
Article:
Paller, A.S., Wollenberg, A., Siegfried, E. et al. (2021) Laboratory safety of dupilumab in patients aged 6–11 years with severe atopic dermatitis : results from a phase III clinical trial. Pediatric Drugs, 23 (5). pp. 515-527. ISSN: 1174-5878

https://doi.org/10.1007/s40272-021-00459-x

Pediatric Drugs (2021) 23:515–527
https://doi.org/10.1007/s40272-021-00459-x

ORIGINAL RESEARCH ARTICLE

Laboratory Safety of Dupilumab in Patients Aged 6–11 Years with Severe Atopic Dermatitis: Results from a Phase III Clinical Trial

Amy S. Paller[1] · Andreas Wollenberg[2] · Elaine Siegfried[3] · Diamant Thaçi[4] · Michael J. Cork[5] · Peter D. Arkwright[6] · Melinda Gooderham[7,8] · Xian Sun[9] · John T. O'Malley[10] · Faisal A. Khokhar[9] · Jignesh Vakil[11] · Ashish Bansal[9] · Karli Rosner[12] · Brad Shumel[9] · Noah A. Levit[9]

Accepted: 23 June 2021 / Published online: 31 August 2021

Abstract

Background Previous studies of dupilumab in adolescents and adults with moderate-to-severe atopic dermatitis (AD) showed no clinically meaningful adverse changes in laboratory parameters.

Objective The aim of this study was to assess laboratory outcomes in children aged 6–11 years with severe AD in a randomized, placebo-controlled, phase III trial of dupilumab.

Methods Children aged 6–11 years with severe AD were randomized 1:1:1 to 16 weeks of dupilumab 300 mg every 4 weeks, 100 or 200 mg every 2 weeks, or matching placebo, all with concomitant topical corticosteroids (TCS). Blood samples were collected at baseline and Weeks 4, 8, and 16; urine samples were collected at baseline and Weeks 4 and 16.

Results Of 367 patients enrolled in the study, 362 were included in the safety analysis, 351 completed study treatment, and 4 withdrew due to treatment-emergent adverse events not related to laboratory abnormalities. Both dupilumab + TCS groups showed overall trends toward increases in mean blood levels of eosinophils and alkaline phosphatase, and decreases in mean blood levels of platelets, neutrophils, and lactate dehydrogenase levels, without corresponding mean changes in the placebo + TCS group. None of these changes were associated with symptoms or clinically meaningful adverse outcomes, and none led to treatment modification. No clinically significant changes or trends were observed for other measured laboratory parameters.

Conclusion There were no clinically meaningful adverse changes in routine laboratory parameters attributable to treatment with dupilumab + TCS. Changes in platelet counts and lactate dehydrogenase levels likely reflect reduced inflammation. These results confirm similar findings in adults and adolescents, and suggest that there is no need for routine laboratory monitoring of children aged 6–11 years treated with dupilumab + TCS for severe AD.

Trial Registration ClinicalTrials.gov Identifier: NCT03345914.

Digital Features for this article can be found at https://doi.org/10.6084/m9.figshare.14825760.

✉ Noah A. Levit
noah.levit@regeneron.com

1 Northwestern University Feinberg School of Medicine, Chicago, IL, USA

2 Ludwig Maximilian University of Munich, Munich, Germany

3 Saint Louis University, St. Louis, MO, USA

4 Institute and Comprehensive Center for Inflammation Medicine, University of Lübeck, Lübeck, Germany

5 Sheffield Dermatology Research, University of Sheffield, Sheffield, UK

6 Lydia Becker Institute of Immunology and Inflammation, University of Manchester, Manchester, UK

7 Probity Medical Research, Peterborough, ON, Canada

8 SKiN Centre for Dermatology, Peterborough, Queen's University, Kingston, ON, Canada

9 Regeneron Pharmaceuticals, Inc., 777 Old Saw Mill River Road, Tarrytown, NY, USA

10 Sanofi, Cambridge, MA, USA

11 Sanofi, Bridgewater, NJ, USA

12 Sanofi Genzyme, Cambridge, MA, USA

Key Points

Baseline and follow-up laboratory tests are required for patients with atopic dermatitis (AD) treated with systemic immunosuppressants.

Previous studies of dupilumab (a monoclonal antibody that specifically inhibits signaling of interleukin-4 and interleukin-13) in adolescents and adults with moderate-to-severe AD demonstrated no changes in laboratory parameters necessitating modification of treatment.

This randomized, placebo-controlled, phase III clinical trial of dupilumab with concomitant topical corticosteroids (TCS) for children aged 6–11 years with severe AD also demonstrated no significant changes in laboratory parameters, supporting the use of dupilumab + TCS without routine laboratory monitoring in patients aged ≥ 6 years.

1 Introduction

For children with severe atopic dermatitis (AD), use of systemic corticosteroids and other immunosuppressive therapies is associated with safety risks [1–3]. Standard-of-care use of these drugs requires baseline and follow-up laboratory tests to monitor for evidence of myelosuppression, lipid abnormalities, and/or organ toxicity [4]. The need for serial venipuncture with such therapies may have significant tolerability implications in children, particularly when access to dedicated pediatric phlebotomy is not available [5].

Dupilumab is a fully human VelocImmune®-derived [6, 7] monoclonal antibody that blocks the shared receptor component for interleukin (IL)-4 and IL-13, thus inhibiting signaling of both IL-4 and IL-13, which are key and central drivers of type 2 inflammatory diseases [8]. Clinical trials of dupilumab with or without topical corticosteroids (TCS) in adults and adolescents with moderate-to-severe AD and in children aged 6–11 years with severe AD have shown significant improvement in signs and symptoms of AD and patient quality of life with dupilumab treatment, with an acceptable safety profile [9–15]. No clinically significant adverse changes in laboratory parameters in adults and adolescents were attributable to dupilumab, supporting its use for treatment of moderate-to-severe AD without routine laboratory monitoring [16, 17]. To characterize the impact of dupilumab on laboratory findings in children, we analyzed the laboratory safety data from a phase III clinical trial conducted in children aged 6–11 years with severe AD [15].

2 Methods

2.1 Study Design, Patients, and Treatment

LIBERTY AD PEDS (ClinicalTrials.gov Identifier: NCT03345914) was a randomized, double-blinded, placebo-controlled phase III clinical trial [15]. Details of the study design and patient enrollment criteria have been previously published [15]. In brief, patients were aged 6–11 years with severe AD [18] inadequately controlled with topical AD medications. Study participants underwent a screening/washout period that lasted up to 9 weeks and a 2-week TCS standardization period, after which they were randomized 1:1:1 to receive subcutaneous dupilumab 300 mg every 4 weeks (q4w); dupilumab every 2 weeks (q2w) at a dose of either 100 mg (if baseline weight < 30 kg) or 200 mg (if baseline weight ≥ 30 kg); or matching placebo. All groups received concomitant medium-potency TCS (or low-potency TCS on skin where continuous treatment with medium-potency TCS was considered unsafe). Treatment continued for 16 weeks, followed by a 12-week follow-up period or enrollment in an open-label extension study (LIBERTY AD PED-OLE; ClinicalTrials.gov Identifier: NCT02612454) [14]. Patients eligible for LIBERTY AD PEDS had an Investigator's Global Assessment score of 4 (on a scale of 0–4), an Eczema Area and Severity Index ≥ 21, a Pruritus Numerical Rating Scale score ≥ 4, and body surface area affected ≥ 15%. Patients were excluded from the trial if they were on current treatment for hepatic disease or had evidence of liver disease as indicated by persistent (confirmed by repeated tests ≥ 2 weeks apart) elevated transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) > 3 times the upper limit of normal (ULN) during the screening period; or had any of the following laboratory abnormalities at screening: platelet count ≤ 100×10^3/μL, neutrophil count < 1.5×10^3/μL, creatine phosphokinase (CPK) > 5 × ULN, or serum creatinine > 1.5 × ULN.

2.2 Ethics

The study was conducted following the ethical principles derived from the Declaration of Helsinki, the International Council for Harmonisation guidelines, Good Clinical Practice guideline, and local applicable regulatory requirements. Written informed consent was obtained from all patients and the patients' parents/guardians prior to commencement of any study treatment.

