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SHORT REPORT

Association between maternal dupilumab exposure and pregnancy outcomes in patients with moderate-to-severe atopic dermatitis: A nationwide retrospective cohort study

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Abstract

Background: There is limited epidemiological evidence on outcomes associated with dupilumab exposure during pregnancy; monitoring pregnancy outcomes in large populations is required.

Objective: To investigate the potential association between exposure to dupilumab in pregnant women with atopic dermatitis and any adverse pregnancy, neonatal, congenital and post-partum outcomes.

Methods: We performed a multicentre retrospective cohort study across 19 Italian tertiary referral hospital. Childbearing women were eligible if aged 18–49 years and carried out the pregnancy between 1 October 2018 and 1 September 2022.

Results: We retrospectively screened records of 5062 patients receiving dupilumab regardless of age and gender, identifying 951 female atopic dermatitis patients of childbearing age, 29 of whom had been exposed to the drug during pregnancy (3%). The median duration of dupilumab treatment prior to conception was 22.5 weeks (range: 3–118). The median time of exposure to the drug during pregnancy was 6 weeks (range: 2–24). All the documented pregnancies were unplanned, and the drug was discontinued in all cases once pregnancy status was reported. The comparison of the study cohort and the control group found no significant drug-associated

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risk for adverse pregnancy, congenital, neonatal or post-partum outcomes. The absence of a statistically significant effect of exposure on the event was confirmed by bivariate analysis and multivariate analysis adjusted for other confounding factors.
Conclusions: This cohort of pregnant patients exposed to dupilumab adds to the existing evidence concerning the safety of biologic agents in pregnancy. No safety issues were identified regarding the primary outcome assessed. In clinical practice, these data provide reassurance in case of dupilumab exposure during the first trimester. However, the continuous use of dupilumab throughout pregnancy warrants further research.

INTRODUCTION

Dupilumab is an IgG4 human monoclonal antibody directed against the common interleukin (IL)-4 receptor alpha (IL-4Rα) subunit of both the IL-4 and the IL-13, key drivers of Type 2 inflammation. The drug is the first biological being licensed for atopic dermatitis (AD).[1,2] In pregnancy, AD frequently has a deleterious course and may relevantly impact quality of life.[3] Although there is no specific concern regarding the potential risks secondary to dupilumab exposure in pregnancy, current recommendations suggest the use of other systemic drugs in pregnant women with AD, while dupilumab should be reserved for special circumstances in light of the little evidence available.[4–6]

This study sought to address this knowledge gap by investigating the potential association between exposure to dupilumab in pregnant women with AD and any adverse pregnancy, congenital, neonatal and post-partum outcomes.

METHODS

Study design and patient population

We performed a multicentre retrospective cohort study across 19 Italian tertiary referral hospitals. Childbearing women were eligible if aged 18–49 years and if they got pregnant and carried out the pregnancy between 1 October 2018 and 1 September 2022. The exposed cohort consisted of patients with moderate-to-severe AD who received at least 1 dose of dupilumab administered at standard dosage within 8 weeks prior to conception and at any time during pregnancy. All pregnant patients who did not meet the criteria for exposure were defined as unexposed. Patients were enrolled from each centre through a retrospective review of electronic health records. The Institutional Review Board approved the study protocol (n. 003370) and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed.[7]

Data collection

Data including maternal demographics, medical history, AD severity, pregnancy outcomes and live-births characteristics were collected (Table 1). Information was collected at different timepoints: at each pregnancy trimester, at delivery or pregnancy termination, at 40 days the post-partum period; offspring outcomes data were retrieved up to the study end cut-off date. The primary outcome was defined as the presence of any adverse pregnancy, congenital, neonatal or post-partum events, as summarized in Table 2. The occurrence of adverse events in the offspring was also evaluated. For each exposed patient we assessed whether dupilumab was discontinued, as well as the duration of its exposure, AD severity and its impact on quality of life assessed by means of Dermatology Life Quality Index. Furthermore, in both patient cohorts, the topical and/or systemic medications taken during pregnancy were assessed (Table 3).

Statistical analysis

Descriptive analyses were performed and stratified with respect to the exposure of interest and an appropriate bivariate test was used to describe the association between each variable and exposure; in particular, Kruskal–Wallis, chi-squared and Wald tests were used for continuous, categorical and primary outcome variables, respectively. In the concluding stage of the analysis, a multiple logistic regression model was employed to refine the initial estimation derived from the Wald test, considering the impact of various variables and confounders. The objective was to more precisely evaluate the relationship between adverse events during pregnancy and exposure to dupilumab. Covariates for the model were selected primarily based on clinical criteria and subsequently refined through a stepwise selection algorithm, incorporating backward elimination with specified p-value criteria (entry at 0.30 and retention at 0.25). All tests were 2-sided, and $p < 0.05$ was considered statistically significant. All analyses were performed with SAS®, version 9.4 (SAS Institute Inc., Cary, NC, USA). Data analysis was conducted from 15 January 2023 to 15 February 2023.

