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COVID-19 in DMARD-treated patients with inflammatory rheumatic diseases: Insights from an analysis of the World Health Organization pharmacovigilance database

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Abstract

Background: To determine whether the use of disease-modifying antirheumatic drugs (DMARDs) is linked to the risk of COVID-19 among patients with inflammatory rheumatic diseases (IRDs).

Methods: We performed a disproportionality analysis of the World Health Organization pharmacovigilance database between January 1, 2020, and June 10, 2020. The frequency of COVID-19 reports for all DMARD classes identified was compared with that for all other reports for all other drugs and quoted as the reporting odds ratio (ROR) (95% confidence interval [CI]).

Results: Among 980,446 individual case-safety reports voluntarily recorded in the database, 398 identified COVID-19 in DMARD-treated patients with IRDs. There were 177 (44.5%) patients with rheumatoid arthritis (RA), 120 (30.1%) with ankylosing spondylitis (AS), 93 (23.4%) with psoriatic arthritis (PsA), and 8 (2.0%) with juvenile idiopathic arthritis. Most of the cases of COVID-19 occurred in patients taking anti-TNF agents (84.2%), resulting in a significant disproportionality signal (ROR [95% CI]: 8.31 [7.48–9.23]) – particularly in patients with RA, AS or PsA. A significant inverse disproportionality was found for the anti-IL-6 agent tocilizumab (ROR [95% CI]: 0.12 [0.02–0.88]) and JAK inhibitors (ROR [95% CI]: 0.33 [0.19–0.58]) in patients with RA – suggesting that these two drug classes are safer in the context of RA.

Conclusion: Our results are in line with the literature on a potentially better safety profile for anti-IL-6 agents and JAK inhibitors. The WHO pharmacovigilance data suggest that COVID-19 is significantly more frequent in patients with IRDs treated with TNF inhibitors.

Abbreviations: ADR, adverse drug reaction; AS, ankylosing spondylitis; COVID-19, coronavirus 2019 disease; DMARD, disease-modifying antirheumatic drug; EULAR, European league against rheumatism; IBD, inflammatory bowel disease; ICSR, individual case safety report; IL, interleukin; IRD, inflammatory rheumatic disease; JAK, Janus kinase; PsA, psoriatic arthritis; RA, rheumatoid arthritis; ROR, reporting odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF, tumor necrosis factor; WHO, World Health Organization.

KEYWORDS
COVID-19, DMARDs, inflammatory rheumatic disease, Pharmacovigilance database (VigiBase®)

1 | INTRODUCTION

Late 2019 was marked by the emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which soon led to a global pandemic of coronavirus 2019 disease (COVID-19) [1,2]. The initial cohort studies soon found that patients aged 65 or more and/or those with certain comorbidities (e.g., diabetes, arterial hypertension, and obesity) were more likely to develop severe forms of COVID-19 [1,2]. The immunosuppressants taken by transplant recipients and individuals with neoplasia have been also linked to severe forms of COVID-19 and an elevated mortality rate [1,3,4]. It is widely recognized that biologic, immunosuppressive, targeted, disease-modifying antirheumatic drugs (DMARDs) are associated with greater susceptibility to viral reactivation and complicated seasonal influenza [5–7]. However, the increasingly available data on COVID-19 infection rates and outcomes among patients receiving DMARDs for inflammatory rheumatic diseases (IRDs) are quite reassuring [8–11]. Indeed, some studies suggested that the incidence, clinical course, and mortality rate for COVID-19 among these patients are similar to those recorded in the general population [10,11]. In the largest yet study (n = 600) of COVID-19 in patients with rheumatic diseases, only moderate-to-high doses of glucocorticoids (but not biologic DMARDs) and the above-mentioned general risk factors were associated with a higher risk of hospitalization for COVID-19 [8]. Furthermore, biologic DMARDs (e.g., anti-IL-6 and anti-IL-1 agents, and Janus kinase (JAK) inhibitors) are being investigated as treatments for severe COVID-19 pneumonia because they might prevent the harmful effects of cytokine release syndrome [12,13]. Nevertheless, even though few life-threatening cases of COVID-19 have been reported in patients on DMARDs, the disease's clinical forms and prognosis might differ from one drug to another [8,9].