2.3 Laboratory Assessment

Blood samples were collected for laboratory assessment at baseline and Weeks 4, 8, and 16, and urine samples were collected at baseline and Weeks 4 and 16; samples were analyzed by two central laboratories (PPD Global Central Labs LLC, Highland Heights, KY, USA; and PPD Global Central Lab BVBA, Zaventem, Belgium). The laboratory parameters that were assessed are shown in Supplemental Table S1 (see electronic supplementary material [ESM]), and include hematologic (red blood cell, platelet, and white blood cell), serum chemistry (metabolic, electrolyte, renal, liver, and lipid), and urinalysis parameters.

In cases of significantly abnormal laboratory values, as determined by the study investigator, the test was repeated, and ancillary investigations were performed as needed. Abnormal laboratory findings were reported as a treatment-emergent adverse event (TEAE) based on the following criteria, as determined by study investigators: if findings were accompanied by symptoms, and/or required additional diagnostic testing or medical/surgical intervention, and/or led to a change in dosing (outside of protocol-stipulated dose adjustments, patient withdrawal from the study, or significant additional concomitant drug treatment or other therapy).

Temporary discontinuation of study treatment was required for patients who developed the following laboratory abnormalities: AST and/or ALT values $> 3 \times$ ULN but $\leq 5 \times$ ULN; neutrophil count $< 1.5 \times 10^3/\mu L$ but $> 0.5 \times 10^3/\mu L$; platelet count $\leq 100 \times 10^3/\mu L$ but $> 50 \times 10^3/\mu L$; CPK $> 5 \times$ ULN; serum creatinine $> 1.5 \times$ ULN; or eosinophil count $> 5000/\mu L$. Treatment was permanently discontinued in patients with neutrophil count $\leq 0.5 \times 10^3/\mu L$; platelet count $\leq 50 \times 10^3/\mu L$; ALT and/or AST $> 3 \times$ ULN with total bilirubin $> 2 \times$ ULN (unless elevated bilirubin is related to confirmed Gilbert's syndrome); or confirmed AST and/or ALT $> 5 \times$ ULN for >2 weeks.

2.4 Statistical Analysis

This analysis was based on all randomized patients who received one or more dose of study drug, as treated (i.e., the safety analysis set). All statistics are descriptive and computed based on the number of available samples at each time point; no imputation for missing values was used. Analyses included baseline value, median values at each time point, and change from baseline at each time point reported as mean with standard deviation. The number and proportion of patients with one or more laboratory abnormality that was reported as a TEAE during the 16-week treatment period was also assessed. TEAEs are presented as Medical Dictionary for Regulatory Activities Preferred Terms (MedDRA PTs). TEAEs were classified as mild, moderate, and severe, per clinician's assessment (Supplemental Methods, see ESM). In addition, the proportion of patients whose values for platelets, eosinophils, neutrophils, and lactate dehydrogenase (LDH) shifted between low, normal, and high by visit (baseline and Weeks 4, 8, and 16) were assessed. Finally, the proportions of patients in each grade of severity for key outcomes (red blood cell parameters, platelets, eosinophils, neutrophils, alkaline phosphatase [ALP], bilirubin, ALT, AST, creatinine, and potassium) were evaluated, regardless of whether the outcomes were reported as TEAEs. Grades (defined as Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe or medically significant [but not immediately life-threatening], and Grade 4 = potentially life-threatening) were based on the Common Terminology Criteria for Adverse Events (CTCAE); Version 5.0 [19], except for eosinophilia, for which grades were defined according to the Nordic study group on myeloproliferative disorders [20].

3 Results

3.1 Patients

A total of 367 patients were enrolled in the study, and 362 were included in the safety analysis set. Five patients (2 in the placebo + TCS group, 2 in the dupilumab 300 mg q4w + TCS group, and 1 in the dupilumab 100/200 mg q2w + TCS group) were randomized but did not receive study treatment and were therefore excluded from the safety analysis set.

Overall, 96% of patients completed the study. No patients withdrew from the study due to laboratory abnormalities, and no patients temporarily or permanently discontinued study treatment due to laboratory abnormalities. Two patients in the placebo + TCS group reported TEAEs (1 each of asthma, and AD) unrelated to laboratory parameters that led to permanent dose discontinuation, as did two in the dupilumab 100/200 mg q2w + TCS group (1 each of food allergy and bacterial conjunctivitis). The proportion of patients with one or more laboratory abnormalities reported as TEAEs was low (1.7%, 0.8%, and 2.5% in patients treated with placebo + TCS, dupilumab 300 mg q4w + TCS, and dupilumab 100/200 mg q2w + TCS, respectively; Table 1).

3.2 Red Blood Cells and Platelets

No clinically significant changes from baseline and no consequential differences between treatment groups were observed during the 16-week treatment period for hemoglobin level and platelet count (Fig. 1a, b) or other red blood cell parameters (Supplemental Table S2a–c, see ESM), although there was a trend toward decreasing platelet counts

Table 1 Laboratory abnormalities reported as TEAEs

TEAEs by MedDRA SOC and PT, *n* (%)	Placebo + TCS (*n* = 120)	Dupilumab 300 mg q4w + TCS (*n* = 120)	Dupilumab 100/200 mg q2w + TCS (*n* = 122)
Patients with ≥ 1 laboratory abnormality reported as TEAE	2 (1.7)	1 (0.8)	3 (2.5)
Blood and lymphatic system disorders (SOC)			
Eosinophilia (PT)	0	0	1 (0.8)[a]
Thrombocytopenia (PT)	0	0	1 (0.8)[b]
Thrombocytosis (PT)	0	1 (0.8)[c]	0
Investigations (SOC)			
Blood potassium increased (PT)	1 (0.8)[d]	0	0
Renal and urinary disorders (SOC)			
Proteinuria (PT)	1 (0.8)[e]	0	1 (0.8)[f]

This table includes all TEAEs reported by investigators that were PTs related to laboratory assessments in the listed SOCs

MedDRA Medical Dictionary for Regulatory Activities, *n* total number of patients in the treatment group, *PT* MedDRA Preferred Term, *q2w* every 2 weeks, *q4w* every 4 weeks, *SOC* MedDRA System Organ Class, *TCS* topical corticosteroid, *TEAE* treatment-emergent adverse event

[a]The patient had an elevated eosinophil count at baseline (4.3×10^9/L) that increased to 7.8×10^9/L at Week 4 (age-adjusted normal range 0–0.5×10^9/L); the eosinophil count decreased to 5.3×10^9/L at Week 8. This TEAE was classified as moderate in intensity, was not considered related to study drug, and did not require any treatment or withdrawal of study drug

[b]The patient had a normal platelet count at baseline (273×10^9/L) that decreased to 56×10^9/L at Week 8 (age-adjusted normal range 130–382 $\times 10^9$/L); the platelet count normalized by Week 10 to 226×10^9/L. This TEAE was classified as moderate in intensity, was considered related to study drug, and did not require any treatment or withdrawal of study drug

[c]The patient had a baseline platelet count of 442×10^9/L that increased to 747×10^9/L at Week 8 (age-adjusted normal range 130–382×10^9/L); the platelet count decreased by Week 10 to 416×10^9/L. This TEAE was classified as moderate in intensity, was considered related to study drug, and did not require any treatment or withdrawal of study drug

[d]The patient had a normal blood potassium level at baseline (4.3 mmol/L) that increased to 6.1 mmol/L at Week 8 (age-adjusted normal range 2.8–6.3 mmol/L); the potassium level normalized by Week 12 to 4.8 mmol/L. This TEAE was classified as mild in intensity, was not considered related to study drug, and did not require any treatment or withdrawal of study drug

[e]The patient had no proteinuria at baseline (0 mg/dL); proteinuria was detected at a level of 30 mg/dL at Week 4, and protein levels returned to baseline by Week 8 to 0 mg/dL. This TEAE was classified as mild in intensity, was not considered related to study drug, and did not require any treatment or withdrawal of study drug

[f]The patient had an isolated elevated baseline proteinuria (30 mg/dL) that increased to 100 mg/dL at Week 4; protein levels normalized to 0 mg/dL by Week 16. This TEAE was classified as mild in intensity, was not considered related to study drug, and did not require any treatment or withdrawal of study drug

in both dupilumab + TCS groups over 16 weeks (Fig. 1b; Supplemental Fig. S1, see ESM). There were no clinically meaningful differences between treatment groups in shifts from baseline levels of platelets (Table 2). No patients reported TEAEs related to red blood cells, and none had Grade 3 anemia (Supplemental Table S2c, see ESM) or other abnormalities in red blood cell parameters (data not shown).

