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Title: A single-center real-life experience on effectiveness and safety of dupilumab in adolescents with severe atopic dermatitis in treatment with cyclosporine A.

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Dupilumab, a fully human monoclonal antibody that inhibits the IL-4 receptor α subunit, has been recently approved for adolescents with inadequately controlled moderate-to-severe atopic dermatitis (AD). Although large clinical trials in adolescents have demonstrated its safety and efficacy^{1,2}, few real life data are still available³. Studies carried out required a 4-week washout period for any systemic immunosuppressants prior to starting dupilumab. However in clinical practice this procedure is not often performed.

To evaluate dupilumab treatment associated to systemic immunosuppressant in adolescents, in daily practice, clinical baseline data of adolescents with severe AD inadequately controlled with CsA and treated with dupilumab were collected. Evaluation was performed at baseline (T0) and at 4 and 16 weeks. Disease severity score was assessed through the Eczema Area and Severity Index (EASI)⁴, Investigator Global Assessment (IGA), Peak Pruritus Numerical Rating Scale (NRS-itch)⁵, VAS-sleep and Children's Dermatology Life Quality Index (CDLQI) questionnaire⁶. All patients received an induction dose of 600 mg (Dupixent®), then a subcutaneous 300 mg dose every 2 weeks. All the patients were on treatment with CsA at 5 mg/kg/day. The mean duration of CsA therapy was 37.6 weeks (**Table 1**).

Five adolescents (2 female and 3 males) treated with dupilumab for at least 16 weeks (mean 27.2 weeks, mean age to treatment 15.2y) from January to December 2020, were included. All patients had severe AD with visible areas involved⁷ and three patients had allergic comorbidities (**Table 1**). The mean EASI decreased from 26 at T0, to 11.4 and 10.75 at T4 and T16 respectively. The reduction between T0 and T16 was 15.25. Three patients achieved EASI 75, respectively at week 4, 16 and 32 (**Fig 1a**). Scores for disease severity and quality of life evaluation showed relevant improvements in all cases (**Fig 1b**).

Patient 1 had the highest EASI value at baseline (30) despite concomitant CyA therapy. After a first 65% reduction of EASI at T4, he experienced a severe rebound mostly on face and neck after a first attempt of CyA discontinuation at T8. It was therefore reintroduced at full dosage with adequate disease control and gradually tapered until final suspension at 24 weeks. Patient 4 stopped CsA at T4 due to the onset of gingival hyperplasia without presenting an exacerbation of the disease, but achieving an EASI score reduction of no more than 40%. During the follow-up no important side effects were detected and no patient suspended the biological therapy. Conjunctivitis occurred in three patients and subsided completely within 20 days of ophthalmologic therapy⁸.

All patients showed a reduction in EASI score and a gradual withdrawal of CsA with introduction of dupilumab. Curiously, the only patient who did not achieve EASI 50 suspended CsA after 4 weeks, due to onset of gingival hyperplasia⁹.

To our knowledge, there are no previous studies on dupilumab treatment in adolescents receiving CsA at T0. Our data on effectiveness of dupilumab are in line with

reports in literature and with the main trials in adolescents with AD^{1,2}. Interestingly the persistence of moderate EASI values observed was conditioned mainly by an average delayed improvement of the face and neck regions¹⁰. It is notable the only patient who experienced a flare-up of AD when CsA was discontinued at T8 had the highest EASI value at baseline (30).

In conclusion, we recommend a gradual discontinuation of cyclosporine after at least 8 weeks of dupilumab, to avoid rebound effects. Severe forms of atopic dermatitis (EASI $\geq$ 30), erythrodermic phenotype or cases with visible areas involvement, may present a slower improvement and could need a longer association with immunosuppressant. These observational data should be validated by larger studies.

