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CASE REPORT OPEN ACCESS

Hyperthyroidism in a 15-year-old adolescent treated with Dupilumab for severe allergic asthma and atopic dermatitis

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Abstract
Dupilumab is a biologic, acting on IL-4 and IL-13 pathways. Dupilumab has a pediatric indication for treating severe asthma and atopic dermatitis. We report a pediatric case concerning paucisymptomatic, transient, and self-resolving hyperthyroidism. The updated literature includes the case of an adult patient who reported with hyperthyroidism, which was transient and self-resolving. Despite that these cases were transient and self-resolving, we would suggest that thyroid function assessment could be included in the follow-up of patients treated with Dupilumab. Dupilumab discontinuation is not required pending endocrinological assessment, mainly if there is an optimal clinical response to the biologic.

Introduction

Dupilumab is a fully human monoclonal antibody (IgG4) that blocks interleukins 4 (IL-4) and 13 (IL-13), the key cytokines in type 2 inflammation. In particular, this biologic acts by binding to the α-chain (IL-4R) of both ligand-binding domains (IL-4R/ IL-13R1; equally IL-4 and IL-13 specific) of the IL-4 receptor.[1] Its efficacy and safety in the treatment of moderate-severe asthma with eosinophilia has been well established.[2,3]

Concerning the pediatric age, Dupilumab has also been approved for use as a treatment option for severe atopic dermatitis since 2020.[4,5] Furthermore, in Italy, in 2022, the AIFA (Agenzia Italiana del Farmaco) has also approved the reimbursement of the drug for treating severe atopic dermatitis in the 6-11-year-old age group.

Other potential new off-label indications include other skin diseases (such as prurigo nodularis, nummular eczema, allergic contact dermatitis, chronic hand eczema, spontaneous chronic urticaria, alopecia areata, bullous pemphigoid, and Netherton syndrome) and as well as respiratory diseases (such as allergic bronchopulmonary aspergillosis, chronic eosinophilic pneumonia, and allergic rhinitis). Other new research horizons include conditions such as eosinophilic

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gastrointestinal disorders (particularly eosinophilic esophagitis) and food allergy.[6]

Although the tolerability of the drug proved to be good among the children treated at our clinic, we now report an unusual case of a patient with hyperthyroidism, occurred during Dupilumab therapy for severe allergic asthma and atopic dermatitis. Only one similar case has been reported in the literature concerning a 49-year-old patient who presented with hyperthyroidism and thyroiditis with lymphocytic infiltration 4 months after starting Dupilumab therapy.[7] In that case, the initial hyperthyroidism changed to hypothyroidism after 3 weeks. However, given the excellent skin response to Dupilumab treatment, therapy was continued in the patient with spontaneous normalization of thyroid function after 6 months, without specific therapies.

To our knowledge, the present patient should be the first described case of iatrogenic hyperthyroidism by Dupilumab in pediatrics.

Case Illustration

Clinical presentation

Family history was missing as the child was adopted. He was of Asian origin and also a carrier of a Thalassemic trait.

Regarding dermatological diseases, the patient had congenital ichthyosis vulgaris, although no data regarding the particular genetic subtype are available. The patient suffered from atopic dermatitis from the first months of their life. The patient was also treated with systemic corticosteroid courses for long periods and off-label cyclosporine once. The atopic dermatitis had gradually improved over the years, and emollient creams and topical corticosteroids are sufficient presently.

Concerning endocrine diseases, the patient was monitored for short stature (−2.2 SD), perhaps also as a consequence of the prolonged treatment with systemic corticosteroids. At the age of 12, an Arginine test demonstrated a reduced growth hormone (GH) peak (7.85ng/mL). This GH defect was confirmed 4 months later using the Insulin tolerance test (GH peak 3.65ng/mL). Therefore, replacement therapy with somatotropin was started, still ongoing at a dosage of 0.027 mg/kg/day. However, the stature gap from the parental genetic target could not be determined due to a lack of data on the biological parents. The progression of pubertal development was regular, with sex hormones in the normal range. No thyroid disorder was reported in the personal (and, of course, family) history.

Regarding allergic diseases, the patient suffered from egg allergy. The intake of eggs was gradually introduced after an oral provocation test performed in 2021. Presently, he suffers from polysensitization to common inhalants, foodstuffs (hazelnut, peach, egg, and kiwi), and hymenopter venom (yellow wasp). In addition, the patient has severe allergic asthma (resistant to inhaled corticosteroids, even at high dosages) from preschool age. In October 2020, despite high-dose inhaled corticosteroids (Fluticasone 500 µg/day) associated with long-acting ß2-agonist (Formoterol 20 µg/day), the patient was hospitalized due to severe asthma exacerbation. In January 2021, Dupilumab was started due to poor asthma control associated with atopic dermatitis. The schedule considered a subcutaneous injection every 14 days with an initial dosage of 200 mg (corresponding to approximately 6mg/kg).

