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Article type : Letter to the Editor

Effect of dupilumab on atopic manifestations in patients treated for atopic dermatitis in real life practice

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bjd.17629

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Funding sources: none

Conflict of interest disclosures: CP: Investigator and consultant for Sanofi-Regeneron, for the other authors: none declared.

Dupilumab has demonstrated efficacy in atopic dermatitis (AD)¹⁻³, asthma⁴, perennial allergic rhinitis⁵ and chronic sinusitis⁶. The objectives of this prospective observational, single-centre study were to assess 1) dupilumab efficacy in real-life practice and 2) the evolution of atopic comorbidities and specific immunoglobulin E (IgE) levels during dupilumab treatment.

All adult patients with moderate-to-severe AD who displayed contraindication, failure or intolerance to ciclosporin were eligible to receive dupilumab in the context of a national patient access program authorized by the French medical agency. AD and atopic comorbidities were evaluated using the SCORAD (SCORing AD), visual analogue scales (VAS) for sleep and pruritus, Investigator's Global Assessment (IGA), topical treatments used during the last month, Dermatology Life Quality Index (DLQI), Asthma Control Test (ACT), fractional exhaled nitric oxide (FeNO), spirometry and complete ophthalmologic and ear nose and throat (ENT) examinations. The concentrations of total and specific IgE (tIgE, sIgE) directed against allergen extracts of *Malassezia spp.* or *Staphylococcus aureus* enterotoxins were measured using the ImmunoCAP™ technique (ICAP). ImmunoCAP™ ISAC 112 IgE biochip was also performed in all patients.

Nineteen patients were included (15 men, 79%) with a median age of 38 years. Follow-up efficacy data, available for 18 patients, were reported as observed. Ten patients had more than two atopic comorbidities including asthma (n=15), allergic rhinitis, allergic conjunctivitis or food allergy. Total IgE serum level was above normal in all patients but one. The median SCORAD was 49 (IQR: 32.5-58.5) with median pruritus and sleep VAS scores of 5 and 3. Eleven patients had a DLQI $\geq$ 10. Of note, there was neither overlap therapy nor wash-out period in the whole cohort. The median ACT score was 20.5 indicating controlled asthma, the median FeNO was normal at 15 ppb (IQR: 10-34), as well as the spirometry measures. The ophthalmologic examination was abnormal in ten patients at inclusion with one acute allergic conjunctivitis, six dry eye syndromes, five conjunctival papillae and two blepharitis. The ENT examination showed two cases of seasonal rhinitis and 13 cases of perennial rhinitis or rhinosinusitis (five with marked mucosal oedema). At week 16, the median SCORAD decreased by 55% (IQR: 28.2-74) ($p < 0.001$, Fig. 1a). Twenty-two percent of patients achieved a reduction of $\geq 75\%$. Fourteen patients had at least an 8.7 points improvement in their

SCORAD indicating a clinically relevant improvement⁷. The percentage of patients with an IGA 0/1 increased from 5% to 61% ($p<0.01$). The DLQI, pruritus and sleep VAS scores and the amount of topical potent corticosteroids (Figs 1b-d) and tacrolimus (data not shown) also decreased significantly. There were no significant changes in ACT and spirometry in the whole cohort and in the subgroup of patients with a baseline ACT score below 20 indicating uncontrolled asthma ($n=8$). A significant decrease in the FeNO was observed with a median value of 10 ($p<0.05$, Fig. 1e). All six patients with an elevated FeNO at inclusion normalised their values at week 16. The ophthalmologic examination at week 16 showed a worsening of the conjunctivitis in $n=5/10$ patients, stability in $n=4/10$ patients and improvement in one. Three patients developed *de novo* conjunctivitis. One of them experienced severe bilateral kerato-conjunctivitis. No patient had to stop dupilumab. The ENT examination at week 16 showed stability for $n=10/15$ patients, improvement for $n=4/15$ patients and worsening in one. The median tIgE plasma level decreased at week 16 with a median of 2447kU/l compared to 5157 before dupilumab initiation ($p<0.001$, Fig. 1f). There was a significant decrease of the sum of sIgE measured by ISAC. sIgE antibodies to *S. aureus* or *Malassezia* decreased for respectively 88% and 71% of patients. The decrease in tIgE was positively correlated with the decrease in anti-*Malassezia* ($p=0.01$). There was no correlation between clinical response as assessed by SCORAD and decreases in total or sIgE levels to *S. aureus* and *Malassezia*.

Dupilumab reduces global severity, pruritus, sleep loss and improves quality of life in AD in real-life clinical practice. In the four available phase 3 RCTs the least-squares mean percent reduction in SCORAD at week 16 varied from 50 to 63 compared to a mean percent reduction of 50.1 in our cohort¹⁻³. This discrepancy may be due to a higher baseline severity of the patients included in RCTs than in our cohort because of the absence of a wash-out period (artificially increasing the AD severity at randomization) in real-life clinical practice. The significant decrease of FeNO under dupilumab may be interpreted as a marker of IL-4/IL-13 blockade as the NO is produced with chronic airways inflammation⁸. Conjunctivitis was reported in up to 28% of patients^{1-3,9}. IL-4/IL-13 blockade may increase the activity of the OX40 ligand involved in atopic kerato-conjunctivitis⁹. The precise mechanism of conjunctivitis remains undetermined. Conjunctivitis requires collaboration with an experienced ophthalmologist. We recommend a graded approach, with artificial tears followed by antiallergic or steroids drops. For resistant cases, we recommend ciclosporin drops. No significant correlation was seen between IgE reduction and AD severity. Limitations of this study include the small numbers of patients, the single-centre and observational nature and the short follow-up period. Longer term observational studies should confirm that dupilumab improves atopic co-morbidities in real-life practice.

Figure legend

Figure 1. Dupilumab efficacy in real life practice.

Boxplot of AD-related clinical severity measured by the SCORAD (a), quality of life measured by the DLQI (b), pruritus and sleep loss VAS scores (c), total amount in grams of highly potent topical corticosteroids used by patients in the last month (d), exhaled nitric oxid (e) and total IgE plasma level (f) before (left box) and after 16 weeks of dupilumab treatment (right box). *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

Abbreviations: DLQI= Dermatology Life Quality Index; IgE= Immunoglobulin E; SCORAD= SCORing Atopic Dermatitis; VAS= Visual Analogical Scale.

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