RESULTS

Patients' characteristics

At the cut-off date for this analysis, we retrospectively screened records of 5062 patients receiving dupilumab regardless of age and gender, identifying 951 female AD patients of childbearing age, 29 of whom had been exposed to the drug

TABLE 1 Baseline and demographic characteristics.

	Unexposed (*N* = 93)	Exposed (*N* = 28)	Total (*N* = 121)	*p*-Value
Age				0.1332[a]
N	91	28	119	
Mean (SD)	33.6 (3.84)	32.4 (7.46)	33.4 (4.92)	
Median	33	30	33	
Range	26.0–45.0	19.0–45.0	19.0–45.0	
Dupilumab exposure prior to conception (*n* weeks)				-
N	-	28	-	
Mean (SD)	-	36.8 (37.97)	-	
Median	-	22.5	-	
Range	-	3.0–118.0	-	
Total number of weeks in pregnancy during dupilumab[b]				-
N	93	28	121	
Mean (SD)	-	6.4 (4.21)	-	
Median	-	6	-	
Range	-	2.0–24.0	-	
Duration of gestation (*n* weeks)				0.2974[a]
N	90	28	118	
Mean (SD)	33.3 (12.45)	32.8 (11.69)	33.2 (12.23)	
Median	39	38	39	
Range	5.0–45.0	6.0–44.0	5.0–45.0	
Age of the offspring at the study end date (*n* months)				-
N	93	21	114	
Mean (SD)	44 (–)	16.4 (9.21)	38.9 (–)	
Median	-	16	-	
Range	3.0–26.0	1.0–36.0	1.0–26.0	
Infant's weight at birth (kg)				0.5373[a]
N	75	19	94	
Mean (SD)	3.1 (0.43)	3.3 (0.37)	3.2 (0.42)	
Median	3.2	3.2	3.2	
Range	1.7–3.9	2.8–4.2	1.7–4.2	
Race, *n* (%)				0.1282[c]
Asian	1 (1.1%)	1 (3.6%)	2 (1.7%)	
Caucasian	90 (98.9%)	26 (92.9%)	116 (97.5%)	
Black	0 (0.0%)	1 (3.6%)	1 (0.8%)	
Missing	2	0	2	
Maternal body mass index, *n* (%)				0.0032[a]
Underweight	2 (2.2%)	0 (0.0%)	2 (1.6%)	
Normal weight	77 (82.8%)	21 (75%)	98 (81%)	
Overweight	12 (12.9%)	1 (3.6%)	13 (10.7%)	
Obese (Class I)	0 (0%)	5 (17.8%)	5 (4.1%)	
Missing	2	1	3	
Smoke in the month prior to conception or in pregnancy, *n* (%)				0.8940[c]
No	79 (86.8%)	18 (85.7%)	97 (86.6%)	
Yes	12 (13.2%)	3 (14.3%)	15 (13.4%)	
Missing	2	7	9	
Alcohol intake during the first trimester or in pregnancy, *n* (%)[d]				0.0076[c]
No	91 (100.0%)	24 (92.3%)	115 (98.3%)	

TABLE 1 (Continued)