During Dupilumab therapy, inhaled corticosteroids were maintained at the same dosage. After a few months, asthma control markedly improved, the daily need for bronchodilators significantly diminished, and he had no more asthma exacerbations. However, the lung function assessment showed a mild bronchial obstruction, and the bronchodilation test was inconstantly positive. Consistently, atopic dermatitis improved with rare flares. The SCORAD (SCORing Atopic Dermatitis) score (updated to April 2022) was 4 points, indicating mild disease severity.

Figure 1 shows the total serum IgE levels from 2 years before Dupilumab started (January 2021) to January 2022. The trend improved after the start of therapy. The result was even more important considering the values reported in 2012 (24,600 KU/L).

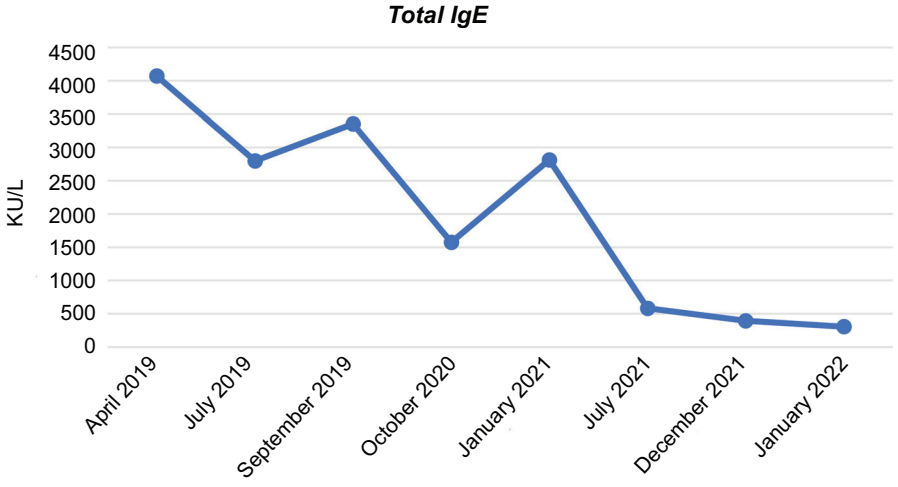

Figure 1 The total serum IgE levels from 2 years before start of Dupilumab (January 2021–January 2022).

Diagnostic workup

In April 2022, during a routine endocrinological visit, the patient reported of the appearance of asthenia and thermophylia. The first assessment of thyroid function was normal, even if FT4 was in the upper tertile of the reference range (thyroid-stimulating hormone [TSH] 0.893 μU/mL, FT4 1.52 ng/mL). On reassessment (3 weeks later), TSH was below the normal range (0.283 μU/mL) and FT4 was above the reference range (2.29 ng/dL), as was FT3 (14.8 pg/mL). Antithyroid and anti-TSH-receptor antibodies were absent. Table 1 shows the thyroid function trend.

Serum thyroglobulin was normal (3.95 ng/mL; reference range 1.4-78 ng/mL). A neck ultrasound showed no relevant morpho-structural alteration other than a slightly below-normal gland size.

Therapeutic intervention

As referred symptoms were not clinically relevant, no specific therapy was started, but monitoring of hormones, blood pressure, and heart rate was prescribed. As a precautionary measure, Dupilumab was discontinued. Subsequent evaluations showed FT4 normalization after 1 week and TSH normalization after 2 weeks. At the subsequent quarterly follow-up, the thyroid function always remained normal, and the patient never presented symptoms attributable to hyperthyroidism. However, as asthma control and atopic dermatitis worsened, Dupilumab therapy was restarted in August 2022.

Current status

At the last follow-up (October 2022), the patient had well-controlled asthma, used bronchodilators very rarely, eosinophil count was normal, had no asthma exacerbation, and atopic dermatitis was controlled (SCORAD 3). In addition, thyroid function was normal (TSH 1.42; FT4 1.24; FT3 3.18) and autoantibodies were still absent: TPO 18 (normal range 0-115). TGA < 9 (normal range 0–34) and anti-TSH receptor was 0.8 (normal range 0–1.2).

Discussion

Based on the best of our knowledge, this was the first pediatric patient who reported with hyperthyroidism during Dupilumab therapy. The only other reported case in the literature was that of an adult patient.[7]

The clinical characteristics of the two patients were different in different aspects, as reported in Table 2.

While the present patient was paucisymptomatic, the adult patient had hyperthyroidism signs (such as tachycardia, fatigue, mild hypertension, and goiter). Notably, the current case reported of thermophylia, paradoxically attributable to hypothyroidism. Nevertheless, both patients

Table 1 Thyroid function parameters over time.

	April 2022 (after 14 months of treatment)	+3 weeks	+4 weeks	+5 weeks	+6 weeks	+15 weeks	+16 weeks
TSH (Ref. range 1–5 μU/mL)	0.893	0.283	0.223	1.45	1.3	0.939	1.990
FT4 (Ref. range 0.9–1.53 ng/dL)	1.52	2.29	1.03	1.07	1.35	1.38	1.04
FT3 (Ref. range 3.1–4.8 pg/mL)		14.8	3.28	3.07	4.43	3.29	

TSH: Thyroid-stimulating hormone

Table 2 Clinical characteristics observed in the two patients with hyperthyroidism during Dupilumab treatment.