One patient in the dupilumab 300 mg q4w + TCS group reported an isolated drop in platelet count that met the criteria for Grade 3 thrombocytopenia (change from baseline -245×10^9/L) at Week 8; platelet count reverted to normal by Week 16 without modification in therapy (change from baseline: -6×10^9/L; Supplemental Table S2b, Supplemental Fig. S2, see ESM); this was not reported as a TEAE. Thrombocytopenia was reported as a TEAE in one patient in the dupilumab 100 mg q2w + TCS group; this patient had a normal platelet count at baseline (273×10^9/L; age-adjusted normal range 130–382×10^9/L) that decreased to 56×10^9/L at Week 8 and normalized by Week 10 (226×10^9/L; Table 1). There were no bleeding or bruising abnormalities reported in patients who had decreased platelet count recorded either as a TEAE or meeting the criteria for Grade 3 thrombocytopenia. Moderate thrombocytosis was reported as a TEAE in one patient in the dupilumab 300 mg q4w + TCS group; the patient had a baseline platelet count of 442×10^9/L that increased to 747×10^9/L at Week 8 (age-adjusted normal range 130–382×10^9/L) and decreased by Week 16 to near baseline values (416×10^9/L; Table 1).

3.3 White Blood Cells

Summary statistics for white blood cell parameters are presented in Supplemental Table S3a (see ESM). No clinically

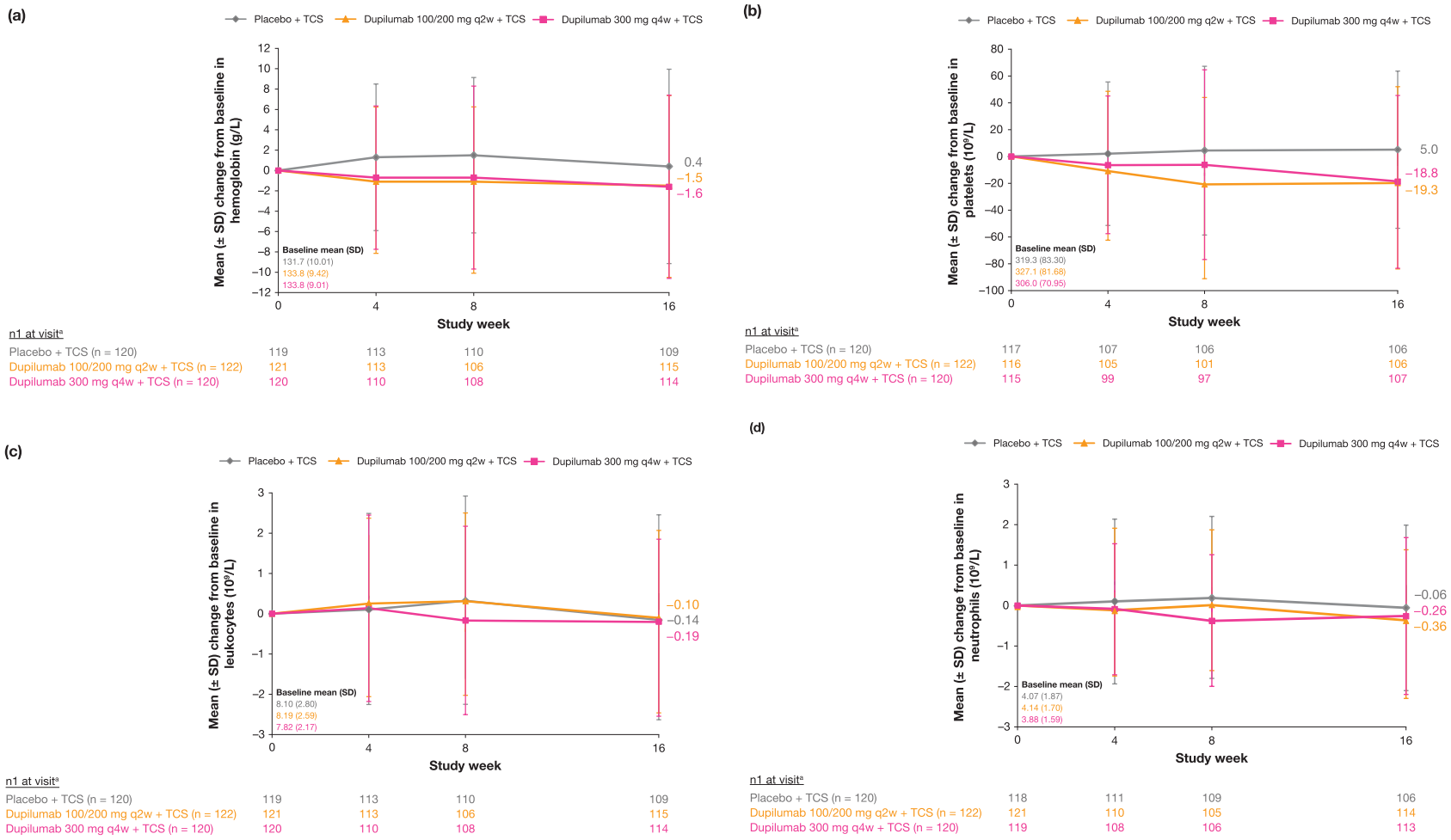

Fig. 1 Mean change from baseline over time in **a** hemoglobin level, **b** platelet count, **c** leukocyte count, **d** neutrophil count, **e** eosinophil count, and **f** absolute eosinophil levels. White horizontal lines indicate medians. X depicts mean values. Top and bottom of each box represents Q3 and Q2, respectively. Upper and lower vertical bars represent Q4 and Q1, respectively; horizontal segments on each end of the vertical bars represent minimum and maximum values. Red dashed line represents upper limit of normal (0.5×10^9/L). *n1* number of patients with evaluation level at visit, *Q* quartile, *q2w* every 2 weeks, *q4w* every 4 weeks, *SD* standard deviation, *TCS* topical corticosteroid. [a]Number of patients with a value for change from baseline. [b]Number of patients with a value for absolute count

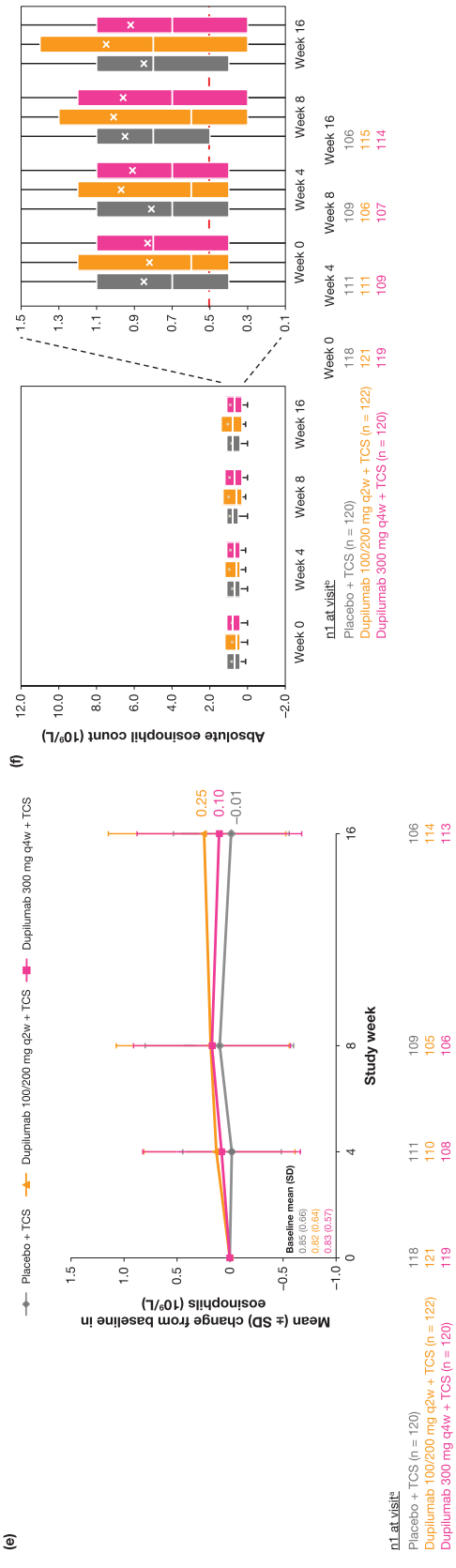

Fig. 1 (continued)

significant changes from baseline and no meaningful differences between treatment groups were observed in mean counts for leukocytes, neutrophils, or most other white blood cell parameters in any treatment group (Fig. 1c, d; Supplemental Table S3a, see ESM).