	Unexposed ($N=93$)	Exposed ($N=28$)	Total ($N=121$)	p-Value
Yes	0 (0.0%)	2 (7.7%)	2 (1.7%)	
Missing	2	2	4	
Work involving night shifts during the period of conception and gestation, *n* (%)				0.0037[c]
No	66 (72.5%)	24 (100.0%)	90 (78.3%)	
Yes	25 (27.5%)	0 (0.0%)	25 (21.7%)	
Missing	2	4	6	
Exposure to pesticides in the first 3 months of pregnancy?, *n* (%)				0.0553[c]
No	91 (100.0%)	24 (96.0%)	115 (99.1%)	
Yes	0 (0.0%)	1 (4.0%)	1 (0.9%)	
Missing	2	3	5	
Previous cyclosporine therapy, *n* (%)				<.0001[c]
No	91 (100.0%)	1 (3.6%)	92 (77.3%)	
Yes	0 (0.0%)	27 (96.4%)	27 (22.7%)	
Missing	2	0	2	
Patient's partner aged 40 years old, *n* (%)				0.5510[c]
No	67 (73.6%)	19 (67.9%)	86 (72.3%)	
Yes	24 (26.4%)	9 (32.1%)	33 (27.7%)	
Missing	2	0	2	
Recurrent pregnancy loss, *n* (%)[e]				0.0831[c]
No	83 (98.8%)	25 (92.6%)	108 (97.3%)	
Yes	1 (1.2%)	2 (7.4%)	3 (2.7%)	
Missing	9	1	10	
Parity, *n* (%)				0.0667[c]
Nulliparous	61 (67.0%)	12 (42.9%)	73 (61.3%)	
Pluriparous	8 (8.8%)	5 (17.9%)	13 (10.9%)	
Primiparous	22 (24.2%)	11 (39.3%)	33 (27.7%)	
Missing	2	0	2	
Concomitant gynaecological diseases, *n* (%)				0.0139[c]
No	77 (82.8%)	17 (60.7%)	94 (77.7%)	
Yes	16 (17.2%)	11 (39.3%)	27 (22.3%)	
Concomitant thyroid diseases, *n* (%)				0.0459[c]
No	73 (80.2%)	26 (96.3%)	99 (83.9%)	
Yes	18 (19.8%)	1 (3.7%)	19 (16.1%)	
Missing	2	1	3	
Concomitant autoimmune diseases, *n* (%)				0.4464[c]
No	84 (92.3%)	27 (96.4%)	111 (93.3%)	
Yes	7 (7.7%)	1 (3.6%)	8 (6.7%)	
Missing	2	0	2	
Adverse pregnancy/neonatal/congenital/post-partum events in previous pregnancies, *n* (%)[f]				0.0004[c]
No	45 (54.2%)	24 (92.3%)	69 (63.3%)	
Yes	38 (45.8%)	2 (7.7%)	40 (36.7%)	
Missing	10	2	12	

[a]Kruskal–Wallis p value.

[b]Only one patient had exposure to dupilumab extended into the second trimester of pregnancy.

[c]Chi-squared p value.

[d]At least three alcoholic beverages per week.

[e]Recurrent pregnancy loss is defined as the spontaneous loss of two or more clinically recognized pregnancies.

[f]These events are defined as following: spontaneous abortion = pregnancy loss within 20 weeks' gestation.

TABLE 2 Events and outcomes.

	Unexposed (*N* = 93)	Exposed (*N* = 28)	Total (*N* = 121)	*p*-Value
Events summaries				
Primary outcome[a]				
Events/*N*	33/93	15/28	48/121	
Event rate (95% CI)	0.35 (0.26–0.45)	0.54 (0.35–0.72)	0.40 (0.31–0.48)	
Odds ratio[b] (95% CI)	Reference	2.10 (0.89–4.94)		0.0896[2]
Adjusted odds ratio (95% CI)[c]	Reference	3.842 (0.962–15.343)		0.0568[2]
Pregnancy outcomes				
Events/*N*	27/93	9/28	36/121	
Event rate (95% CI)	0.29 (0.20–0.38)	0.32 (0.15–0.49)	0.30 (0.22–0.38)	
Odds ratio[b] (95% CI)	Reference	1.16 (0.47–2.88)		0.7524[2]
Neonatal outcomes				
Events/*N*	21/93	8/28	29/121	
Event rate (95% CI)	0.23 (0.14–0.31)	0.29 (0.12–0.45)	0.24 (0.16–0.32)	
Odds ratio[b] (95% CI)	Reference	1.37 (0.53–3.56)		0.5160[2]
Congenital anomalies				0.1613[1]
No	70 (93.3%)	28 (100.0%)	98 (95.1%)	
Yes	5 (6.7%)	0 (0.0%)	5 (4.9%)	
Missing	18	0	18	
Post-partum outcomes				
Events/*N*	3/93	2/28	5/121	
Event rate (95% CI)	0.03 (0.00–0.07)	0.07 (0.00–0.17)	0.04 (0.01–0.08)	
Odds ratio[b] (95% CI)	Reference	2.31 (0.37–14.55)		0.3734[2]
Events details[d]				
Pregnancy outcomes				
Hypertension gravidarum	7 (7.5%)	0 (0%)	7 (5.8%)	
Gestational diabetes	5 (5.4%)	1 (3.6%)	6 (5%)	
Post-partum haemorrhage	4 (4.3%)	1 (3.6%)	5 (4.1%)	
Oligohydramnios	2 (2.2%)	2 (7.1%)	4 (3.3%)	
Pre-eclampsia	3 (3.2%)	0 (0%)	3 (2.5%)	
Placenta previa	1 (1.1%)	0 (0%)	1 (0.8%)	
Polydramnios	1 (1.1%)	0 (0%)	1 (0.8%)	
Others[e]	11 (11.8%)	5 (17.9%)	16 (13.2%)	
Miscarriage	2 (18.2%)	5 (100%)	7 (43.8%)	
Autoimmune hyperthyroidism only in pregnancy	2 (18.2%)	0 (0%)	2 (18.2%)	
Preterm premature rupture of membranes	2 (18.2%)	0 (0%)	2 (12.5%)	
Intracranial extra-axial meningioma with tumour-associated haemorrhage	1 (9.1%)	0 (0%)	1 (6.3%)	
Hyperemesis gravidarum	1 (9.1%)	0 (0%)	1 (6.3%)	
Cholestasis gravidarum	1 (9.1%)	0 (0%)	1 (6.3%)	
Nonautoimmune hypothyroidism in pregnancy only	1 (9.1%)	0 (0%)	1 (6.3%)	
Toxoplasmosis	1 (9.1%)	0 (0%)	1 (6.3%)	
Neonatal outcomes				
Prematurity	10 (10.8%)	7 (25%)	17 (14%)	
Respiratory distress	1 (1.1%)	1 (3.6%)	2 (1.7%)	
Hyperbilirubinaemia	12 (12.9%)	0 (0%)	12 (9.9%)	

