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™)

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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 could 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. 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. 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.

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
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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\textsuperscript{3,4}. Biologic agents targeting IL-4, IL-13, IL-17, IL-23, IL-31, or IL-33 could help manage particularly refractory patients\textsuperscript{3,4}.

Dupilumab (Dupixent\textsuperscript{®}, 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 polyposis resulting in chronic sinusitis. Commonly reported side-effects include allergic reactions, cold sores, and ocular reactions, such as inflammation of the cornea, among others\textsuperscript{5}. It has been approved by the US Food and Drug Administration (FDA) for use in patients aged six years and older\textsuperscript{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\textsuperscript{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\textsuperscript{™}, 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\textsuperscript{™}.

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

where

\[
N_{\text{expected}} = \frac{N_{\text{drug}} \cdot N_{\text{reaction}}}{N_{\text{total}}}
\]

\(N_{\text{expected}}\) can be defined as the number of case reports expected for the given drug-effect pairwise association, whereas \(N_{\text{observed}}\) can be defined as the actual number of case reports for the drug-ADR combination under study. \(N_{\text{drug}}\) is the number of all case reports for the medicine under scrutiny, regardless of the effects reported, and, conversely, \(N_{\text{reaction}}\) 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 (CI), with IC\textsubscript{0.25} and IC\textsubscript{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\textsubscript{0.25}) yields a positive value. IC\textsubscript{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.
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 pre-term 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.
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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.

References