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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™)

R. KHAMISY-FARAH[1], G. DAMIANI[2,3,4], J.D. KONG[5], J. WU[5], N.L. BRAGAZZI[5]

[1]Clalit Health Service, Akko, Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel
[2]Clinical Dermatology, IRCCS Istituto Ortopedico Galeazzi, Milan, Italy
[3]Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy
[4]Department of Pharmaceutical and Pharmacological Sciences, University of Padua, Padua, Italy
[5]Laboratory for Industrial and Applied Mathematics (LIAM), Department of Mathematics and Statistics, York University, Toronto, ON, Canada

Rola Khamisy-Farah and Giovanni Damiani are co-first authors

Abstract. – Atopic dermatitis, known also as atopic eczema, represents a commonly diagnosed, chronic or recurrent/relapsing inflammatory disorder. From a clinical point of view, it is characterized by acute flare-ups of intense itching, eczematous pruritic lesions involving dry skin. Dupilumab is the only biologic agent approved to treat moderate to severe course of atopic dermatitis, which can be particularly severe during pregnancy causing distress and impacting on maternal and fetal health. However, there is a dearth of data concerning the safety profile of Dupilumab during gestation. Therefore, we took advantage of a large global pharmacovigilance database. From inception up to March 9, 2021, 94,065 adverse drug reactions (ADRs) from 37,848 unique reports were retrieved. Of these, 36 reports related to pregnancy, puerperium and perinatal ADR could be extracted from the pharmacovigilance database. More than half of reports (n = 21; 58.3%) were spontaneous abortion, followed by other events, including exposure to the drug during the pregnancy (n = 8; 22.2%). Two cases of abortion were reported. No studied pregnancy, puerperium and perinatal ADR was found to be associated with the use of Dupilumab. The only OR significantly greater than 1 was the OR associated with the risk of developing heterotopic pregnancy (21.66 [95% CrI 2.95-159.02]) even if the IC was highly imprecise (1.45 [95% CrI from -2.34 to 3.09]), probably because of the single case of heterotopic pregnancy reported. In conclusion, Dupilumab use appears safe during gestation. Further studies are needed, especially to better understand the mechanisms underlying the pharmacological actions and ADR of Dupilumab.

Key Words:
Big data, Data mining, Disproportionality analysis, Pharmacovigilance, Dupilumab, Atopic dermatitis.

Introduction

Atopic dermatitis, known also as atopic eczema, represents a commonly diagnosed, chronic or recurrent/relapsing inflammatory disorder. From a clinical point of view, it is characterized by acute flare-ups of intense itching, eczematous pruritic lesions involving dry skin[1]. The etiopathogenesis of this disease is particularly complex, and multifactorial, including as potential explanations structural/functional impairments of the skin as a barrier, alterations of the skin microbiome, potential environmental triggers, such as air pollution, and involvement of interleukins (ILs) and thymic stromal lymphopoietin cascades, among others[2,3]. From an epidemiological standpoint, atopic dermatitis generally starts in early childhood, affecting up to 15-20% of children and about 1-3% of adults, globally[1].

In most cases, atopic dermatitis has a mild to moderate course, which can be kept under control utilizing topical immunomodulators or moisturizers. In case of failure of corticosteroids or calcineurin inhibitors, more aggressive therapeutic options can be considered, including phototherapy and systemic immunosuppressors. Biologic agents can be another possible treatment. A biologic

Corresponding Author: Nicola Luigi Bragazzi, MD: email: robertobragazzi@gmail.com

drug, also termed as biologic, is a product that is produced and released from living organisms or contains components of living organisms. Biologic drugs include a wide variety of products derived from human, animal sources, or microorganisms by using biotechnology[3,4]. Biologic agents targeting IL-4, IL-13, IL-17, IL-23, IL-31, or IL-33 could help manage particularly refractory patients[3,4].

Dupilumab (Dupixent®, Sanofi and Regeneron) is a fully human monoclonal antibody, binding IL-4 receptor alpha (IL-4Rα), and thus, inhibiting the signaling pathways of IL-4 and IL-13 signalling. Due to its blockade properties, it is utilized for the treatment and management of patients suffering from allergic diseases including eczema/moderate-to-severe atopic dermatitis, asthma and chronic sinusitis with nasal polyps resulting in chronic sinusitis. Commonly reported side-effects include allergic reactions, cold sores, and ocular reactions, such as inflammation of the cornea, among others[5]. It has been approved by the US Food and Drug Administration (FDA) for use in patients aged six years and older[5].