TABLE 2 (Continued)

	Unexposed (*N* = 93)	Exposed (*N* = 28)	Total (*N* = 121)	*p*-Value
Other	2 (2.2%)	1 (3.6%)	5 (4.1%)	
Pulmonary hypertension	0 (0%)	1 (100%)	1 (20%)	
Episodes of apnoea	1 (50%)	0 (0%)	1 (20%)	
Intensive care unit observation for aspiration of amniotic fluid	1 (50%)	0 (0%)	1 (20%)	
Post-partum outcomes				
New-onset hypertension	3 (3.2%)	0 (0%)	3 (2.5%)	
Clostridium infection	1 (1.1%)	0 (0%)	1 (0.8%)	
Post-partum depression	0 (0%)	1 (3.6%)	1 (0.8%)	
Idiopathic anaphylaxis	0 (0%)	1 (3.6%)	1 (0.8%)	
Congenital anomalies				
Ventricular septal defect	2 (2.2%)	0 (0%)	2 (1.7%)	
Atrial septal defect	1 (1.1%)	0 (0%)	1 (0.8%)	
Duane's syndrome	1 (1.1%)	0 (0%)	1 (0.8%)	
Tetralogy of Fallot	1 (1.1%)	0 (0%)	1 (0.8%)	
Offspring outcomes				
Atopic dermatitis	0 (0%)	2 (7.1%)	2 (1.7%)	
Solitary cutaneous mastocytoma	0 (0%)	1 (3.5%)	1 (0.8%)	
Bronchiolitis complicated by COVID-19	1 (1.1%)	0 (0%)	1 (0.8%)	
Growth hormone deficiency	1 (1.1%)	0 (0%)	1 (0.8%)	

[a]The primary outcome was defined as the presence of any adverse pregnancy, congenital, neonatal or post-partum events.

[b]Odd ratio (OR) is calculated considering as reference group unexposed patients.

[c]In a logistic model, with the following covariates: exposure, age, smoke, partner age, concomitant gynaecological disease, concomitant thyroid disease, history of pregnancy/neonatal/congenital/post-partum complications.

[d]These events are defined as following: spontaneous abortion = pregnancy loss within 20 weeks' gestation; stillbirth = pregnancy loss later than 20 weeks' gestation; preterm birth = gestational age of less than 37 weeks; small for gestational age = below the 10th percentile of the gestational-age-specific birth weight; low birth weight = <2500 g.

[e]Percentages are based on subgroup 'others' values.

[1]Chi-Square *p*-value; [2]Type-3 Wald *p*-value.

during pregnancy (3%). Only one patient was excluded due to her ongoing pregnancy status. The median age of pregnant women was 30 years (range: 19–45) and 33 years (range: 26–45) in exposed and unexposed cohorts, respectively. The median duration of dupilumab treatment prior to conception was 22.5 weeks (range: 3–118). All the documented pregnancies were unplanned, and the drug was immediately discontinued in all cases. The median time of exposure to the drug was 6 weeks (range: 2–24). The effects of discontinuing dupilumab during pregnancy AD are illustrated in Figure 1a. As for baseline and demographics characteristics, no statistically significant differences were documented.

Risk factors

Comparing exposed and unexposed cohort regarding collected risk factors for the primary outcome, we found a significant difference in the following variables: alcohol intake in pregnancy (*p*-value: 0.0076), presence of any gynaecological disease (*p*-value: 0.0139), night shift working (*p*-value: 0.037) and history of adverse pregnancy, neonatal or post-partum outcomes (*p*-value: 0.0004). Concerning the first two variables, we documented higher frequency of alcohol intake in the first trimester of pregnancy (7.7% vs. 0%) and any gynaecological disease at the time of conception (39.3% vs. 17.2%) in the exposed cohort. On the contrary, night shift working (0% vs. 27.5%) and history of adverse pregnancy, neonatal or post-partum outcomes (7.7% vs. 45.8%) were less common in exposed patients.

