Sci USA* 2016; **113**:E1236–45.
- Soufir N, Ged C, Bourillon A et al. A prevalent mutation with founder effect in xeroderma pigmentosum group C from North Africa. *J Invest Dermatol* 2010; **6**:1537–942.
- Cartault F, Nava C, Malbrunot AC et al. Gene splicing mutation has lead to the highest worldwide prevalence of xeroderma pigmentosum in black Mahori patients. *DNA Repair* 2011; **10**:577–585.
- Ijaz A, Basit S3, Gul A et al. XPC gene mutations in families with xeroderma pigmentosum from Pakistan; prevalent founder effect. *Congenit Anom (Kyoto)* 2019; **59**:18–21.
- Tahmankar PM, Iyer SV, Ravindran S et al. Clinical profile and mutation analysis of xeroderma pigmentosum in Indian patients. *Indian J Dermatol Venereol Leprol* 2015; **81**:16–22.
- Falik Zaccari TC, Erel-Segal R, Horev L et al. A novel XPD mutation in a compound heterozygote; the mutation in the second allele is present in three homozygous patients with mild sun sensitivity. *Environ Mol Mutagen* 2012; **53**:505–14.

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Treatment of moderate-to-severe atopic dermatitis with dupilumab in real clinical practice: a multicentre, retrospective case series

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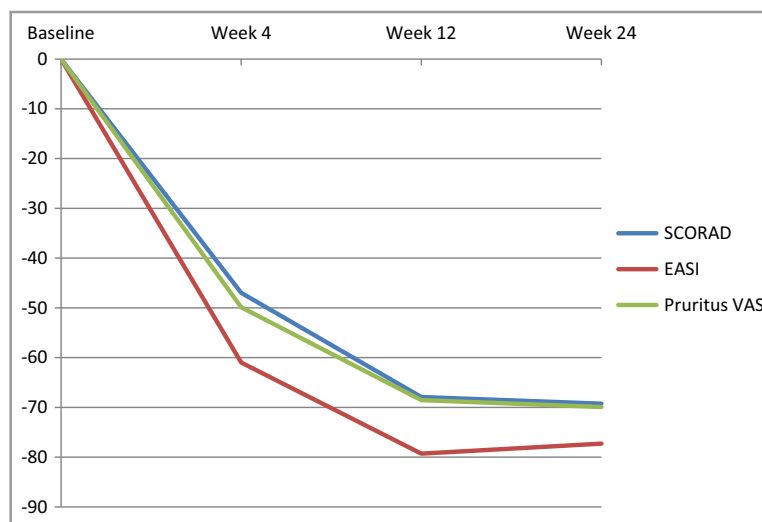
DEAR EDITOR, Atopic dermatitis (AD) is a chronic, inflammatory and pruritic skin disease, with a prevalence of 1–3% of the adult population.¹ The physiopathology of AD is multifactorial, with interaction of genetic disposition and environmental triggers coexisting with a marked skin barrier dysfunction and type 2-driven immune dysregulation. In AD, T helper 2 lymphocytes secrete several cytokines. Interleukin (IL)-4 and IL-13 play a key role in the proinflammatory loop, decreasing the expression of structural proteins of the epidermis, and leading to the formation of inflammatory and very pruritic lesions.² AD is frequently associated with elevated levels of serum IgE, individual or family history of type I allergies, allergic rhinitis and asthma.³ The strong burden of symptoms, systemic inflammation and comorbidities in these patients highly impairs their quality of life, resulting in a growing problem to healthcare systems.^{4,5}

Dupilumab is a fully human monoclonal antibody that targets IL-4 receptor subunit α , the common subunit of the type 2 cytokines IL-4 and IL-13, blocking signalling of both cytokines and consequently inhibiting the entire type 2 pathway.^{6,7} Its extended use has recently begun in Spain. As evidence of real-world experience with dupilumab is limited to date,⁸ it is necessary to assess the performance of this treatment in real clinical practice.

We present a series of 70 patients from 13 Spanish reference hospitals included in the expanded access programme of dupilumab for adult patients with moderate-to-severe AD, between October 2017 and May 2018. In total 79% of the patients were male, as women of childbearing potential were excluded following the inclusion criteria for the expanded access programme established by the Spanish Medicines and Medical Products Agency. The median age was 38.8 years (range 18–70) and the mean duration of AD evolution was 26.2 years (median 26, range 4–56). The main comorbidities were allergic rhinitis (57%), asthma (53%) and conjunctivitis (49%). Regarding previous treatments, all patients had received oral corticosteroids, 97% had used ciclosporin and 67% phototherapy. Overall, 31% of this cohort had used off-label biologic therapy (mainly omalizumab, ustekinumab, efalizumab and tralokinumab). In total 74% of the patients had undergone three or more previous systemic treatments.