The objective of the present study of an international pharmacovigilance database was to determine whether the risk of COVID-19 was associated with exposure to DMARDs in patients with IRD.

2 | METHODS

2.1 | Data source

Individual case safety reports (ICSRs) were collected from VigiBase®, the largest pharmacovigilance database curated by the World Health Organization (WHO). VigiBase® contains over 20 million ICSRs on suspected adverse drug reactions (ADRs); the records are submitted voluntarily by more than 150 countries participating in the WHO's Program for International Drug Monitoring [14]. The database contains information on the patient, the drugs (coded according to the Anatomical Therapeutic Classification), and the ADRs (coded according to the Medical Dictionary for Regulatory Activities (MedDRA)) [15]. There are five levels in the MedDRA hierarchy, ranging from the most general ("system organ classes" (SOCs)) to the most specific ("lowest level terms"). An ADR is categorized as "serious" if it results in any untoward medical occurrence that results in death, requires or prolongs hospitalization, results in persistent or significant disability/incapacity, is life threatening, or results in another medically important condition. According to probability scales based on chronologic, semiologic, and/or bibliographic criteria, a drug considered to be probably or definitely responsible for the ADR is defined as being "suspect." In the absence of probable or definite responsibility, the drug is defined as "concomitant."

2.2 | Study design

Firstly, we selected cases; these were defined as ICSRs labelled with the MedDRA preferred terms "coronavirus infection," "coronavirus test positive," "COVID-19," "COVID-19 pneumonia," "SARS-CoV-2 carrier," or "SARS-CoV-2 infection" and having been recorded in VigiBase® between January 1, 2020, and June 10, 2020. Secondly, we selected records involving a DMARD (conventional synthetic DMARDs: methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, and apremilast; biologic DMARDs: adalimumab, etanercept, infliximab, golimumab, certolizumab, abatacept, rituximab, tocilizumab, sarilumab, secukinumab, canakinumab, and anakinra; targeted synthetic DMARDs: baricitinib, and tofacitinib) and that were identified as being "suspect." Thirdly, by checking the drug indications, we selected patients with IRDs.

2.3 | Statistical analysis

In our descriptive analysis, categorical variables were expressed as the number (percentage) and continuous variables were expressed as the mean ± standard deviation (SD) or, if appropriate, the median (range).

We performed a disproportionality analysis of the reports by calculating the reporting odds ratio (ROR) and its 95% confidence interval (CI) as a gauge of the putative association between DMARDs and the occurrence of COVID-19 in all ICSRs over the study period. Calculation of the ROR has been described elsewhere [16]. Briefly, ROR = (a/c)/(b/d), where (a) is the number of COVID-19 cases with a suspect DMARD, (b) is the number of COVID-19 cases with all other drugs, (c) is the number of ADRs other than COVID-19 with a suspect DMARD, and (d) is the number of ADRs other than COVID-19 with all other drugs. It is important to notice that disproportionality studies are exploratory, and do not allow one to quantify the true risk. If the ROR and the lower boundary of the 95% CI are greater than 1, the ADR of interest is reported more frequently with the drug of interest than with all other drugs. Moreover, it has been suggested that an ROR greater than 4 corresponds to a "large" effect size [16].

Lastly, we stratified the RORs by the drug indication.

As described by Pariente and Salvo, an ADR other than that of interest but that is strongly associated with the drug of interest can introduce event-competition bias. In turn, this bias can reduce the ROR (by inflating the denominator) and prevent the detection of potential signals for the drug of interest [17,18]. We therefore performed sensitivity analysis by removing the most frequently reported ADRs for each drug of interest. We also compared patients with IRD vs patients with inflammatory bowel diseases (IBDs), that is, other patients using the same drug classes.

