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Higher rates of COVID-19 but less severe infections reported for patients on Dupilumab: a Big Data analysis of the World Health Organization VigiBase

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Abstract. – OBJECTIVE: Dupilumab (Dupixent®) is a monoclonal antibody that inhibits IL-4 and IL-13 signaling used for the treatment of allergic diseases. Whilst biologic therapy is traditionally regarded as immunosuppressive and capable to increase the infectious risk, Dupilumab does not display these characteristics and may be even protective in certain cases. We investigated the link between Dupilumab therapy and SARS-CoV-2 infection.

MATERIALS AND METHODS: We carried out a comprehensive data mining and disproportionality analysis of the WHO global pharmacovigilance database. One asymptomatic COVID-19 case, 106 cases of symptomatic COVID-19, and 2 cases of severe COVID-19 pneumonia were found.

RESULTS: Dupilumab treated patients were at higher risk of COVID-19 (with an $IC_{0.25}$ of 3.05), even though infections were less severe ($IC_{0.25}$ of -1.71). The risk of developing COVID-19 was significant both among males and females (with an $IC_{0.25}$ of 0.24 and 0.58, respectively). The risk of developing COVID-19 was significant in the age-group of 45-64 years (with an $IC_{0.25}$ of 0.17).

CONCLUSIONS: Dupilumab use seems to reduce COVID-19 related severity. Further studies are needed to better understand the immunological mechanisms and clinical implications of these findings. Remarkably, the heterogenous nature of the reports and the database structure did not allow to establish a cause-effect link, but only an epidemiologically decreased risk in the patients subset treated with dupilumab.

Key Words:
Data mining, Big data, Pharmacovigilance, Dupilumab, Biologic therapy, Atopic dermatitis, Nasal polyposis, Asthma, COVID-19, SARS-CoV-2.

Introduction

The "Severe Acute Respiratory Syndrome-related Coronavirus type 2" (SARS-CoV-2) is an emerging respiratory coronavirus responsible for the still ongoing "Coronavirus Disease 2019" (COVID-19) pandemic[1]. Infection with SARS-CoV-2 can be asymptomatic, or, if it is clinically manifested, it generally produces a mild to moderate disease[2]. Several immunological processes have been described to be involved in the pathogenesis of COVID-19[3,4]; however, patients with

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severe COVID-19 exhibit different extents of immunological dysregulation and misfiring[5], the magnitude of which is linked to disease mortality. Accordingly, several immunosuppressive or immunomodulatory agents have shown some efficacy in severe COVID-19 pneumonia. Tocilizumab, for instance, an anti-interleukin (IL)-6 agent, has been reported to be effective in patients with severe COVID-19[6-9], as well as other biologics such as IL-17, TNF alpha and PDE4 inhibitors. However, the same agents and especially corticosteroids have been shown to be detrimental when used early in the course of COVID-19[10].

Some biologics, such as those used for treating psoriasis, may increase the risk of infections up to 11%[11,12]. Dupilumab (Dupixent®, Sanofi and Regeneron) is a fully human monoclonal antibody, binding IL-4 receptor alpha (IL-4Rα), and thus, inhibiting IL-4 and IL-13 signaling. Due to its dual blockade properties, it is utilized for the treatment and management of patients suffering from allergic diseases, including prurigo nodularis, moderate-to-severe atopic dermatitis (AD), asthma and chronic sinusitis with nasal polyps[11,12]. Commonly reported side-effects of Dupilumab include site injection reactions and flares of allergic diseases, Herpes simplex, and ocular reactions, such as inflammation of the cornea, among others[13].

As for Dupilumab before the pandemic of COVID-19, several scientific dermatological societies have stated that the use of Dupilumab in the COVID-19 era is safe, however, there is a dearth of data that can support these statements. Moreover, Th2 cytokines and Th2 pathway related immune cells have been incriminated in severe COVID-19 and it is not completely clear what is the outcome of blocking the Th2 pathway and leaving Th17 and Th1 pathways relatively unopposed. Therefore, we took advantage of a global pharmacovigilance database, carrying out a comprehensive data mining and disproportionality analysis to look at the risk of developing the emerging coronavirus infection in patients under anti IL-4/13 therapy.