Some biologics, such as the tumor necrosis factor (TNF) inhibitors which are used for treating psoriasis and other rheumatic conditions, are compatible with pregnancy[6-9], but the safety of other biologics has to be elucidated yet, with some of them known to increase the risk of adverse drug reactions (ADR) during pregnancy. To the best of our knowledge, there is a paucity of data concerning the safety profile of Dupilumab among pregnant women. There, we took advantage of a large pharmacovigilance database to investigate this issue.

Material and Methods

Database

VigiBase™, the global pharmacovigilance database developed and maintained by the Swedish World Health Organization (WHO) Collaborating Centre for International Drug Monitoring, named as the Uppsala Monitoring Centre (UMC), was mined from inception up to March 9, 2021. UMC collects and curates more than 20 million individual case safety reports (ICSRs) of suspected adverse drug reactions (ADRs), spontaneously forwarded by over 140 countries, members of the WHO Program for International Drug Monitoring. Even if the database includes data not completely homogenous in terms of the relationship between the pharmaceutical product/drug and the reported ADR, it is acknowledged that Big Data-based comprehensive, quantitative screenings are vital for a rapid and effective pharmacovigilance.

Disproportionality Analysis

To assess the relationship between the drug and the suspected ADR, various disproportionality measures between the observed and the expected reporting of a medicine-ADR pair can be computed, including odds-ratio (OR) and the information component (IC). The latter was originally formulated through the Bayesian Confidence Propagation Neural Network (BCPNN): if IC is a positive (or negative) value, this means that the pair under study is reported more often (or less frequently) than expected, based on all the reports included in VigiBase™.

$$IC = \log_2\left(\frac{N_{observed} + 0.5}{N_{expected} + 0.5}\right)$$

where

$$N_{expected} = \frac{N_{drug} \cdot N_{reaction}}{N_{total}}$$

$N_{expected}$ can be defined as the number of case reports expected for the given drug-effect pairwise association, whereas $N_{observed}$ can be defined as the actual number of case reports for the drug-ADR combination under study. N_{drug} is the number of all case reports for the medicine under scrutiny, regardless of the effects reported, and, conversely, $N_{reaction}$ is the number of case reports for the given side-effect under study, regardless of the specific type of medicine. All these disproportionality measures are calculated with their 95% credible interval (CrI), with $IC_{0.25}$ and $IC_{97.5}$ being the lower- and upper-bound values, respectively.

In the present investigation, we reported both OR and IC. Interpretation of the IC is as follows: IC is statistically significant when its lower-bound ($IC_{0.25}$) yields a positive value. $IC_{0.25}$ is, indeed, the traditional threshold employed in the statistical signal detection analysis of pharmacovigilance databases. We reported both disproportionality measures because, whereas, on the one hand, OR is more commonly utilized in the biomedical field, IC, being based on data mining techniques, enables to curb the risk of detecting spurious statistically significant associations.

Table I. Reported pregnancy, puerperium and perinatal adverse-drug reactions potentially associated with use of Dupilumab in pregnant women.

Pregnancy, puerperium and perinatal ADR	Number
Abortion	2
Spontaneous abortion	21
Pre-eclampsia	1
Ectopic pregnancy	1
Heterotopic pregnancy	1
Pre-term premature rupture of membranes	1
Neonatal jaundice	1
Others (exposure to drug during pregnancy)	8

Adverse Drug Reactions Categorization and Classification

The Medical Dictionary for Drug Regulatory Authorities (MeDRA) ontology at the System Organ Class (SOC) level was used to categorize suspected ADRs related to Dupilumab. Pregnancy, puerperium and perinatal conditions were considered in this study.