All analyses were performed using R software (version 3.6.0, R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

Of the 980,446 ICSRs voluntarily registered in VigiBase® from January 1, 2020 to June 10, 2020, a total of 668 corresponded to patients with COVID-19 receiving at least one DMARD. Of these 668 ICSRs, 398 were in patients with an IRD (Figure 1). Almost all the observations (384 out of 398) came from European countries; there were none from Asia. The patients' clinical features and the types of DMARD are described in Table 1. There were 177 (44.5%) patients with rheumatoid arthritis (RA), 120 (30.1%) with ankylosing spondylitis (AS), 93 (23.4%) with psoriatic arthritis (PsA), and only 8 (2.0%) with juvenile idiopathic arthritis (JIA). In all disease groups, COVID-19 occurred mostly among patients taking TNF-inhibitors (335 of 398). With regard to other biologic DMARDs, only a few cases featured anti-IL-17 agents (22 of 398). Only three cases with tocilizumab were reported. Thirteen cases of COVID-19 were reported in patients with RA taking JAK inhibitors. Corticosteroid or nonsteroidal antiinflammatory drugs were never reported as suspect drugs.

Details of COVID-19-related symptoms were available for 171 (43%) patients, and prognostic information was available for all patients (Table 1). Fever was reported only in 26 of the 171 cases with data (15.2%). Most of the patients (279 out of 398) experienced serious COVID-19 but only 13 of them (3.3%) died.

Regardless of the treatment indication, significant disproportionality was found for TNF inhibitors as a whole (ROR [95% CI]: 8.31 [7.48–9.23]) (including the monoclonal antibodies (6.40 [5.69–7.21]) and etanercept (10.33 [8.71–12.26])), tocilizumab (3.22 [1.78–5.83]), abatacept (3.08 [1.85–5.12]), secukinumab (2.98 [2.18–4.08]), JAK inhibitors (2.88 [2.12–3.91]), methotrexate (2.57 [1.79–3.70]), leflunomide (3.40 [1.27–9.09]), and sulfasalazine (3.23 [1.04–10.05]). No disproportionality was found for rituximab or apremilast (Figure 2).

The stratified analyses in RA, AS, and PsA patients showed significant disproportionality only for TNF inhibitors as a whole (ROR [95% CI]: 2.96 [2.05–4.28], 2.21 [1.24–3.95], and 4.55 [2.65–7.80] for the three diseases, respectively). In RA and PsA, the RORs [95% CI] were higher for patients treated with etanercept (3.15 [2.33–4.26] and 3.50 [2.19–5.60], respectively) than for patients treated with monoclonal antibodies (1.32 [1.15–2.33] and 1.75 [1.16–2.64], respectively; Figure 2). In stratified analyses, there was no disproportionality for biologic DMARDs (except for TNF inhibitors). In patients with RA, there were fewer reports than expected for tocilizumab (ROR [95% CI]: 0.12 [0.02–0.88]) and JAK inhibitors (ROR [95% CI]: 0.33 [0.19–0.58]).

In patients with IBD, the RORs [95% CI] were significant for anti-TNF monoclonal antibodies (1.49 [1.17–2.27] and for the JAK inhibitor tofacitinib (7.11 [3.54–14.26]).

The RORs [95% CI] for conventional synthetic DMARDs were no longer significant in the stratified analyses; this was especially true for apremilast in PsA patients, which was less frequently reported than expected (ROR [95% CI]: 0.11 [0.03–0.45]).

During the study period, infections were the most frequently reported ADRs for biologic DMARDs (29.6% for TNF inhibitors as a whole (including 28.4% for monoclonal antibodies and 33.5% for etanercept), 26.4% for tocilizumab, 25.7% for abatacept, 20.6% for rituximab, and 18.0% for secukinumab) and for JAK inhibitors (26.1%). Gastrointestinal disorders were the most frequently reported ARDs for methotrexate (22.1%), leflunomide (27.5%), and apremilast (44.7%). Skin eruptions were the most frequently reported ADRs for sulfasalazine (54.6%). Hence, in our sensitivity analyses, we removed ADRs related to the "infections and infestations" SOC (except for COVID-19) for biologic DMARDs