Materials 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 the lower bound of IC is positive, that is to say >0 (or negative, <0), 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 drug 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 drug.

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: as previously mentioned, IC is statistically significant when its lower-bound ($IC_{0.25}$) yields a posi-

Table I. Risk of COVID-19 in patients under Dupilumab.

		OR 95% CrI			IC 95% CrI	
Patient status	**OR**	**0.25**	**97.5**	**IC**	**0.25**	**97.5**
COVID-19	10.73	8.85	13.00	3.33	3.05	3.60
Severe COVID-19	2.34	0.58	9.36	0.88	-1.71	2.24
SARS-CoV-2 positive	7.30	1.02	52.45	1.23	-2.57	2.87

Table II. Risk of contracting COVID-19 in patients under Dupilumab stratified according to gender.

			OR 95% CrI		IC 95% CrI		
Patients' status	**Gender**	**OR**	**0.25**	**97.5**	**IC**	**0.25**	**97.5**
COVID-19	Male	2.76	1.43	5.31	1.33	0.24	2.12
	Female	3.09	1.75	5.45	1.51	0.58	2.21
	Not known	27.42	21.74	34.57	4.36	4.03	4.65
Severe COVID-19	Male	2.90	0.41	20.67	0.83	-2.97	2.47
	Not known	8.30	1.11	62.20	1.26	-2.54	2.90
SARS-CoV-2 positive	Not known	49.81	5.18	478.94	1.51	-2.29	3.15

tive 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.

ADRs 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.

Results

From inception up to March 9, 2021, 94,065 ADRs from 37,848 unique reports were retrieved. Of these, 127 concerned COVID-19 infection: in particular, 1 asymptomatic COVID-19 case, 108 cases of ascertained, symptomatic COVID-19, and 18 cases of suspected COVID-19 infection. 107 from the Americas, 19 from Europe, 1 from Asia, and none from Oceania. Patients under Dupilumab were at higher risk for contracting COVID-19 (with an $IC_{0.25}$ of 3.05) and developing COVID-19 like symptoms (with an $IC_{0.25}$ of 2.38). The risks of being SARS-CoV-2 positive (with an $IC_{0.25}$ of -2.57) and developing severe COVID-19 pneumonia (with an $IC_{0.25}$ of -1.71) were not statistically significant. Further details are reported in Table I, to which the reader is referred. When stratifying according to gender, the risk of developing COVID-19 was significant both among males and females (with an $IC_{0.25}$ of 0.24 and 0.58, respectively), whereas the risk of developing COVID-19 with symptoms achieved statistical threshold only among females (with an $IC_{0.25}$ of 0.08), as shown in Table II. When stratifying according to age-groups, the risk of COVID-19 being reported was significant in the age-group of 45-64 years (with an $IC_{0.25}$ of 0.17), as reported in Table III.

Discussion

Patients treated with Dupilumab showed a higher risk for developing COVID-19 but, on the other hand, a less severe disease. In the existing literature, very few anecdotal cases of COVID-19 infection in patients under Dupilumab are reported. Ferrucci et al[14] reported two clinical cases, a 40-year-old man and a 56-year-old woman, who developed COVID-19 on the third and fourth

Table III. Risk of contracting COVID-19 in patients under Dupilumab stratified according to age-groups.