Eosinophil counts at baseline were elevated above the normal range in all treatment groups (Fig. 1e, f; Supplemental Table S3a, see ESM). Mean eosinophil counts increased over time from baseline, peaking at Week 8 in the dupilumab 300 mg q4w + TCS and placebo + TCS groups, and increasing to Week 16 in the dupilumab 100/200 mg q2w + TCS group (Fig. 1e, f). The mean changes from baseline to Week 16 were 0.10×10^9/L and 0.25×10^9/L in the dupilumab 300 mg q4w + TCS and dupilumab 100/200 mg q2w + TCS groups, respectively, compared with -0.01×10^9/L in the placebo group (Supplemental Table S3a, see ESM). In contrast, median eosinophil counts showed little variation over time (median counts, range: placebo + TCS, 0.7–0.8 × 10^9/L; dupilumab 300 mg q4w + TCS, 0.7–0.8 × 10^9/L; dupilumab 100/200 mg q2w + TCS, 0.6–0.8 × 10^9/L; Fig. 1f; Supplemental Table S3a, see ESM). Similar proportions of patients in each treatment group shifted from high eosinophil counts at baseline to normal counts at Week 16 (Table 3).

Grade 3 eosinophilia (i.e., > 5.00 × 10^9/L, severe) was reported at one or more post-baseline time points for five, two, and one patient(s) in the dupilumab 300 mg q4w + TCS, 100/200 mg q2w + TCS, and placebo + TCS groups, respectively; no patients had Grade 3 eosinophilia at baseline (Table 4). Eosinophil counts declined after the Grade 3 events for four of the seven dupilumab + TCS-treated patients and the placebo + TCS-treated patient; for the remaining three dupilumab + TCS-treated patients, Grade 3 eosinophilia was first reported at Week 16 (Supplemental Fig. S3, see ESM). No symptoms were associated with any of the Grade 3 eosinophilia events. All eight patients with Grade 3 eosinophilia had a history of other type 2 inflammatory disorders, including asthma, allergic rhinitis, chronic rhinosinusitis, food or other allergies, allergic conjunctivitis, and hives (Supplemental Fig. S3, see ESM), and all had previously used systemic non-steroidal immunosuppressant therapies for AD. In addition, four of the patients with Grade 3 eosinophilia had TEAEs of type 2 inflammatory disorders (MedDRA PTs) as follows: moderate eosinophilia and mild allergic rhinitis (1 patient, dupilumab 100 mg q2w + TCS [note: the TEAE of moderate eosinophilia coincided with the event of Grade 3 eosinophilia; see in the following]); mild asthma and mild urticaria (1 patient, dupilumab 300 mg q4w + TCS); moderate allergic conjunctivitis and moderate atopy (1 patient, dupilumab 300 mg q4w + TCS); and severe AD (1 patient [2 events], placebo + TCS) (Supplemental Fig. S3, see ESM). For the patient in the dupilumab 100 mg q2w + TCS group with both a TEAE of moderate eosinophilia and Grade 3 eosinophilia, the eosinophil count was

Table 2 Shift from baseline: platelets ($\times 10^9$/L)

Study week	Evaluation n1/N2 (%)	Placebo + TCS ($n = 120$)			Dupilumab 300 mg q4w + TCS ($n = 120$)			Dupilumab 100/200 mg q2w + TCS ($n = 122$)		
		Baseline status								
		Low	Normal	High	Low	Normal	High	Low	Normal	High
4	Low	0/1	1/65 (1.5)	0/41	1/2 (50.0)	0/53	0/44	0/0	1/57 (1.8)	0/48
	Normal	1/1 (100)	48/65 (73.8)	4/41 (9.8)	1/2 (50.0)	43/53 (81.1)	13/44 (29.5)	0/0	47/57 (82.5)	14/48 (29.2)
	High	0/1	16/65 (24.6)	37/41 (90.2)	0/2	10/53 (18.9)	31/44 (70.5)	0/0	9/57 (15.8)	34/48 (70.8)
8	Low	0/1	0/61	0/44	0/4	1/53 (1.9)	0/40	0/0	2/55 (3.6)	0/46
	Normal	1/1 (100)	45/61 (73.8)	8/44 (18.2)	3/4 (75.0)	44/53 (83.0)	17/40 (42.5)	0/0	44/55 (80.0)	14/46 (30.4)
	High	0/1	16/61 (26.2)	36/44 (81.8)	1/4 (25.0)	8/53 (15.1)	23/40 (57.5)	0/0	9/55 (16.4)	32/46 (69.6)
16	Low	1/2 (50)	1/59 (1.7)	0/45	1/4 (25.0)	2/61 (3.3)	0/42	0/0	2/59 (3.4)	1/47 (2.1)
	Normal	1/2 (50)	46/59 (78.0)	9/45 (20.0)	2/4 (50.0)	55/61 (90.2)	15/42 (35.7)	0/0	47/59 (79.7)	15/47 (31.9)
	High	0/2	12/59 (20.3)	36/45 (80.0)	1/4 (25.0)	4/61 (6.6)	27/42 (64.3)	0/0	10/59 (16.9)	31/47 (66.0)

Normal range: age 1–6 years: male, 197–382 $\times 10^9$/L; female, 213–363 $\times 10^9$/L; age 7–12 years: male, 175–311 $\times 10^9$/L; female, 130–314 $\times 10^9$/L

n total number of patients in the treatment group, *n1* number of patients with evaluation level (low, normal, high) at visit, *N2* number of patients with baseline status, *q2w* every 2 weeks, *q4w* every 4 weeks, *TCS* topical corticosteroid

elevated at baseline (4.3×10^9/L; age-adjusted normal range, 0–0.5×10^9/L), increasing to 7.8×10^9/L at Week 4 (Grade 3, $> 5.0 \times 10^9$/L) and decreasing to 5.3×10^9/L at Week 8 and 5.5×10^9/L at Week 16 (Table 1; Supplemental Fig. S3, see ESM [patient 1]). The other seven patients did not report any TEAEs during the period when they had Grade 3 eosinophilia. In addition, none of the patients with Grade 3 eosinophilia had any findings suggestive of gastrointestinal disorders, vasculitis, or other adverse events associated with autoimmune conditions, and none had known helminthic infections.

No clinically meaningful adverse changes from baseline and no meaningful differences between treatment groups were observed in neutrophil counts, although both dupilumab + TCS groups showed a trend to decrease in mean neutrophil counts from baseline to Week 16 (Fig. 1d; Supplemental Table S3a, see ESM). Compared with placebo + TCS, a numerically higher proportion of patients in the dupilumab 300 mg q4w + TCS group, but not the dupilumab 100/200 mg q2w + TCS group, shifted from normal levels of neutrophils at baseline to low levels at Week 16 (Table 5). Three patients had Grade 3 neutropenia at baseline

Table 3 Shift from baseline: eosinophils ($\times 10^9$/L)

