Dupilumab (DUPI) is an anti-interleukin-4-receptor-α monoclonal antibody that blocks signalling of interleukin 4 and interleukin 13, which are involved in numerous allergic diseases ranging from asthma to atopic dermatitis (1). DUPI was approved as first-line treatment for moderate-to-severe adult atopic dermatitis (AD) in 2017. We report here our experience of DUPI in children with AD.

PATIENTS, METHODS AND RESULTS

A monocentric retrospective observational analysis was conducted of 4 cases of children with AD treated with DUPI after failure of other conventional treatment. Clinical efficacy was assessed using body surface area (BSA), SCORing Atopic Dermatitis (SCORAD) score, and Investigator Global Assessment (IGA). Subjective symptoms, including pruritus and insomnia, were quantified using a numerical rating scale (NRS) ranging from 0 to 10 at weeks W0, W4, W16 and W52. Global tolerance was also evaluated.

All patients received a loading dose of 600 mg, then a 300 mg dose of DUPI every 2 weeks via subcutaneous injections, as prescribed for adults with AD. DUPI was administered by a home nurse. Other systemic AD therapies were prohibited, but allowed as rescue treatment for intolerable symptoms. Topical corticosteroids during the first 3 months of DUPI treatment. Other immunosuppressive treatments were not required.

Demographic and clinical-biological characteristics

Four adolescents were included (1 female and 3 males). The mean age at initiation of DUPI was 16.75 years (range 16–17 years). The mean ± standard deviation (SD) duration of progression of AD was 17 ± 0.9 years and the age of onset of signs was 4.5 ± 1.5 months. The mean ± SD follow-up time was 14.5 ± 5.9 months.

All patients had allergic rhinitis and a nut allergy; 3 had allergic asthma. Fifty percent of patients had a history of recurrent herpes and, among them, one patient had herpes virus Kaposi-Juliusberg syndrome; and one patient had regular xerophthalmia and atopic blepharoconjunctivitis. All patients had been treated locally (corticosteroids and tacrolimus), 3 (75%) had received methotrexate for 25.4 ± 5.9 months.

Table I. Dupilumab in paediatric patients with atopic dermatitis

<table>
<thead>
<tr>
<th>Study</th>
<th>Cork et al. (2)</th>
<th>Simpson et al.1</th>
<th>Treister &amp; Lio (3)</th>
<th>Present study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>40</td>
<td>251</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Dosage</td>
<td>2 or 4 mg/kg</td>
<td>DUPI 300 mg q4w</td>
<td>DUPI 200 mg/300 mg q2w</td>
<td>DUPI 600 mg and 300 mg q2w</td>
</tr>
<tr>
<td>Reduction in SCORAD at W16 (%)</td>
<td>EASI score –81% and –82%</td>
<td>–47.5</td>
<td>–51.6</td>
<td>ND</td>
</tr>
<tr>
<td>IGA 0–1 at W16 (%)</td>
<td>10% and 35%</td>
<td>17.9</td>
<td>24.4</td>
<td>50</td>
</tr>
<tr>
<td>Improvement in pruritus NRS score ≥ 4 at W16 (%)</td>
<td>ND</td>
<td>26.5</td>
<td>36.6</td>
<td>ND</td>
</tr>
<tr>
<td>Reduction in pruritus NRS score (%)</td>
<td>–61% and –66%</td>
<td>–45.5</td>
<td>–47.9</td>
<td>ND</td>
</tr>
</tbody>
</table>

SCORAD: SCORing Atopic Dermatitis; EASI: Eczema Area and Severity Index; IGA: Investigator General Assessment; NRS: numerical rating scale; ND: not determined.

Clinical evaluation of dupilumab efficacy

The mean SCORAD decreased from 57.5 at W0 to 24.9, 15.5 and 9.4 at W4, W16 and W52, respectively. The reduction in mean SCORAD from W0 to W4, W16 and W52 was −58%, −73% and −84%, respectively (Table I).

At initiation of DUPI treatment, all patients had an IGA score ranging between 3 and 4. At W16, 75% of patients were IGA 0 or 1; at W52, 100% of patients were IGA 0 or 1.

Mean BSA decreased from 38.75% at W0 to 12.5% at W4, 6% at W16, and 4.34% at W52.