			OR 95% CrI		IC 95% CrI		
Patients' status	Gender	OR	0.25	97.5	IC	0.25	97.5
COVID-19	18-44	2.88	1.19	6.93	1.29	-0.23	2.29
	45-64	3.07	1.46	6.46	1.43	0.17	2.30
	65-74	2.14	0.30	15.26	0.63	-3.16	2.27
	Not known	15.99	12.99	19.70	3.83	3.52	4.11
Severe COVID-19	45-64	4.16	0.58	29.68	1.02	-2.78	2.66
	Not known	4.46	0.62	32.05	1.05	-2.75	2.69

month of Dupilumab therapy respectively and improved after receiving proper pharmacological treatment. Dupilumab therapy was not stopped during the disease. The same authors found that only 2 out of 245 (0.82%) patients in therapy with Dupilumab contracted COVID-19. Carugno et al[15] from Bergamo-Lombardy, a highly endemic area of COVID-19 in Italy, documented a cohort of 30 patients (20 males, 10 females, mean age 35.5±11.9 years, range 19-54 years) and found no evidence of higher risk for developing COVID-19 in patients under Dupilumab. The authors concluded, based on their findings, the mechanism of action of Dupilumab, and data available, that COVID-19 risk in patients treated with Dupilumab is insignificant.

From an immunological standpoint, the use of Dupilumab may be expected to potentially lower the severity and morbidity of COVID-19. Vaz de Paula et al[16] found that IL-4/IL-13 pathway plays a major role in remodeling lung injury, being significantly linked with COVID-19 severity and mortality[16]. The authors compared the expression of immunological markers in 6 lung biopsy samples of patients who died of SARS-CoV-2, versus 10 lung samples obtained from patients who died of H1N1pdm09 and 11 patients who died of other causes without lung injury serving as the control group. At the histological level, the COVID-19 lung showed increased staining for both IL-4 and M2 macrophages when compared to H1N1pdm09.

A role for IL-13 in the pathology of COVID-19 is also supported by Donlan et al[17], who reported elevated IL-13 levels in severe COVID-19 patients. The authors also found that the use of Dupilumab was associated with reduced COVID-19 severity. To dissect the cellular basis underlying the mechanisms of the action of Dupilumab, the authors used a murine model, discovering that IL-13 blockade reduced COVID-19 severity and mortality. If indeed IL-4 and IL-13 driven immune responses were detrimental, then, it could be expected that Th2 driven diseases such as Asthma and Atopic Dermatitis would have an increased COVID-19 severity. The general consensus is that Asthma is indeed associated with more severe COVID-19[18]. Despite this, eosinophilic asthma was associated with increased survival when compared to other asthmatic types[19], this is of interest as IL-5 driven eosinophilic dominant disease, independent of IL-4, can exist[19,20].

It is also important to consider the role of IL-6 in this discussion. IL-6 participates in the so-called "cytokine storm"[21], that may be present in some severe COVID-19 cases[22]. Normally, in the presence of IL-4, IL-6 promotes the differentiation of CD4+ T cells into effector cells, shifting the Th1/Th2 balance towards the Th2 direction, and inhibits Th1 cytokines such as in the case of interferon-gamma (IFN-γ) inhibition. Secondary, HLH (hemophagocytic lymphohistiocytosis) which is commonly associated with cytokine storm and macrophage activation syndrome, can also be induced by IL-4, independently of T-cells IFN-γ[23].

Moreover, IL-4 neutralization may lead to reduced lung remodeling *via* fibrin degradation promotion and M2 type macrophages inhibition. Furthermore, Th1/Th17 hyper-activation results in increased expression, production and release of pro-inflammatory cytokines and blockage of the Th2 pathway could contribute to enhanced immunity in this pathway.

All this could explain the higher risk of contracting the infection among atopic dermatitis patients under Dupilumab, even though of a less severe and deadly form.

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 shortcomings that should be properly acknowledged. Limitations include: the heterogeneous nature of the database sources. Furthermore, 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. Apparently no COVID-19 related deaths could be detected, but the lack of information concerning COVID-19 induced mortality requires further elucidation.

Conclusions

Dupilumab use appears to reduce COVID-19 related severity. Further studies are needed, especially to better elucidate the mechanisms underlying the pharmacological action of Dupilumab, as well as its clinical implications in terms of immunological pathways serving as targets for future therapies.

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Conflict of Interest
The authors declare that they have no competing interests.

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