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Efficacy of Dupilumab for controlling severe atopic dermatitis with dominant-negative *CARD11* variant

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Dear Editor, Hypomorphic dominant-negative mutations in Caspase Recruitment Domain-containing Protein 11 (CARD11) is a rare cause of severe atopic dermatitis. (1) CARD11 is a membrane protein involved in TCR signalling via the NF- κ B pathway that has been identified as a predisposition locus for severe atopy. (2) A loss of function activity of CARD11 due to a dominant-negative effect of *CARD11* variant leads to severe atopic dermatitis associated with a defective T cell response that polarize toward a Th2 phenotype. (3) We report the successful treatment of severe atopic dermatitis with *dominant-negative CARD11* variant with Dupilumab.

A 47-year-old patient had a long history of severe chronic neutropenia from 9 to 35 years-old, spontaneously resolved and chronic eczema since childhood, an auricular polychondritis, aphthous stomatitis and recurrent dental infections complicated by complete edentulism at 37 years old. Whole-exome sequencing allowed the identification of the heterozygous p.Arg72Gln –c.215G>A variant located in the CARD domain of *CARD11*. His sister carrier of the same variant exhibited the same phenotype.

He developed at the age of 42 year old a severe, chronic and diffuse eczema associated with prurigo nodules involving lower and upper limbs and face. (Figure 1A-F). He was treated with prolonged ultra-high potency class I topical corticosteroid daily associated with oral corticosteroid cures with partial efficacy.

Standardized questionnaires revealed severe atopic dermatitis: SCORAD (scoring atopic dermatitis) 60/103, EVA pruritus 9/10, with a profound impaired quality of life, DLQI (dermatology life quality index) 21/30. Blood tests displayed normal eosinophilic rate. Skin biopsy confirmed the diagnosis of eczema.

Dupilumab was started subcutaneously with the dosing regimen approved for adult atopic dermatitis: 600 mg SC initially followed by 300 mg SC /14 days.

Within one month, he reported a rapid improvement allowing oral corticosteroid withdrawal.

At 6 months, he reported a dramatic clinical response with disappearance of eczema and prurigo lesions and improvement of clinical scores (SCORAD 16.5/103, EVA pruritus 4/10 and DLQI = 11/30). (Figure 1A-G). He was still in partial remission at 12 month without adverse events.

Main Th2 cytokines, involved in eczema and atopic dermatitis, include interleukin (IL)-4, IL-5, IL-13 and IL-31. (4) A recent ex vivo study of cytokine secretion profiles of lymphocytes from patients with *CARD11* loss of function found an increase in IL-5 without increase in IL-4 or IL-13 levels. (1) Dupilumab, an antibody directed against the IL-4R subunit α of IL-4 and IL-13 receptors shows efficacy in atopic dermatitis and prurigo by significantly reducing expression of genes involved in type 2 inflammation.(5–8)

This observation suggests that Th2-mediated signalling plays a central role in atopic dermatitis associated with dominant-negative *CARD11* variant. Dupilumab could be considered for these patients as a first line therapy.

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Figure legends

Figure 1

a–f Comparative photographs of the patient's skin lesions, taken before dupilumab initiation (upper panels) and after 6 months of treatment (lower panels).

Fig. 1

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