Study week	Evaluation n1/N2 (%)	Placebo + TCS ($n = 120$)			Dupilumab 300 mg q4w + TCS ($n = 120$)			Dupilumab 100/200 mg q2w + TCS ($n = 122$)		
		Baseline status								
		Low	Normal	High	Low	Normal	High	Low	Normal	High
4	Low	0/0	0/45	0/66	0/0	0/37	0/71	0/0	0/49	0/61
	Normal	0/0	33/45 (73.3)	14/66 (21.2)	0/0	34/37 (91.9)	14/71 (19.7)	0/0	37/49 (75.5)	13/61 (21.3)
	High	0/0	12/45 (26.7)	52/66 (78.8)	0/0	3/37 (8.1)	57/71 (80.3)	0/0	12/49 (24.5)	48/61 (78.7)
8	Low	0/0	0/45	0/64	0/0	0/39	0/67	0/0	0/49	0/56
	Normal	0/0	31/45 (68.9)	9/64 (14.1)	0/0	32/39 (82.1)	14/67 (20.9)	0/0	34/49 (69.4)	11/56 (19.6)
	High	0/0	14/45 (31.1)	55/64 (85.9)	0/0	7/39 (17.9)	53/67 (79.1)	0/0	15/49 (30.6)	45/56 (80.4)
16	Low	0/0	0/41	0/65	0/0	0/42	0/71	0/0	0/53	0/61
	Normal	0/0	26/41 (63.4)	15/65 (23.1)	0/0	34/42 (81.0)	14/71 (19.7)	0/0	30/53 (56.6)	15/61 (24.6)
	High	0/0	15/41 (36.6)	50/65 (76.9)	0/0	8/42 (19.0)	57/71 (80.3)	0/0	23/53 (43.4)	46/61 (75.4)

Normal range: age 1–6 years, 0–0.6×10^9/L; age 7–12 years, 0–0.5×10^9/L

n total number of patients in the treatment group, *n1* number of patients with evaluation level (low, normal, high) at visit, *N2* number of patients with baseline status, *q2w* every 2 weeks, *q4w* every 4 weeks, *TCS* topical corticosteroid

Table 4 Proportion of patients with Grade 1–3 eosinophilia, n1/N1 (%)

Time point	Grade	Placebo + TCS (n = 120)	Dupilumab 300 mg q4w + TCS (n = 120)	Dupilumab 100/200 mg q2w + TCS (n = 122)
Baseline	Grade 1 (Mild): 0.50×10^9/L–1.50×10^9/L	68/118 (57.6)	71/119 (59.7)	64/121 (52.9)
	Grade 2 (Moderate): > 1.50×10^9/L–5.00×10^9/L	14/118 (11.9)	13/119 (10.9)	13/121 (10.7)
	Grade 3 (Severe): > 5.00×10^9/L	0/118	0/119	0/121
Week 4	Grade 1 (Mild): 0.50×10^9/L–1.50×10^9/L	72/111 (64.9)	57/109 (52.3)	50/111 (45.0)
	Grade 2 (Moderate): > 1.50×10^9/L–5.00×10^9/L	6/111 (5.4)	18/109 (16.5)	17/111 (15.3)
	Grade 3 (Severe): > 5.00×10^9/L	1/111 (0.9)	1/109 (0.9)	1/111 (0.9)
Week 8	Grade 1 (Mild): 0.50×10^9/L–1.50×10^9/L	67/109 (61.5)	50/107 (46.7)	44/106 (41.5)
	Grade 2 (Moderate): > 1.50×10^9/L–5.00×10^9/L	15/109 (13.8)	13/107 (12.1)	21/106 (19.8)
	Grade 3 (Severe): > 5.00×10^9/L	1/109 (0.9)	3/107 (2.8)	1/106 (0.9)
Week 16	Grade 1 (Mild): 0.50×10^9/L–1.50×10^9/L	63/106 (59.4)	55/114 (48.2)	56/115 (48.7)
	Grade 2 (Moderate): > 1.50×10^9/L–5.00×10^9/L	14/106 (13.2)	15/114 (13.2)	20/115 (17.4)
	Grade 3 (Severe): > 5.00×10^9/L	0/106	3/114 (2.6)	2/115 (1.7)

Patients may have had a grade change at more than one time point

Grades were determined based on Nordic study group on myeloproliferative disorders guidelines for the diagnosis and treatment of eosinophilia. 2nd version, September 2012 [20]

n total number of patients in the treatment group, *n1/N1* number of patients with grade/number of patients with assessment at visit, *q2w* every 2 weeks, *q4w* every 4 weeks, *TCS* topical corticosteroid

(1 patient, dupilumab 300 mg q4w + TCS) or Week 16 (1 patient, placebo + TCS; 1 patient, dupilumab 200 mg q2w + TCS) (Supplemental Table S3b, see ESM); review of laboratory reports found no attributable causes for these events.

3.4 Serum Chemistry

No clinically meaningful trends were observed for most serum chemistry parameters, including markers of metabolic function, electrolytes, renal function, liver function, or lipids, in any treatment group (Supplemental Table S4a–e, see ESM).

Mean LDH level decreased from baseline in both dupilumab + TCS treatment groups but remained stable in the placebo + TCS group (Fig. 2a; Supplemental Table S4d, see ESM). More patients in the dupilumab + TCS groups than in the placebo + TCS group shifted from high levels of LDH at baseline to normal levels at Week 16 (Supplemental Table S4f, see ESM). Mean ALP levels increased from baseline in both dupilumab + TCS treatment groups but not in the placebo + TCS group (Fig. 2b; Supplemental Table S4d, see ESM), whereas mean ALT levels remained relatively stable in all three treatment groups (Fig. 2c; Supplemental Table S4d, see ESM). No patients had increases beyond Grade 2 in ALP, bilirubin, ALT, AST, or creatinine (Supplemental Table S5a–e, see ESM). Two patients in the placebo + TCS group had transient Grade 3 increases in potassium at Week 8 (Supplemental Table S5f, see ESM). A mild increase in blood potassium level was reported as a TEAE in one patient in the placebo + TCS group; the patient had a normal blood potassium level at baseline (4.3 mmol/L) that increased to 6.1 mmol/L at Week 8 (age-adjusted normal range 2.8–6.3 mmol/L) and normalized by Week 12 to 4.8 mmol/L (Table 1).

3.5 Urinalysis

No clinically meaningful adverse changes in urine parameters were observed (Supplemental Table S6, see ESM). Two cases of mild proteinuria were reported as TEAEs: one each in the placebo + TCS and dupilumab 100 mg q2w + TCS groups (Table 1). The patient in the placebo + TCS group had no proteinuria at baseline (0 mg/dL), but levels increased to 30 mg/dL at Week 4, and then returned to normal by Week 8 (0 mg/dL). The patient in the dupilumab 100 mg q2w + TCS group had isolated proteinuria at baseline (30 mg/dL) that increased to 100 mg/dL at Week 4 and normalized by Week 16 (0 mg/dL); Week 8 data were not reported for this patient.

Table 5 Shift from baseline: neutrophils ($\times 10^9$/L)

Study week	Evaluation n1/N2 (%)	Placebo + TCS ($n = 120$)			Dupilumab 300 mg q4w + TCS ($n = 120$)			Dupilumab 100/200 mg q2w + TCS ($n = 122$)		
		Baseline status								
		Low	Normal	High	Low	Normal	High	Low	Normal	High
4	Low	1/7 (14.3)	1/101 (1.0)	0/3	2/5 (40.0)	2/102 (2.0)	0/1	3/8 (37.5)	2/100 (2.0)	0/2
	Normal	6/7 (85.7)	97/101 (96.0)	3/3 (100)	3/5 (60.0)	96/102 (94.1)	1/1 (100)	4/8 (50.0)	94/100 (94.0)	2/2 (100)
	High	0/7	3/101 (3.0)	0/3	0/5	4/102 (3.9)	0/1	1/8 (12.5)	4/100 (4.0)	0/2
8	Low	2/7 (28.6)	1/99 (1.0)	0/3	1/4 (25.0)	1/101 (1.0)	0/1	5/7 (71.4)	3/97 (3.1)	0/1
	Normal	5/7 (71.4)	94/99 (94.9)	1/3 (33.3)	3/4 (75.0)	99/101 (98.0)	1/1 (100)	2/7 (28.6)	89/97 (91.8)	1/1 (100)
	High	0/7	4/99 (4.0)	2/3 (66.7)	0/4	1/101 (1.0)	0/1	0/7	5/97 (5.2)	0/1
16	Low	1/5 (20.0)	4/98 (4.1)	0/3	3/4 (75.0)	12/108 (11.1)	0/1	5/8 (62.5)	2/104 (1.9)	0/2
	Normal	4/5 (80.0)	90/98 (91.8)	3/3 (100)	1/4 (25.0)	93/108 (86.1)	1/1 (100)	3/8 (37.5)	102/104 (98.1)	1/2 (50.0)
	High	0/5	4/98 (4.1)	0/3	0/4	3/108 (2.8)	0/1	0/8	0/104	1/2 (50.0)

Normal range: age 1–6 years, 1.5–8.5 $\times 10^9$/L; age 7–12 years, 1.8–8.0 $\times 10^9$/L

n total number of patients in the treatment group, *n1* number of patients with evaluation level (low, normal, high) at visit, *N2* number of patients with baseline status, *q2w* every 2 weeks, *q4w* every 4 weeks, *TCS* topical corticosteroid

4 Discussion

This analysis confirms that a 16-week course of dupilumab + TCS in children aged 6–11 years with severe AD did not lead to any clinically relevant mean changes in laboratory parameters requiring treatment modification.