Disease severity was measured by Eczema Area and Severity Index (EASI), Scoring Atopic Dermatitis (SCORAD) and pruritus visual analogue scale (VAS) scores at the baseline visit and at weeks 4, 12 and 24. Quality of life was assessed with Dermatology Life Quality Index (DLQI). The mean percentage changes in EASI, SCORAD and pruritus VAS are shown in Figure 1. At baseline, the mean EASI in this series was 28.1,

Fig 1. Mean percentage change in Eczema Area and Severity Index (EASI), Scoring Atopic Dermatitis (SCORAD) and pruritus visual analogue scale (VAS) scores from baseline through week 24 in patients treated with dupilumab.



SCORAD was 62.1 and pruritus VAS was 7.9. At the follow-up visit at week 24, EASI decreased to 6.5 (79.3% reduction), SCORAD diminished to 15 (by 69.3%) and pruritus VAS reduced to 2.4 (by 69.9%). Regarding quality of life, the mean baseline DLQI value was 13.2, reaching 4.9 (62.8% reduction) at week 24.

Concomitant treatment was prescribed according to clinical decision by the investigators. Topical corticosteroids or calcineurin inhibitors were used in 66 patients at baseline, maintaining their use to week 24 in 29 cases. Antihistamine use also diminished from 10 to seven patients during follow-up. Oral corticosteroids were prescribed to five patients at baseline, being necessary in two cases at week 24. No patients received concomitant systemic therapy.

The safety profile was favourable, with six reported cases of mild conjunctivitis, all in patients who had a history of allergic conjunctivitis. This was positively managed with ophthalmic corticosteroids and topical anti-H₁, without dupilumab withdrawal. No injection-site reactions were reported.

The clinical efficacy and safety of dupilumab in our series were consistent with those observed in clinical trials. Dupilumab improved significantly the signs and symptoms of AD, measured by EASI, SCORAD and pruritus VAS, as well as quality of life. The value added by this multicentre, retrospective study comes from the necessity of real-world assessment of new treatments addressing AD, as their performance has only been proven in clinical trials.

The limitations of this study are the small sample size and the short follow-up period. Future studies should assess the real clinical practice response to dupilumab in a broader population with longer follow-up periods. In this series, dupilumab showed a favourable efficacy and safety profile, especially in this long-evolution, multifailure, difficult-to-treat population, a faithful reflection of patients included in this type of expanded access programme. In real clinical practice, dupilumab must be considered as an effective and safe treatment in a broader population not only with severe disease. It could

also be a valuable therapeutic option for women of childbearing potential, who were excluded from this series.

Further research should investigate the different patterns of response to treatment according to different phenotypes, as AD has a tremendously heterogeneous pathology. Further work would also highlight the promising role of blocking IL-4 and IL-13 as upstream players in the inflammatory cascade and the clinical implications in real medical practice.

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References

- 1 Sicras-Mainar A, Navarro-Artieda R, Carrascosa Carrillo JM. Economic impact of atopic dermatitis in adults: a population-based study (IDEA Study). *Actas Dermosifiliogr* 2018; **109**:35–46.
- 2 Guttman-Yassky E, Bissonnette R, Ungar B et al. Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis. *J Allergy Clin Immunol* 2019; **143**:155–72.
- 3 Silvestre Salvador JF, Romero-Pérez D, Encabo-Durán B. Atopic dermatitis in adults: a diagnostic challenge. *J Investig Allergol Clin Immunol* 2017; **27**:78–88.

- 4 Silverberg JI. Selected comorbidities of atopic dermatitis: atopy, neuropsychiatric, and musculoskeletal disorders. *Clin Dermatol* 2017; **35**:360–6.
- 5 Boguniewicz M, Alexis A, Beck L et al. Expert perspectives on management of moderate-to-severe atopic dermatitis: a multidisciplinary consensus addressing current and emerging therapies. *J Allergy Clin Immunol Pract* 2017; **5**:1519–31.
- 6 Serra-Baldrich E, de Frutos JO, Jáuregui I et al. Changing perspectives in atopic dermatitis. *Allergol Immunopathol* 2018; **46**:397–412.
- 7 Sastre J, Dávila I. Dupilumab: a new paradigm for the treatment of allergic diseases. *J Investig Allergol Clin Immunol* 2018; **28**:139–50.
- 8 Ruiz-Villaverde R, Armario-Hita JC, Pereyra-Rodriguez JJ et al. Dupilumab: short-term effectiveness and security in real clinical practice – a retrospective multicentric study. *J Eur Acad Dermatol Venereol* 2019; **33**:e21–2.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Full list of author affiliations.