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Table legend

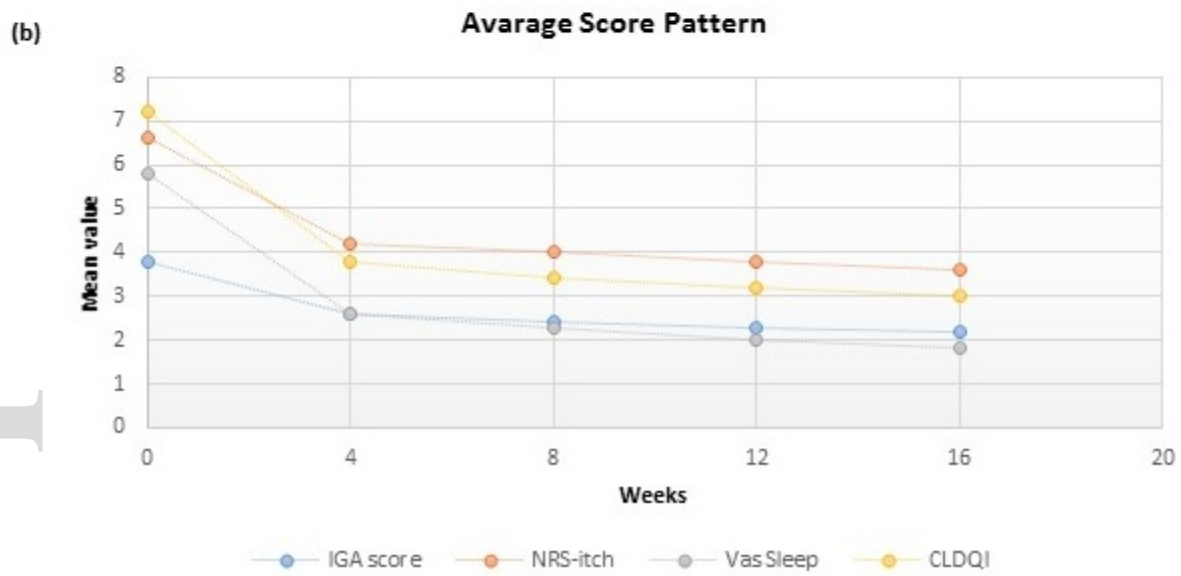
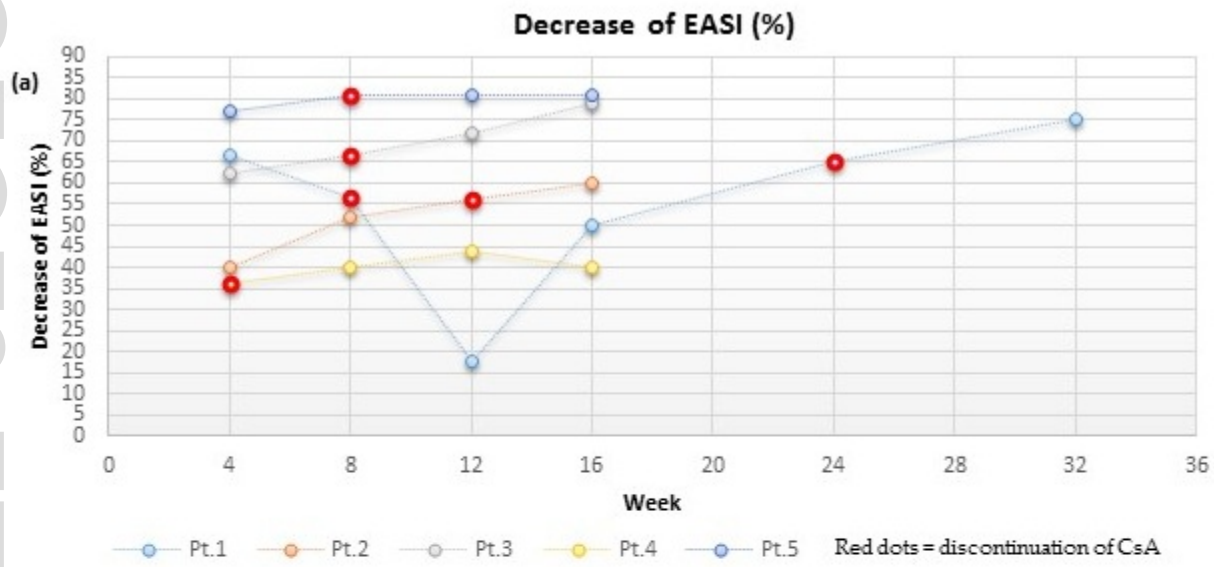
Table 1. Anamnestic summary of five adolescent patients with comorbidities, systemic medication and dupilumab adverse events. A.D: atopic dermatitis; F.A: food allergy; KCA: allergic keratoconjunctivitis; CsA: cyclosporine A; PT: phototherapy; SCS: systemic corticosteroids; AZA: azathioprine, MTX: methotrexate; AE: adverse event.

Figure legend

Fig. 1 (a) Percentage of EASI reduction from baseline. At T4 patient 5 (Pt. 5) achieved EASI 75, patients 1 and 3 presented a reduction of over 60% of EASI score. Patients 2 and 4 had a reduction of about 40% of the value. At T16 and at T32, patients 3 and 1 respectively achieved EASI75. Patient 4 maintained an EASI reduction of around 40%, patient 2 had a subsequent reduction of 20% of EASI score at T16. **(b)** Mean change from baseline in Investigator Global Assessment (IGA), Peak Pruritus Numerical Rating Scale (NRS-itch), VAS-sleep and Children's Dermatology Life Quality Index (CDLQI).

Table 1: Anamnestic summary of five adolescent patients with comorbidities, systemic medication and dupilumab adverse events.

PATIENT	SEX	AGE	AGE A.D ONSET	PHENOTYPE	VISIBLE AREAS	COMORBIDITIES	SYSTEMIC THERAPIES	AE DUPILUMAB
PT.1	M	17	1 M	ERYTHRODERMIC	FACE	SHELLFISH F.A, KCA	CsA, PT, SCS	BILATERAL CONJUNCTIVITIS
PT.2	F	17	3 M	CLASSIC	FACE	NONE	CsA, SCS, AZA, MTX	NONE
PT.3	M	13	3 M	GENERALIZED INFLAMMATORY	FACE	NONE	CsA, SCS	NONE
PT.4	M	16	12 M	GENERALIZED INFLAMMATORY	FACE, HANDS	RINITIS, ASTHMA	CsA, PT, SCS	BILATERAL CONJUNCTIVITIS
PT.5	F	13	4 Y (48 M)	CLASSIC	FACE	RINITIS, HYPOTHYROIDISM, HYPEREOSINOPHILIA	CsA, SCS	BILATERAL CONJUNCTIVITIS



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