Overall, no clinically meaningful adverse trends were found in hematologic parameters. Transient inconsequential TEAEs of thrombocytopenia and thrombocytosis (1 patient each) were reported in the dupilumab 100 mg q2w + TCS and 300 mg q4w + TCS groups, respectively; review of laboratory reports found no attributable cause for either of these TEAEs, such as concurrent viral illness, medication use, or confirmed spurious reporting, all of which are common causes of isolated laboratory value aberrations. One patient in the dupilumab 300 mg q4w + TCS group with a normal platelet count at baseline had a small reduction in platelet count that normalized without modification in therapy by Week 12. Mean platelet counts decreased, but remained within normal range, in both dupilumab + TCS groups, most likely reflecting diminished acute phase reactant activity linked to AD severity [21, 22]. Similar trends were seen in previous studies in adults [16] and adolescents [17], also without adverse clinical implications. AD is a chronic inflammatory condition with a dynamic course characterized by recurrent acute exacerbations, which can cause oscillating levels of acute phase reactants along with chronic elevations of systemic markers of inflammation [21–24].

No trends were observed in most white blood cell parameters, including mean change from baseline in basophils, lymphocytes, monocytes, and leukocytes. There was a trend for a decrease in mean neutrophil counts and a trend for an increase in the number of patients in the dupilumab + TCS groups having Grades 1 and 2 neutropenia at Week 16. Mild increases in mean eosinophil counts were observed in all treatment groups during the treatment period, consistent with previous reports evaluating dupilumab in adults and adolescents with moderate-to-severe AD [9, 16, 17], asthma [25, 26], and chronic rhinosinusitis with nasal polyps [27]. For the placebo and dupilumab q4w groups, these changes were transient, peaking at Week 8 and returning to near baseline by Week 16. In the dupilumab q2w group, mild incremental increases were observed through Week 16. The median values showed even less fluctuation, which, along with the large standard deviation of the means, suggests that the mean changes observed were influenced by a small number of outliers. Fluctuations in eosinophil counts were clinically inconsequential in all patients. A small number of patients had increases in eosinophil count during the treatment period that were reported either as a TEAE (1 dupilumab + TCS-treated patient) or as Grade 3 eosinophilia (7 dupilumab + TCS-treated patients and 1 placebo + TCS-treated patient) at one or more time points in the study, but none had symptoms or evidence suggesting systemic relevance. The eosinophil counts declined after the Grade 3 events for most of these patients, supporting the likelihood that this was a benign transient phenomenon, similar to what has been reported for adolescents and adults [16, 17]. Four of these patients had atopic comorbidities, including one patient with a medical history of asthma and TEAEs of asthma and urticaria; however, no patients had symptoms or findings suggestive of a systemic vasculitis. Eosinophilic granulomatosis with polyangiitis is a rare type of vasculitis that can present with co-occurring asthma and peripheral eosinophilia, but is unlikely in the patient population in this clinical trial, since it more commonly presents in adults with

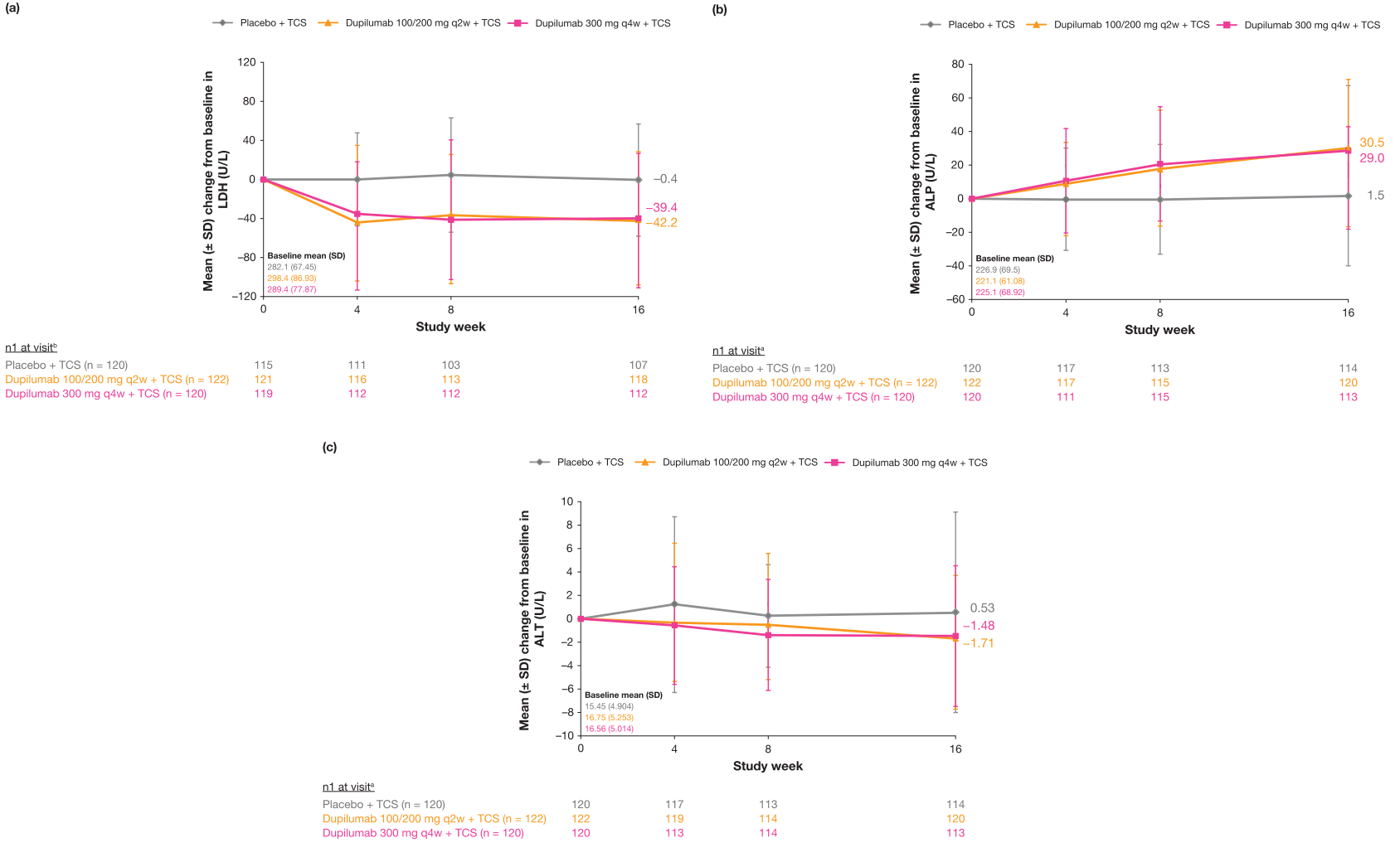

Fig. 2 Mean change from baseline over time in serum levels of **a** LDH, **b** ALP, and **c** ALT. *ALP* alkaline phosphatase, *ALT* alanine aminotransferase, *LDH* lactate dehydrogenase, *n1* number of patients at visit, *q2w* every 2 weeks, *q4w* every 4 weeks, *SD* standard deviation, *TCS* topical corticosteroid. [a]Number of patients with a value for change from baseline

severe asthma rather than in children with AD [28, 29]. No clinically relevant events or untoward outcomes were associated with eosinophilia. Dual blockade of IL-4 and IL-13 with dupilumab inhibits the activity of eosinophils and their recruitment to affected tissue, but not their egress from bone marrow (which is regulated by IL-5) [30–33]. It has been hypothesized that this may result in a transient increase in circulating eosinophils that does not reflect a pathologic process [16, 17, 30].

There were no clinically meaningful differences observed in most serum chemistry parameters, and no clinically meaningful differences were observed in urinalysis parameters among the treatment groups.