	Patient 1 (Present case)	**Patient 2** (Ref. 7)
Ethnicity	Asian	Asian
Age (years)	15	49
Clinical signs/symptoms	Asthenia and thermophylia	Leg edema, fatigue, neck discomfort, mild blood hypertension (140/82 mmHg), tachycardia (108 beats/min), and goiter
Latency from the Dupilumab start (months)	14	2
Ultrasound exam	Substantially negative	Enlarged thyroid gland, with a diffuse hypoechoic area in the left lobe.
Autoantibodies	Negative	Negative
Histological study	Not performed	Lymphocyte infiltration
Scintigraphy	Not performed	Low radioiodine uptake in the thyroid

improved without therapeutic intervention. Interestingly, both patients belonged to the Asian ethnicity. Presently, we cannot exclude that the Asian ethnicity could represent a risk factor for thyroid dysfunction during Dupilumab treatment. However, this hypothesis requires further investigations.

The analysis of the safety reports from Dupilumab trials for atopic dermatitis treatment has produced reassuring data about adverse events. There are no other reports of thyroid dysfunction till now. In particular, in the SOLO 1 and SOLO 2 trials, the most common adverse events were exacerbation of atopic dermatitis, injection site reactions (mostly mild or moderate), and nasopharyngitis. In addition, allergic conjunctivitis was also reported as a possible adverse event.[8] Concerning pediatric trials, the reported adverse events were comparable with adult studies. A study including 6–12-year-old children reported that nasopharyngitis and exacerbation of atopic dermatitis were the most frequent side effects. The overall number of adverse events was higher in patients dosing at 4 mg/kg than in those dosing at 2 mg/kg, particularly when considering skin infections, cough, and infectious dermatitis. Injection site reactions and conjunctivitis were mild, occurring in the 4 mg/kg dose group alone. The overall incidence of severe adverse events was low, with only two patients experiencing severe treatment-emergent adverse events (TEAEs), both belonging to the 4 mg/kg dose group. These events included bacterial arthritis, infectious dermatitis, and atopic dermatitis exacerbation that were judged unrelated to treatment. None of the above events led to the permanent discontinuation of the therapy. In the open-label extension version of the study, the trend in adverse events was similar.[9] Similar data were reported in the adolescent age group (12–18 years). Among 1131 adverse events reported in the study, only 120 were considered attributable to treatment; 12 were severe, and 5 were serious: with one event each of ductus arteriosus pervious, injection site edema, food allergy, herpes simplex infection, and ankle fracture. None of these led to treatment discontinuation. Only one event of moderate bilateral conjunctivitis and one of moderate worsening of atopic dermatitis led to treatment discontinuation. Some unusual events were reported, such as severe viral conjunctivitis, severe allergic conjunctivitis, mild atopic keratoconjunctivitis, mild suicidal ideation, moderate depression, and a moderate allergic reaction to eggs. The most frequently reported TEAEs were nasopharyngitis, upper respiratory tract infection, and headache. Others consistently reported of injection site reactions, bacterial conjunctivitis, viral conjunctivitis, allergic conjunctivitis, and atopic keratoconjunctivitis.[10,11] Interestingly, it has also been reported that the transient increase in peripheral eosinophils and basophils usually associate with conjunctivitis.[12]

Therefore, according to the literature, there are no pediatric cases that reported of hyperthyroidism.

The possible mechanism implicated in the altered thyroid function is currently unknown and certainly needs to be investigated further in future studies. However, it is likely that, as already mentioned in the previous case report, the prolonged use of the biologic might lead to lymphocytic infiltration of the thyroid. In other words, thyroiditis could occur independently of autoimmunity, as autoantibodies were absent, or at least not demonstrable at the time of withdraw of blood samples. This pathogenic mechanism could be linked to the characteristics of Dupilumab. Namely, this biological drug inhibits the IL-4 and IL-13 pathways, indirectly dampening type-2 immune response and consequently promoting type-1 immunity expansion. Consistently, type-1 polarization may be associated with thyroiditis development.[13] As a result, the reduced quote of IL-4-positive lymphocytes (due to the Dupilumab effect) could increase the risk of developing thyroiditis and, potentially, autoimmune disorders.[14]

Conclusions

Although only two cases have been reported until now, the present case suggests that thyroid function assessment could be assessed in the follow-up of children treated with Dupilumab. Thyroid hormones such as TSH may also reflect transient and mild changes in thyroid function, as reported in the present case. It also has to be underlined that the present case had vague symptoms, even paradox, such as thermophylia. Moreover, if the physical examination reveals a thyroid enlargement, neck ultrasound and, eventually, thyroid scintigraphy are indicated, and antithyroid autoantibodies and thyroid biopsy could complete the workup, if necessary.

On the other hand, these reported cases showed that thyroid hyperfunction was transient and self-resolving. Consequently, there is no reason need to discontinue Dupilumab pending endocrinological assessment, mainly if there is a good clinical response to the biologic.

Conflicts of Interest

The authors declare that there are no conflicts of interest to disclose.

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