Mean pruritus NRS score decreased from 6.7 at W0 to 5.3, 3.7 (~45%), and 1.5 at W4, W16 and W52, respectively. The mean reduction in pruritus NRS score was 3 points at W16 and 5.2 points at W52. Regarding sleep, the mean insomnia NRS score decreased from 5.3 at W0 to 3.3, 2.7, and 0.5 at W4, W16 and W52, respectively.

Topical steroids and/or tacrolimus were stopped by 3 patients. Only patient 1 presented with AD flares requiring topical treatment with topical corticosteroids during the first 3 months of DUPI treatment. Other immunosuppressive treatments were not required.

Safety

The mean duration of follow-up of DUPI patients was 8.25 months. During this period, 3 patients presented at least one side-effect that occurred a mean of 1.25 months after starting treatment. No injection site reaction was reported.

Conjunctivitis was observed in 75% of patients. Patients 1 and 2 developed grade 1 conjunctivitis requiring the use of artificial tears. Patient 3 with no history of blepharoconjunctivitis, experienced grade 3 conjunctivitis occurring at M3, which was successively treated with antimistraine eye drops, corticosteroid eye drops, and topical tacrolimus without efficacy. DUPI was then stopped at M6 and ocular symptoms disappeared within 3 months.

Two patients with previous history of herpes infection demonstrated recurrence of grade 1 herpes occurring a mean of 1.5 months after starting treatment. In both cases, prognosis was favourable and did not require discontinuation of DUPI.
DISCUSSION

Although there is a pressing need to try DUPI in paediatric patients who are struggling with AD, data on the use of DUPI in this population are very limited (Table I).

An open-label phase II study and subsequent phase III study of 40 adolescents (2) has demonstrated up to 82% improvement in Eczema Area and Severity Index (EASI) scores. Pruritus NRS improved from baseline by a mean of 61% in the lower-dose group and 66% in the higher-dose group.

Results from a phase III study of 251 adolescents with AD treated with DUPI were reported recently (1). At W16, 24.4% of patients were IGA 0 or 1, compared with 75% in our series and the mean reduction in SCORAD was 51.6% vs. 73% in our cohort. The reduction in mean pruritus NRS score of 47.9% at week 16 was observed compared with 45% in our study.

Treister & Lio (3) have evaluated the efficacy and tolerance of DUPI in 6 children with a mean age of 10.8 years. Their results were similar to those reported in our study, with a mean reduction in IGA score of 2.5 compared with 2.58 in our series.

Compared with double-blind, randomized, placebo-controlled, phase III studies in adults (4–7), the reduction in SCORAD at W16 was 57.7, 53.1 and 63.9%, respectively, vs. 73% in our series, and at W52, 100% of our patients had an IGA of 0 or 1 vs. 36% in the CHRONOS study (7). We also observed a 3-point reduction in pruritus score at week 16, as in the previous studies (4–7).

In terms of clinical efficacy, our results are thus consistent with, and even superior to, those previously reported in paediatric patients and in the original adult studies. However, it should be noted that the paediatric dosage of DUPI is still not determined and may vary between studies.

In our study, the 2 main side-effects of DUPI were conjunctivitis and recurrence of herpes infection.

In a recent analysis of pooled data from 7 randomized, double-blinded, placebo-controlled clinical trials of DUPI in adults with AD, rates of herpesviral infections were slightly higher with DUPI, mostly those due to oral herpes (8).

Conjunctivitis was observed in 75% of our patients, including one requiring discontinuation of DUPI. Patients with AD treated with DUPI had a greater incidence of conjunctivitis (8.6–22.1%) (9). However, a higher frequency of conjunctivitis (38%) was reported in a real-life French multicentre retrospective cohort (10). The exact pathogenesis of conjunctivitis events observed during DUPI treatment is unknown. The development of conjunctivitis was associated with several disease-based factors, including baseline AD severity and previous history of conjunctivitis (9, 10). Currently, there is no consensus on optimal approaches to prevent and manage conjunctivitis in DUPI-treated patients (11).

In conclusion, our results confirm that DUPI is an effective treatment option for adolescents with moderate to severe AD. Data from multicentre, prospective trials are still required to support optimal paediatric dosing (12).

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Conflicts of interest: FA has paid activities as a consultant, advisor or speaker for Abbvie, BMS, Celgene, Novartis, Leo Pharma, and Sanofi. EP has paid activities as a consultant, advisor or speaker for BMS and Sanofi. AM has no conflicts of interest to declare.

REFERENCES