A reduction from baseline in mean LDH levels was observed in both dupilumab + TCS groups but not in the placebo + TCS group, similar to what was seen in dupilumab-treated adults and adolescents with moderate-to-severe AD [16, 17]. Elevation in LDH is associated with inflammation and tissue damage and has been shown to decrease with improvements in clinical disease severity in patients with AD [34]. As noted above, the decline in platelet and neutrophil counts from baseline in the dupilumab + TCS groups may reflect the same process, as platelets and neutrophils are acute phase reactants associated with AD severity [21, 22].

Mild increases in mean ALP levels were observed in both dupilumab + TCS groups, whereas ALP levels remained relatively unchanged in the placebo + TCS group, similar to what was reported in adolescents [17]; however, no such increases were observed in adults [16]. As with the other age groups, there was no corresponding change in other liver function tests, and no corresponding change in parameters related to metabolic function, electrolytes, renal function, or lipids.

5 Limitations

This 16-week study was too short to assess long-term safety. An ongoing open-label extension study will provide more information on the long-term safety profile of dupilumab in children. Since exclusion criteria disallowed patients with evidence of liver disease (including persistent or elevated ALT or AST) or certain other severe laboratory abnormalities, evaluation of patients with these morbidities was not performed. Potential irregularities in handling/processing of samples may not have been fully captured; thus, for example, laboratory artifacts such as pseudothrombocytopenia and hemolysis/potassium may have resulted from such irregularities, but the data do not permit determination of such events. Biomarkers (such as IgE and thymus and activation-regulated chemokine) and anti-dupilumab antibodies were assessed in this cohort; future publications are planned to report these parameters.

6 Conclusions

Treatment with dupilumab + TCS in children aged 6–11 years with severe AD was not associated with clinically meaningful adverse changes in routine laboratory parameters. Dupilumab + TCS-associated decreases in platelet counts and LDH were similar to those reported in adolescents and may represent improvements in AD-associated inflammation. These findings are consistent with outcomes previously reported in adolescents and adults with moderate-to-severe AD [16, 17], support the pivotal efficacy and safety data previously reported for this clinical trial [15], and echo the observed trends in minor laboratory differences seen in adolescents and adults treated with this biologic agent [16, 17]. Together with the results of previous studies in adults and adolescents, these data provide support that dupilumab does not require routine laboratory monitoring before initiation or during treatment in children aged 6–11 years with severe AD.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40272-021-00459-x.

Acknowledgements This research was sponsored by Sanofi and Regeneron Pharmaceuticals, Inc. The authors thank the patients and their families for their participation in these studies, their colleagues for their support, and John Caminis, MD, Adriana Mello, PharmD, PGC Bus (of Sanofi), and Linda Williams, RPh (of Regeneron Pharmaceuticals, Inc.) for their contributions. Medical writing and editorial assistance were provided by Vicki Schwartz, PhD, of Excerpta Medica, funded by Sanofi Genzyme and Regeneron Pharmaceuticals, Inc.

Declarations

Funding Research sponsored by Sanofi and Regeneron Pharmaceuticals, Inc. ClinicalTrials.gov Identifier: NCT03345914. The study sponsors participated in the study design; collection, analysis, and interpretation of the data; writing of the report; and the decision to submit the article for publication. Medical writing/editorial assistance were provided by Vicki Schwartz, PhD, of Excerpta Medica, and was funded by Sanofi Genzyme and Regeneron Pharmaceuticals, Inc., according to the Good Publication Practice guideline: https://www.acpjournals.org/doi/10.7326/M15-0288.

Conflict of interest Amy S. Paller has served as a scientific advisor and/or clinical study investigator for AbbVie, Abeona Therapeutics, Almirall, AnaptysBio, Asana Biosciences, Boehringer Ingelheim, BridgeBio, Dermavant, Dermira, Eli Lilly, Exicure, Forté, Galderma, Incyte, InMed Pharmaceuticals, Janssen, LEO Pharma, LifeMax, Novartis, Pfizer, RAPT Therapeutics, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme, Sol Gel, and UCB. Andreas Wollenberg has been an investigator for Eli Lilly, Galderma, LEO Pharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme, and UCB; has been a consultant for AbbVie, Almirall, Anacor Pharmaceuticals, Arena Pharmaceuticals, Eli Lilly, Galapagos, Galderma, LEO Pharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., and Sanofi Genzyme; and has received research grants from LEO Pharma and Pierre Fabre. Elaine Siegfried has served as a scientific advisor and/or clinical study investigator for Eli Lilly, Janssen, Novan, Novartis,

Regeneron Pharmaceuticals, Inc., Sanofi Genzyme, UCB, and Verrica Pharmaceuticals; as a paid speaker for Regeneron Pharmaceuticals, Inc.; and as a data and safety monitoring board member for GSK, LEO Pharma, Novan, Pfizer, and UCB. Diamant Thaçi has been a consultant, advisory board member, and/or investigator for AbbVie, Almirall, Amgen, Beiersdorf, Boehringer Ingelheim, Dermira, Eli Lilly, Galapagos, Galderma, Janssen-Cilag, Kyowa Kirin, LEO Pharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi, and UCB. Michael J. Cork has received research grants from Astellas Pharma, Atopix, Galopagos, Harvey Water Softeners, Hyphens Pharma, Johnson & Johnson, Kymab, L'Oréal, LEO Pharma, Novartis, Oxagen, Perrigo (ACO Nordic), Pfizer, Reckitt Benkiser, Regeneron Pharmaceuticals, Inc., and Sanofi Genzyme; has been a consultant and/or advisory board member for Astellas Pharma, Atopix, Boots, Dermavent, Galderma, Galopagos, Hyphens Pharma, Johnson & Johnson, Kymab, L'Oréal, LEO Pharma, Menlo, Novartis, Oxagen, Perrigo (ACO Nordic), Pfizer, Proctor & Gamble, Reckitt Benkiser, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme, and UCB; and has served as a voluntary medical advisor to the National Eczema Society, UK. Peter D. Arkwright has served as an advisory board member for and received consulting fees and project grant funding from Sanofi Genzyme; and is an investigator for Regeneron Pharmaceuticals, Inc. Melinda Gooderham has received consulting fees/honoraria from AbbVie, Akros Pharma, Amgen, Arcutis Biotherapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Coherus BioSciences, Dermira, Eli Lilly, Galderma, GSK, Janssen, Kyowa Kirin, LEO Pharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme, Sun Pharma, UCB, and Valeant Pharmaceuticals/Bausch; has received fees for participation in review activities from AbbVie, Akros Pharma, Amgen, Arcutis Biotherapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Janssen, Kyowa Kirin, LEO Pharma, Novartis, Pfizer, Sanofi Genzyme, Sun Pharma, UCB, and Valeant Pharmaceuticals/Bausch; has received payment for lectures and/or service on speakers bureaus from AbbVie, Amgen, Biosciences, Boehringer Ingelheim, Dermira, Eli Lilly, Galderma, Janssen, LEO Pharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme, Sun Pharma, UCB, and Valeant Pharmaceuticals/Bausch; and has served as an investigator, advisor, and/or speaker for AbbVie, Akros Pharma, Amgen, Arcutis Biotherapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Coherus BioSciences, Dermira, Eli Lilly, Galderma, GSK, Janssen, Kyowa Kirin, LEO Pharma, MedImmune, Merck, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Roche, Sanofi Genzyme, Sun Pharma, UCB, and Valeant Pharmaceuticals/Bausch. Xian Sun, Faisal A. Khokhar, Ashish Bansal, Brad Shumel, and Noah A. Levit are employees and shareholders of Regeneron Pharmaceuticals, Inc. John T. O'Malley and Jignesh Vakil are employees of and may hold stock and/or stock options in Sanofi. Karli Rosner is an employee of and may hold stock and/or stock options in Sanofi Genzyme.

Availability of data and material Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymized participant data will be considered for sharing once the indication has been approved by a regulatory body, if there is legal authority to share the data and there is not a reasonable likelihood of participant re-identification. Submit requests to https://vivli.org/.

Ethics approval The study was conducted following the ethical principles that derive from the Declaration of Helsinki, International Council for Harmonisation guidelines, Good Clinical Practice guideline, and local applicable regulatory requirements. The trial was overseen by an independent data and safety monitoring board.