Pregnancy outcomes

The primary outcome of the logistic regression was first analysed through a bivariate analysis: we detected an OR of 2.10 (0.89–4.94) in accordance with the higher event rate in the exposed cohort (0.54 vs. 0.35), albeit without reaching statistical significance (*p*-value: 0.0896). Dupilumab exposure was one of the variables retained in the regression logistic model by applying the stepwise selection algorithm, but the associated estimate again was not statistically significant (OR: 3.842; 95% CI: 0.962–15.343) (Table S1). At the bivariate level, we further investigated the association between dupilumab administration and each of the four event categories selected as primary outcome. No congenital abnormalities were noted in the exposed patient cohort. Point

TABLE 3 Drug exposure other than dupilumab during pregnancy.

	Unexposed (*N* = 93)	Exposed (*N* = 28)	Total (*N* = 121)
Topical medication applied during pregnancy, *n* (%)			
No	93 (100%)	13 (46.4%)	106 (87.6%)
Yes	0 (0%)	15 (53.6%)	15 (12.4%)
Duration of topical medication application (days)			
N	0	13	-
Mean (SD)	-	38.4 (45.75)	-
Median	-	28	-
Range	-	7.0, 183.0	-
Topical medication, *n* (%)			
Methylprednisolone aceponate	0 (0%)	7 (25%)	7 (25%)
Mometasone furoate	0 (0%)	3 (10.7%)	3 (10.7%)
Fusidic acid + betamethasone valerate	0 (0%)	2 (7.1%)	2 (7.1%)
Tacrolimus 0.1%	0 (0%)	2 (7.1%)	2 (7.1%)
Emollient cream	0 (0%)	1 (3.5%)	1 (3.5%)
Desoximetasone	0 (0%)	1 (3.5%)	1 (3.5%)
Fusidic acid	0 (0%)	1 (3.5%)	1 (3.5%)
Rifamycin	0 (0%)	1 (3.5%)	1 (3.5%)
Pregnancy trimester in which topical medications were applied, *n* (%)			
I	0 (0%)	4 (14.2%)	4 (3.3%)
II	0 (0%)	11 (39.2%)	11 (9.1%)
III	0 (0%)	8 (28.5%)	8 (6.6%)
Reason of topical medication application, *n* (%)			
Recurrence of atopic dermatitis	0 (0%)	13 (46.4%)	4 (3.3%)
Impetigo	0 (0%)	1 (3.5%)	1 (0.8%)
Systemic medication taken during pregnancy, *n* (%)			
No	57 (61.3%)	21 (75.0%)	78 (64.5%)
Yes	39 (41.9%)	7 (25.0%)	46 (38%)
Systemic medication, *n* (%)			
Antibiotics	9 (9.7%)	0 (0%)	9 (7.4%)
Antiemetics	7 (7.5%)	0 (0%)	7 (5.8%)
Acetylsalicylic acid	4 (4.3%)	1 (3.5%)	5 (4.1%)
Levothyroxine	4 (4.3%)	1 (3.5%)	5 (4.1%)
Nifedipine	4 (4.3%)	0 (0%)	4 (3.3%)
Methyldopa	2 (2.2%)	0 (0%)	2 (1.7%)
Insulin	2 (2.2%)	0 (0%)	2 (1.7%)
Tapazole	2 (2.2%)	0 (0%)	2 (1.7%)
Antiepileptics	1 (1.1%)	0 (0%)	1 (0.8%)
Antihistamine	0 (0%)	2 (7.1%)	2 (0.8%)
Prednisone	0 (0%)	2 (7.1%)	2 (0.8%)
Ursodeoxycholic acid	1 (1.1%)	0 (0%)	1 (0.8%)
Heparin	1 (1.1%)	0 (0%)	1 (0.8%)
Paracetamol	0 (0%)	1 (3.5%)	1 (0.8%)
Reason of systemic medication use *n* (%)			
Urinary tract infection	8 (8.6%)	0 (0%)	8 (6.6%)
Nausea	7 (7.5%)	0 (0%)	7 (5.8%)
Hypothyroidism	4 (4.3%)	1 (14.3%)	5 (4.1%)
Hypertension	4 (4.3%)	0 (0%)	4 (3.3%)
Gestational diabetes	2 (2.2%)	0 (0%)	2 (1.7%)
Intrahepatic cholestasis of pregnancy	1 (1.1%)	0 (0%)	1 (0.8%)
Migraine	0 (0%)	1 (14.3%)	1 (0.8%)
Raynaud's phenomenon	1 (1.1%)	0 (0%)	1 (0.8%)
Sympathetic ophthalmia	0 (0%)	1 (14.3%)	1 (0.8%)
Preterm premature rupture of membrane	1 (1.1%)	0 (0%)	1 (0.8%)
Thromboembolic risk prevention	0 (0%)	1 (14.3%)	1 (0.8%)
Itching	0 (0%)	2 (7.14%)	2 (1.6%)
Poor AD disease control	0 (0%)	1 (14.3%)	1 (0.8%)
Pre-pregnancy thrombosis	1 (1.1%)	0 (0%)	1 (0.8%)
Pregnancy trimester in which systemic medications were taken, *n* (%)			
I	1 (1.1%)	1 (3.5%)	2 (1.6%)
II	1 (1.1%)	0 (0%)	1 (0.8%)
III	1 (1.1%)	2 (7.1%)	3 (2.5%)
Throughout the entire period of pregnancy	1 (1.1%)	2 (20.0%)	3 (2.5%)