Postzygotic *HRAS* mutation in heterochromia of straight scalp hair

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DEAR EDITOR, The presence of hair of two distinct colours in the same person is a well-described phenomenon, termed heterochromia of the scalp.¹ Three different types of hair heterochromia have been described previously: patchy, segmental and diffuse. Various acquired (e.g. vitiligo, hair regrowth in alopecia areata) and genetic (e.g. Waardenburg syndrome, piebaldism, tuberous sclerosis) conditions may be accompanied by changes in hair colour. A variety of metabolic or nutritional defects, such as iron deficiency anaemia, may also give rise to acquired and usually reversible heterochromia.¹ Naevus-like distribution patterns such as patches or areas along the lines of Blaschko suggest postzygotic mosaicism. Heterochromia of the scalp along Blaschko lines without any associated feature has been reported in a small number of individuals.^{1–4} Postzygotic mosaicism for mutations in various genes is the recognized mechanism behind primary localized pigmentary anomalies and various types of naevi, including woolly hair naevus.⁵ We discuss the molecular basis of heterochromia of straight scalp hair in a boy with a systematized keratinocytic epidermal naevus.

A 12-year-old boy with brown hair and dark-blue eyes presented with an epidermal naevus on his back, upper chest and neck distributed in a linear pattern predominantly on the left

side of his body (Figure 1a, e). The lesions continued onto the scalp, where they consisted of erythema and scales with a Blaschko linear distribution pattern. The hair growing in these areas was blond, in contrast to the surrounding hair, which was brown (Fig. 1b, d). Both types of hair were macroscopically straight. The boy was otherwise healthy, and no asymmetry of the body was noted. No significant cutaneous disorders were reported in the family history.

Informed consent was obtained for further study. Skin biopsies were taken from the epidermal naevus, left retroauricular area and the neck (Fig. 1d, e). Haematoxylin and eosin staining showed acanthosis of the epidermis, elongation of the rete ridges and hyperkeratosis, consistent with a keratinocytic naevus (Figure 1f, g). Buccal swabs were obtained from both cheeks. Bulbs from the dark and blond hairs were obtained from the frontal area. DNA was isolated from formalin-fixed, paraffin-embedded tissue obtained from buccal swabs and hair bulbs (DNA kit; QIAGEN, Hilden, Germany). In a candidate approach, exon 2 of *HRAS*, *NRAS* and *KRAS* were analysed by polymerase chain reaction and subsequent Sanger sequencing performed as described previously.⁶ This revealed a heterozygous pathogenic variant *HRAS* (NM_005343.3) c.34G>A, p.Gly12Ser in lesional skin, the blond hair and, at a low level, in the mucosa of the left cheek. The mutation was not present in DNA extracted from the right oral mucosa or from the dark hair (Fig. 1h). No mutations were found in *NRAS* or *KRAS*.

Our findings demonstrate postzygotic mosaicism for a *HRAS* mutation in heterochromia of straight scalp hair distributed along Blaschko lines. Postzygotic *HRAS* mutations cause keratinocytic naevi, naevus sebaceus and Schimmelpenning syndrome, phacomatosis pigmentokeratitica and woolly hair naevus.⁵ Somatic *HRAS* mutations occur in various cancers (COSM480). Germline monoallelic *HRAS* mutations cause Costello syndrome, with c.34G>A (p.Gly12Ser) being the most common.

The *HRAS* proto-oncogene GTPase (*HRAS*) mutation p.Gly12Ser is located within the finger loop of *HRAS*, replacing a glycine residue with a slightly larger serine, which has been shown to be less activating than arginine, aspartic acid or valine substitutions.⁷ It is notable that *HRAS* p.Gly12Ser can cause both woolly hair and heterochromia of straight scalp hair. The mechanisms explaining these phenotypes remain elusive. This phenotypic divergence may derive from the presence of the mutant allele in different stem cell populations in the hair follicle in the two conditions. The melanocyte stem cells adhere directly to hair follicle stem cells, and reside in the hair follicle bulge-sub-bulge area, to serve as a melanocyte reservoir for skin and hair pigmentation.⁸ We hypothesize that *HRAS* p.Gly12Ser may affect melanocyte stem cells and influence hair colour.

The main limitation of this study is the fact that we studied one case only, owing to the rarity of this condition. Moreover, the number of plugged hairs and consequently the amount of DNA were limited, not allowing more extensive analyses. We hypothesize that there is genetic heterogeneity,

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