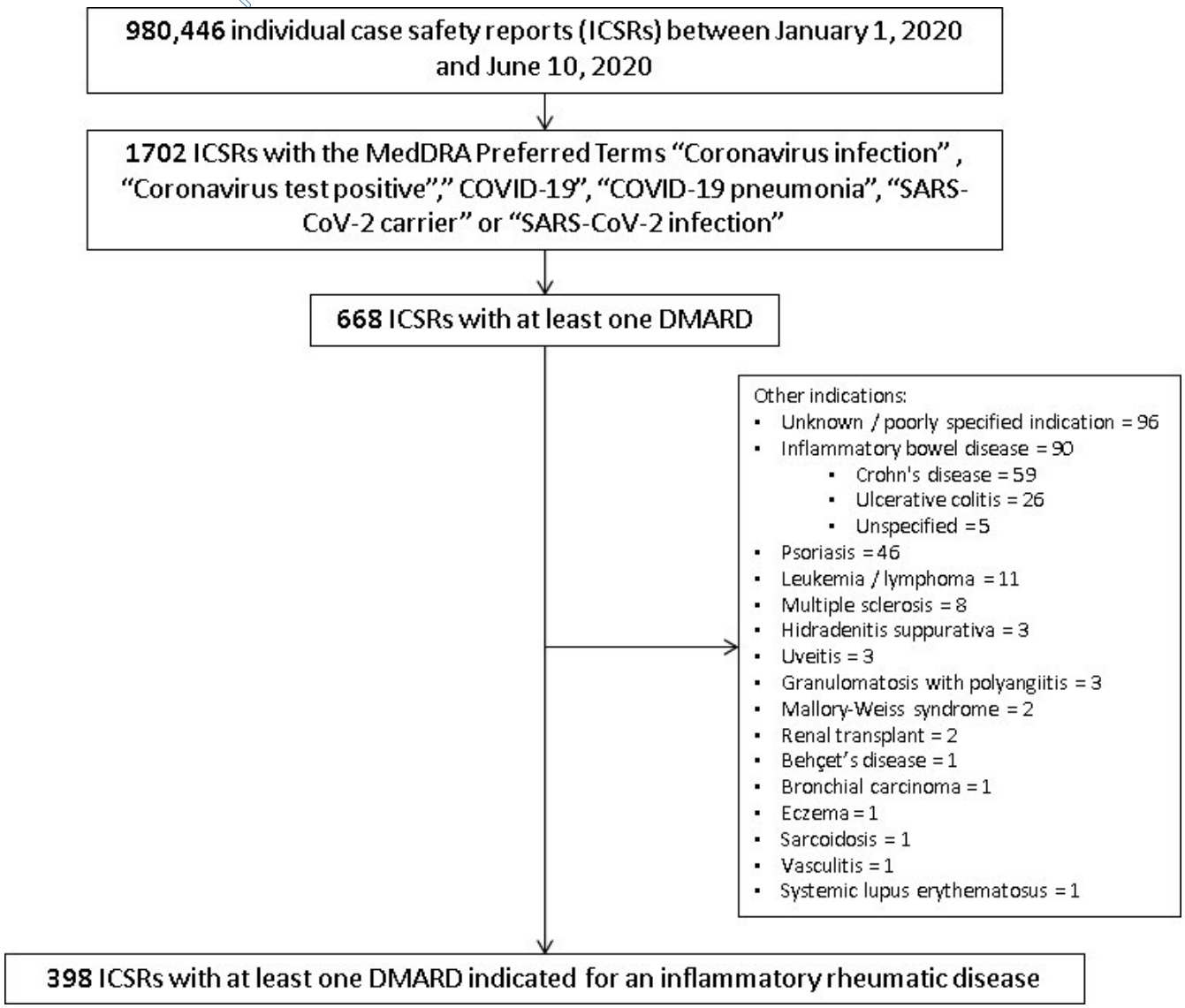

FIGURE 1 The study population selection process, based on VigiBase®. DMARD, disease- modifying anti-rheumatic drug

and JAK inhibitors, those related to the "gastrointestinal disorders" SOC for methotrexate, leflunomide, and apremilast, and those related to the "skin and subcutaneous tissue disorders" SOC for sulfasalazine.

The results of the sensitivity analyses were consistent with our main analysis, particularly for TNF inhibitors in patients with IRDs (ROR [95% CI]: 4.28 [3.26–5.60]), for tocilizumab in patients with RA (0.13 [0.01–0.95]), and for JAK inhibitors in patients with RA (0.33 [0.19–0.58]) or with IBD (7.66 [3.80–15.45], Figure 3).