Abbreviation: AD, atopic dermatitis.

estimates for event rates in exposed patients were higher for pregnancy (OR: 0.32 [95% CI: 0.15–0.49] vs. OR: 0.29 [95% CI: 0.20–0.38]), neonatal (OR: 0.29 [95% CI: 0.12–0.45] vs. OR: 0.23 [95% CI: 0.14–0.31]), and post-partum (OR: 0.07 [95% CI: 0.00–0.17] vs. OR: 0.03 [95% CI: 0.00–0.07]) complications (Figure 1b–e). However, the overlap of confidence intervals and inferential results for OR indicates that, similar to the primary outcome, none of the previously mentioned differences were statistically significant.

DISCUSSION

The primary reason for this study was to contribute to the debate concerning the safety of dupilumab when used during the first trimester of pregnancy by providing real-life data relating to the routine use of the drug in Italy. The treatment was stopped in all cases as soon as the women reported that they were pregnant, which reflects the physicians' attitude to

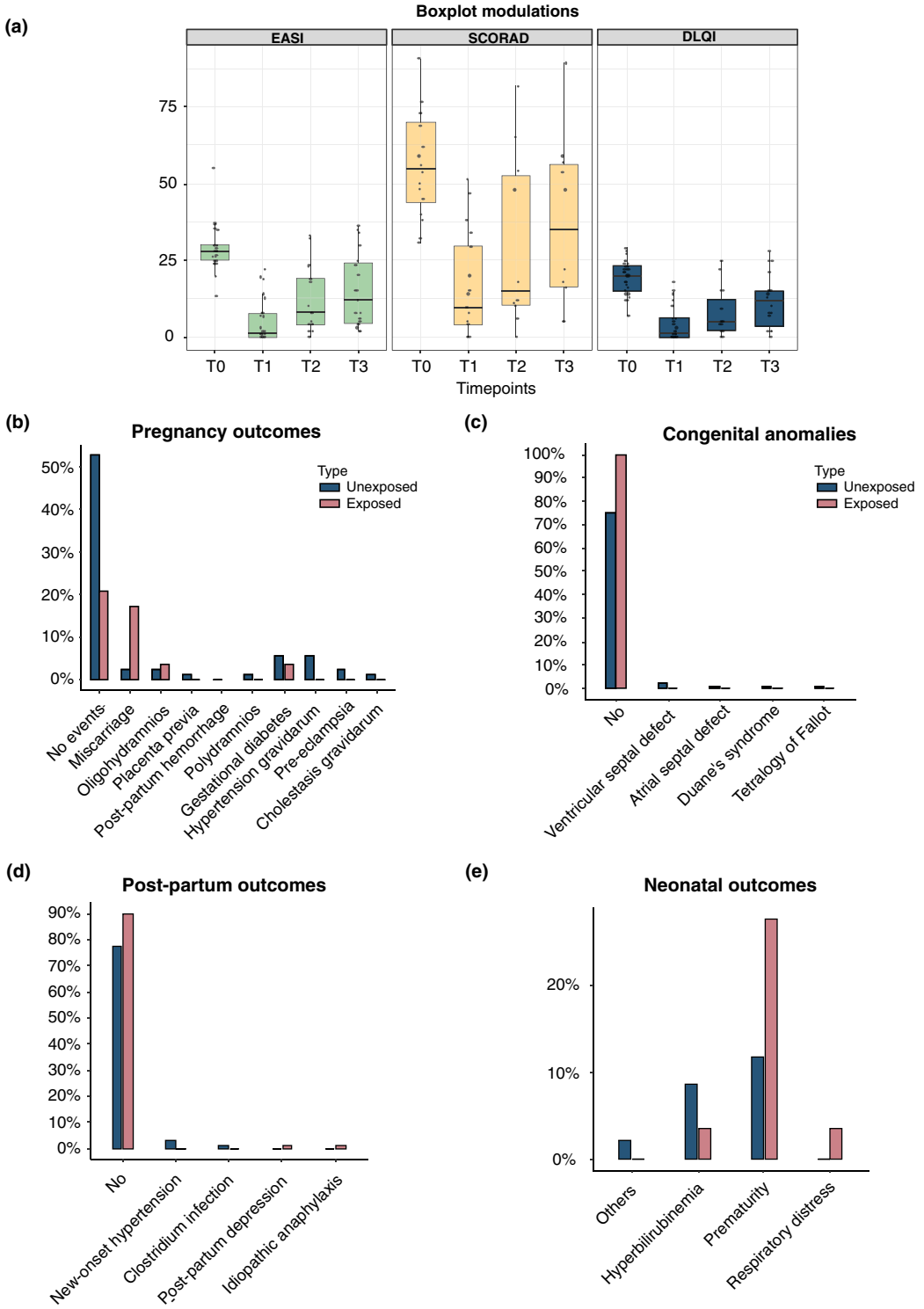

FIGURE 1 (a) Boxplots representing the values of EASI, DLQI, and SCORAD at the initiation of dupilumab therapy (baseline) and at three different time points following discontinuation of the drug, namely 3 months (T1), 6 months (T2) and 9 months (T3). DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; SCORAD, SCORing Atopic Dermatitis (b–e). Barplots showing the difference between any adverse pregnancy, congenital, post-partum and neonatal events in the exposed group to dupilumab compared to the non-exposed group.

the use of dupilumab during pregnancy in a large and representative sample of our country. The relatively small proportion of women who became pregnant during the treatment was probably secondary to the common habit to discontinue the drug before planning a parenthood, due to the potential harmful effects to the fetus. As expected, drug discontinuation worsened the severity of AD in the majority of cases (Table S2), consequently leading to a poorer quality of life for the patients.

While no significant differences were detected in the assessed outcomes, there was an increased incidence of preterm births among those exposed to dupilumab. We hypothesize that the observed trend might be linked to a rebound immune system activation following the discontinuation of dupilumab, albeit the exact causes remain undetermined. Although the incidence of miscarriage in the unexposed patient group is lower than indicated by existing literature,[8] this disparity does not weaken our conclusion. Indeed, this suggests a possibly higher odd ratio that would diminish upon incidence adjustment, reinforcing our finding that there is no heightened risk of miscarriage in the exposed group. Our results are in line with previous case reports, case series and pharmacovigilance data of pregnant women with AD exposed to dupilumab, all suggesting a favourable safety profile.[3,9–15] Similarly, animal studies showed no fetal abnormalities or effects on fertility.[6] However, the current evidence is not yet sufficient to definitively recommend the use of dupilumab during pregnancy.[4,5,16]