Results

From inception up to March 9, 2021, 94,065 ADRs from 37,848 unique reports were retrieved. Of these, 36 reports related to pregnancy, puerperium and perinatal ADR could be extracted from the pharmacovigilance database. More than half of reports (n = 21; 58.3%) were spontaneous abortion, followed by other events, including exposure to the drug during the pregnancy (n = 8; 22.2%). Two cases of abortion were reported. Further details are reported in Table I. No studied pregnancy, puerperium and perinatal ADR was found to be associated with the use of Dupilumab. Most OR were below 1: abortion (0.18 [95% CrI 0.04-0.70]; with an IC of -2.24 [95% CrI from -4.83 to -0.88]), induced abortion (0.11 [95% CrI 0.02-0.81]; with an IC of -2.63 [95% CrI from -6.43 to -0.99]), and spontaneous abortion (0.57 [95% CrI 0.37-0.88]; with an IC of -0.78 [95% CrI from -1.47 to -0.23]). Other OR were not significant: pre-eclampsia (0.27 [95% CrI 0.04-1.95]; with an IC of -1.46 [95% CrI from -5.26 to 0.18]), ectopic pregnancy (0.17 [95% CrI 0.02-1.22]; with an IC of -2.07 [95% CrI from -5.87 to -0.43]), pre-term premature rupture of membranes (1.12 [95% CrI 0.16-7.96]; with an IC of 0.11 [95% CrI from -3.69 to 1.75]), and neonatal jaundice (0.46 [95% CrI 0.06-3.24]; with an IC of -0.84 [95% CrI from -4.64 to 0.80]). The only OR significantly greater than 1 was the OR associated with the risk of developing heterotopic pregnancy (21.66 [95% CrI 2.95-159.02]) even if the IC was highly imprecise (1.45 [95% CrI from -2.34 to 3.09]), probably because of the single case of heterotopic pregnancy reported. More details are shown in Table II.

Discussion

Dupilumab appears to be safe and can be administered to pregnant women, posing no preterm or small for gestational age risks, even if a certain degree of risk for developing heterotopic pregnancy appears to exist, but given its high imprecision, needs to be further investigated by ad hoc epidemiological surveys.

Table II. Disproportionality analysis of pregnancy, puerperium and perinatal adverse-drug reactions potentially associated with use of Dupilumab in pregnant women.

Pregnancy, puerperium and perinatal ADR	OR	$OR_{0.25}$	$OR_{97.5}$	IC	$IC_{0.25}$	$IC_{97.5}$
Abortion	0.18	0.04	0.70	-2.24	-4.83	-0.88
Induced abortion	0.11	0.02	0.81	-2.63	-6.43	-0.99
Spontaneous abortion	0.57	0.37	0.88	-0.78	-1.47	-0.23
Pre-eclampsia	0.27	0.04	1.95	-1.46	-5.26	0.18
Ectopic pregnancy	0.17	0.02	1.22	-2.07	-5.87	-0.43
Heterotopic pregnancy	21.66	2.95	159.02	1.45	-2.34	3.09
Preterm premature rupture of membranes	1.12	0.16	7.96	0.11	-3.69	1.75
Neonatal jaundice	0.46	0.06	3.24	-0.84	-4.64	0.80

Since atopic dermatitis, as other inflammatory and autoimmune diseases, affects females more than males, it is of crucial importance to investigate the safety profile of pharmacologic options, including biologic agents, during pregnancy. This is even more important and urgent considering that biologic agents are increasingly prescribed and administered to manage patients suffering from severe diseases, helping to maintain remission and avoid relapses/recurrence in a high portion of individuals with systemic inflammatory/autoimmune disorders.

Atopic dermatitis often has a serious course during pregnancy, which can cause a significant level of distress and substantially impact on global health, perceived quality of life, and related outcomes, both maternal and fetal ones[7,8].

However, pharmacological trials are particularly challenging to design and implement for women during pregnancy and lactation, therefore there is a significant dearth of data regarding safety during gestation. Pharmacology scholars can rely only on observational and real-life investigations, with all the limitations and shortcomings that generally plague these study design. Among biologic agents, TNF inhibitors are the only ones for which the potential trans-placental passage and effects on the fetus have been investigated. For certolizumab, the passage through placenta has been ruled out and the drug appears to be relatively safe. Other biologic drugs, like etanercept and eculizumab, seem to be safe, even though data are lacking, and further research is warranted.

As such, to fill in this gap in knowledge, an "European League Against Rheumatism" (EULAR) task force has very recently recommended the establishment of prospective pregnancy registries[9]. We exploited a large pharmacovigilance database to extract relevant information that could inform in a data-driven and evidence-based fashion physicians, practitioners, specialists as well as women planning a pregnancy and other stakeholders.

The present investigation has some strengths, including the reporting of various disproportionality measures that enable a thorough assessment of the drug-ADR pairwise association. However, despite being comprehensive, the present analysis has some shortcomings that should be properly acknowledged. Limitations include: the heterogeneous nature of the database sources. Moreover, a direct causal relationship cannot be inferred from the current investigation and warrants further ad hoc epidemiological surveys and careful clinical assessment for a proper identification and interpretation of the pharmacovigilance alert signals.

Conclusions

In conclusion, Dupilumab use appears safe during gestation. Further studies are needed, especially to better understand the mechanisms underlying the pharmacological actions and ADR of Dupilumab.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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