Consent to participate Written informed consent was obtained from all patients and the patients' parents/guardians prior to commencement of any study treatment.

Consent for publication The authors affirm that written consent was obtained from parents or legal guardians for publishing study information and results.

Author contributions AB, KR, BS, and NAL contributed to study concept and design. ASP, AW, ES, DT, MJC, PDA, and MG acquired data. XS conducted the statistical analyses on the data. KR and NAL drafted the manuscript with the medical writer and created figures. All authors interpreted the data, provided critical feedback on the manuscript, approved the final manuscript for submission, and are accountable for the accuracy and integrity of the manuscript.

Code availability Not applicable.

References

1. Drucker AM, Eyerick K, de Bruin-Weller M, Thyssen JP, Spuls PI, Irvine AD, et al. Use of systemic corticosteroids for atopic dermatitis: International Eczema Council consensus statement. Br J Dermatol. 2018;178(3):768–75.
2. Boguniewicz M, Fonacier L, Guttman-Yassky E, Ong PY, Silverberg J, Farrar JR. Atopic dermatitis yardstick: practical recommendations for an evolving therapeutic landscape. Ann Allergy Asthma Immunol. 2018;120(1):10–22.
3. Wollenberg A, Christen-Zäch S, Taieb A, Paul C, Thyssen JP, de Bruin-Weller M, et al. ETFAD/EADV Eczema task force 2020 position paper on diagnosis and treatment of atopic dermatitis in adults and children. J Eur Acad Dermatol Venereol. 2020;34(12):2717–44.
4. Frantz T, Wright EG, Balogh EA, Cline A, Adler-Neal AL, Feldman SR. Topical and oral therapies for childhood atopic dermatitis and plaque psoriasis. Children (Basel). 2019;6(11):125.
5. McLenon J, Rogers MAM. The fear of needles: a systematic review and meta-analysis. J Adv Nurs. 2019;75(1):30–42.
6. Macdonald LE, Karow M, Stevens S, Auerbach W, Poueymirou WT, Yasenchak J, et al. Precise and in situ genetic humanization of 6 Mb of mouse immunoglobulin genes. Proc Natl Acad Sci U S A. 2014;111(14):5147–52.
7. Murphy AJ, Macdonald LE, Stevens S, Karow M, Dore AT, Pobursky K, et al. Mice with megabase humanization of their immunoglobulin genes generate antibodies as efficiently as normal mice. Proc Natl Acad Sci U S A. 2014;111(14):5153–8.
8. Gandhi NA, Pirozzi G, Graham NMH. Commonality of the IL-4/IL-13 pathway in atopic diseases. Expert Rev Clin Immunol. 2017;13(5):425–37.

9. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med. 2016;375(24):2335–48.
10. Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet. 2017;389(10086):2287–303.
11. de Bruin-Weller M, Thaçi D, Smith CH, Reich K, Cork MJ, Radin A, et al. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to cyclosporine A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFÉ). Br J Dermatol. 2018;178(5):1083–101.
12. Deleuran M, Thaçi D, Beck LA, de Bruin-Weller M, Blauvelt A, Forman S, et al. Dupilumab shows long-term safety and efficacy in patients with moderate to severe atopic dermatitis enrolled in a phase 3 open-label extension study. J Am Acad Dermatol. 2020;82(2):377–88.
13. Simpson EL, Paller AS, Siegfried EC, Boguniewicz M, Sher L, Gooderham MJ, et al. Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: a phase 3 randomized clinical trial. JAMA Dermatol. 2020;156(1):44–56.
14. Cork MJ, Thaçi D, Eichenfield LF, Arkwright PD, Hultsch T, Davis JD, et al. Dupilumab in adolescents with uncontrolled moderate-to-severe atopic dermatitis: results from a phase IIa open-label trial and subsequent phase III open-label extension. Br J Dermatol. 2020;182(1):85–96.
15. Paller AS, Siegfried EC, Thaçi D, Wollenberg A, Cork MJ, Arkwright PD, et al. Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: a randomized, double-blinded, placebo-controlled phase 3 trial. J Am Acad Dermatol. 2020;83(5):1282–93.
16. Wollenberg A, Beck LA, Blauvelt A, Simpson EL, Chen Z, Chen Q, et al. Laboratory safety of dupilumab in moderate-to-severe atopic dermatitis: results from three phase III trials (LIBERTY AD SOLO 1, LIBERTY AD SOLO 2, LIBERTY AD CHRONOS). Br J Dermatol. 2020;182(5):1120–35.
17. Siegfried E, Bieber T, Simpson EL, Paller A, Beck LA, Boguniewicz M, et al. Effect of dupilumab on laboratory parameters in adolescents with atopic dermatitis: results from a randomized placebo-controlled phase 3 clinical trial. Am J Clin Dermatol. 2021;22(2):243–55.
18. Eichenfield L, Hanifin JM, Luger TA, Stevens SR, Pride HB. Consensus conference on pediatric atopic dermatitis. J Am Acad Dermatol. 2003;49(6):1088–95.
19. U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE); Version 5.0. 2017. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed 11 Feb 2021.
20. Nordic study group on myeloproliferative disorders (NMPD). Guidelines for the diagnosis and treatment of eosinophilia. 2nd version. 2012. http://www.myeloid.dk/filearchive/baae3847cc11e0dab52ab8b8f09e8122.pdf. Accessed 11 Feb 2021.
21. Tamagawa-Mineoka R, Katoh N, Ueda E, Masuda K, Kishimoto S. Elevated platelet activation in patients with atopic dermatitis and psoriasis: increased plasma levels of β-thromboglobulin and platelet factor 4. Allergol Int. 2008;57(4):391–6.
22. Tamagawa-Mineoka R. Important roles of platelets as immune cells in the skin. J Dermatol Sci. 2015;77(2):93–101.
23. Brunner PM, He H, Pavel AB, Czarnowicki T, Lefferdink R, Erickson T, et al. The blood proteomic signature of early-onset pediatric atopic dermatitis shows systemic inflammation and is distinct from adult long-standing disease. J Am Acad Dermatol. 2019;81(2):510–9.
24. Gittler JK, Shemer A, Suárez-Fariñas M, Fuentes-Duculan J, Gulewicz KJ, Wang CQF, et al. Progressive activation of Th2/Th22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. J Allergy Clin Immunol. 2012;130(6):1344–54.
25. Rabe K, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med. 2018;378:2475–85.
26. Castro M, Corren J, Pavord I, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med. 2018;378:2486–96.
27. Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. Lancet. 2019;394(10209):1638–50.
28. Groh M, Pagnoux C, Baldini C, Bel E, Bottero P, Cottin V, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. Eur J Intern Med. 2015;26(7):545–53.
29. Furuta S, Iwamoto T, Nakajima H. Update on eosinophilic granulomatosis with polyangiitis. Allergol Int. 2019;68(4):430–6.
30. Le Floc'h A, Allinne J, Nagashima K, Scott G, Birchard D, Asrat S, et al. Dual blockade of IL-4 and IL-13 with dupilumab, an IL-4Rα antibody, is required to broadly inhibit type 2 inflammation. Allergy. 2020;75(5):1188–204.
31. Allinne J, Scott G, Birchard D, Asrat S, Nagashima K, Le Floc'h A, et al. Broader impact of IL-4Rα blockade than IL-5 blockade on mediators of type 2 inflammation and lung pathology in a house dust mite-induced asthma mouse model. Am J Respir Crit Care Med. 2019;199:abstractA5555. https://doi.org/10.1164/ajrccm-conference.2019.199.1_MeetingAbstracts.A5555.
32. Orengo J, Allinne J, Le Floc'h A, Potocky T, Kim JH, Birchard D, et al. Blocking IL-4Ra with dupilumab prevents lung inflammation in a mouse asthma model. Eur Respir J. 2018;52:abstractPA77. https://doi.org/10.1183/13993003.congress-2018.PA977.
33. Gandhi NA, Bennett BL, Graham NMH, Pirozzi G, Stahl N, Yancopoulos GD. Targeting key proximal drivers of type 2 inflammation in disease. Nat Rev Drug Discov. 2016;15(1):35–50.
34. Mukai H, Noguchi T, Kamimura K, Nishioka K, Nishiyama S. Significance of elevated serum LDH (lactate dehydrogenase) activity in atopic dermatitis. J Dermatol. 1990;17(8):477–81.