LIMITATIONS

Study limitations include the retrospective design and the relatively small population of pregnant women exposed to dupilumab. Nonetheless, our study investigates one of the largest patients' samples reported to date. It is well known that human immunoglobulin G crosses the placental barrier in a linear fashion as the pregnancy progresses, with the greatest transfer of IgG in the third trimester.[17] The difficulty of evaluating such effects is an intrinsic limitation of our data, as the drug was discontinued earlier. Finally, the unexposed group data were derived from a gynaecological setting, potentially entailing a higher degree of accuracy.

CONCLUSIONS

This cohort of pregnant patients exposed to dupilumab adds to the existing evidence concerning the safety of biologic agents in pregnancy. No safety issues were identified regarding the primary outcome assessed. In clinical practice, these data provide reassurance in case of dupilumab exposure during the first trimester. However, the continuous use of dupilumab throughout pregnancy warrants further research.

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CONFLICT OF INTEREST STATEMENT
Laura Bonzano has been a speaker for Sanofi Genzyme. Ersilia Tolino acted as speaker and consultant for Sanofi, LEO Pharma, Amgen and MSD. Luigi Gargiulo has been a consultant for Almirall. Antonio Costanzo has served as an advisory board member, consultant and has received fees and speaker's honoraria or has participated in clinical trials for Abbvie, Almirall, Biogen, LEO Pharma, Lilly, Janssen, Novartis, Pfizer, Sanofi Genzyme and UCB-Pharma. Filomena Russo acted as speaker and consultant for Sanofi, Abbvie and Novartis. Cataldo Patruno has served as advisory board member and consultant and has received fees and speaker's honoraria or has participated in clinical trials for AbbVie, Amgen, Leo Pharma, Lilly, Novartis, Pfizer Pierre Fabre and Sanofi Genzyme (dupilumab manufacturer). Caterina Ferreli has participated in clinical trials for AbbVie, Almirall, Sanofi Genzyme, Janssen, Leo Pharma and Novartis. Maddalena Napolitano acted as speaker, consultant and advisory board member for Sanofi, AbbVie, LEO Pharma, Amgen, Pierre Fabre and Eli Lilly. Caterina Foti acted as speaker and consultant for Sanofi. Niccolò Gori has been a speaker or board member for Abbvie, Sanofi Genzyme, Leo-pharma, Pfizer, Novartis and Amgen. Mariateresa Rossi has served as advisory board member and consultant and has received fees and speaker's honoraria or has participated in clinical trials for AbbVie, Leo Pharma, Pfizer and Sanofi Genzyme. Andrea Chiricozzi has served as advisory board member and consultant and has received fees

and speaker's honoraria or has participated in clinical trials for AbbVie, Almirall, Bristol Myers Squibb, Leo Pharma, Lilly, Janssen, Novartis, Pfizer and Sanofi Genzyme (dupilumab manufacturer). Angelo Valerio Marzano reports consultancy/advisory boards disease-relevant honoraria from AbbVie, Boehringer-Ingelheim, Novartis, Pfizer, Sanofi and UCB. No other disclosures were reported.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

ETHICS STATEMENT

The patients in this manuscript have given written informed consent to publication of their case details.

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REFERENCES

1. 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.
2. 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.
3. Kage P, Simon JC, Treudler R. A case of atopic eczema treated safely with dupilumab during pregnancy and lactation. J Eur Acad Dermatol Venereol. 2020;34(6):e256–7.
4. Vestergaard C, Wollenberg A, Barbarot S, Christen-Zaech S, Deleuran M, Spuls P, et al. European task force on atopic dermatitis position paper: treatment of parental atopic dermatitis during preconception, pregnancy and lactation period. J Eur Acad Dermatol Venereol. 2019;33(9):1644–59.
5. Adam DN, Gooderham MJ, Beecker JR, Hong CH, Jack CS, Jain V, et al. Expert consensus on the systemic treatment of atopic dermatitis in special populations. J Eur Acad Dermatol Venereol. 2023;37(6):1135–48.
6. Summary of product characteristics. [cited 2023 Jun 29]. Available from: https://www.ema.europa.eu/en/documents/product-information/dupixent-epar-product-information_en.pdf
7. STROBE statement. [cited 2023 Jun 30]. Available from: https://www.strobe-statement.org/checklists/cohort-studies
8. Quenby S, Gallos ID, Dhillon-Smith RK, Podesek M, Stephenson MD, Fisher J, et al. Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss. Lancet. 2021;397(10285):1658–67.
9. Costley M, Murphy B. Severe atopic dermatitis treated successfully with dupilumab throughout pregnancy. Clin Exp Dermatol. 2022;47(5):960–1.
10. Mian M, Dunlap R, Simpson E. Dupilumab for the treatment of severe atopic dermatitis in a pregnant patient: a case report. JAAD Case Rep. 2020;6(10):1051–2.
11. Khamisy-Farah R, Damiani G, Kong JD, Wu JH, Bragazzi NL. Safety profile of dupilumab during pregnancy: a data mining and disproportionality analysis of over 37,000 reports from the WHO individual case safety reporting database (VigiBase™). Eur Rev Med Pharmacol Sci. 2021;25(17):5448–51.
12. Akhtar NH, Khosravi-Hafshejani T, Akhtar D, Dhadwal G, Kanani A. The use of dupilumab in severe atopic dermatitis during pregnancy: a case report. Allergy Asthma Clin Immunol. 2022;18(1):9.
13. Akuffo-Addo E, Nicholas MN, Lansang P. Reported pregnancy outcomes in women with severe atopic dermatitis treated with dupilumab: a systematic review. J Cutan Med Surg. 2023;27(2):177–8.
14. Escolà H, Figueras-Nart I, Bonfill-Orti M, Coll Puigserver N, Martin-Santiago A, Rodríguez Serna M, et al. Dupilumab for atopic dermatitis during pregnancy and breastfeeding: clinical experience in 13 patients. J Eur Acad Dermatol Venereol. 2023;37(9):e1156–60.
15. Schoder K, Zhu Y, Schneeweiss S, Merola JF, Savage TJ, Gibbs LR, et al. Use of systemic immunomodulating medications in pregnant women with atopic dermatitis: a nationwide US study. J Am Acad Dermatol. 2023;89(1):178–81.
16. Deleuran M, Dézfoulian B, Elberling J, et al. Systemic anti-inflammatory treatment of atopic dermatitis during conception, pregnancy and breastfeeding: Interdisciplinary expert consensus in Northern Europe. J Eur Acad Dermatol Venereol. 2024;38(1):31–41.
17. Sitek AN, Li JT, Pongdee T. Risks and safety of biologics: a practical guide for allergists. World Allergy Organ J. 2023;16(1):100737.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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