4 | DISCUSSION

According to the reports uploaded voluntarily to VigiBase®, most of the DMARD-treated patients with IRDs and COVID-19 were taking a TNF inhibitor – the oldest class of biologic DMARD and the most frequently prescribed for IRDs [19]. However, we found significant disproportionality for this drug class (regardless of the indication), and notably in patients with RA, AS, or PsA. Moreover, RORs were higher for the subset of patients taking etanercept than for the subset taking anti-TNF monoclonal antibodies. Although etanercept and anti-TNF monoclonal antibodies are all potent inhibitors of TNF's activity, there are fundamental differences in their molecular structures, binding specificities, and effects on proinflammatory cytokine release and lymphocyte apoptosis. Anti-TNF monoclonal antibodies are not known to bind to any antigens other than TNF. In contrast, the fusion protein etanercept contains the extracellular domain of the p75 TNF receptor, which binds equally well to the cytokines TNF and lymphotoxin-α (previously called TNF-β) [20]. TNF is a secreted by macrophages and has an essential role in antiviral immune defenses [21,22]. Lymphotoxin-α is considered to

TABLE 1 Characteristics of the study population

	Study population N = 398	RA N = 177	AS N = 120	PsA N = 93	JIA N= 8
Age (years), *mean ± SD*	53.7 ± 14.2	59.5 ± 13.6	49.9 ± 12.2	51.4 ± 10.7	18.4 ±8.4
Females, *n (%)*	230 (57.8)	129 (73.3)	44 (36.7)	49 (52.7)	7 (87.5)
DMARD classes					
Biologics, n (%)					
TNF inhibitors	335 (84.2)	141 (80.1)	107 (89.2)	77 (82.8)	6 (75.0)
adalimumab	167 (42.0)	55 (31.2)	70 (58.3)	40 (43.0)	2 (25.0)
etanercept	129 (32.4)	73 (41.5)	27 (22.5)	24 (25.8)	4 (50.0)
certolizumab pegol	20 (5.0)	8 (4.5)	5 (4.2)	7 (7.5)	0
golimumab	17 (4.3)	6 (3.4)	5 (4.2)	6 (6.5)	0
infliximab	2 (0.5)	2 (1.1)	0	0	0
Anti-IL1					
canakinumab	1 (0.3)	0	0	0	1 (12.5)
Anti-IL-6					
tocilizumab	3 (0.8)	1 (0.6)	1 (0.8)	0	1 (12.5)
Anti-IL-17					
secukinumab	22 (5.5)	0	12 (10.0)	10 (10.8)	0
Anti-CD20					
rituximab	2 (0.5)	2 (1.1)	0	0	0
Anti-CTLA-4					
abatacept	15 (3.8)	15 (8.5)	0	0	0
Targeted synthetic drugs, n (%)					
tofacitinib	10 (2.5)	7 (4.0)	0	3 (3.2)	0
baricitinib	6 (1.5)	6 (3.4)	0	0	0
Conventional synthetic drugs, n (%)					
methotrexate	23 (5.8)	15 (8.5)	4 (3.3)	4 (4.3)	0
sulfasalazine	1 (0.3)	0	1 (0.8)	0	0
leflunomide	2 (0.5)	2 (1.1)	0	0	0
apremilast	3 (0.8)	0	0	3 (3.2)	0
COVID-19 related-symptoms [#], *n (%)*					
cough	23 (13.5)	10 (12.5)	7 (14.3)	5 (13.2)	0
fever	26 (15.2)	12 (15.0)	7 (14.3)	6 (15.8)	1 (33.3)
asthenia	12 (7.0)	3 (3.8)	4 (8.2)	4 (10.5)	0
dyspnea	16 (9.4)	7 (8.8)	6 (12.2)	3 (7.9)	0
headache	8 (4.7)	4 (5.0)	3 (6.1)	1 (2.6)	0
upper respiratory tract infection	17 (9.9)	5 (6.2)	8 (16.3)	4 (10.5)	0
pneumonia	34 (19.9)	19 (23.8)	5 (10.2)	9 (23.7)	1 (33.3)
cutaneous manifestation	6 (3.5)	3 (3.8)	0	2 (5.3)	1 (33.3)
gastrointestinal symptom	15 (8.8)	9 (11.2)	4 (8.2)	2 (5.3)	0
neurological symptom	9 (5.3)	4 (5.0)	3 (6.1)	2 (5.3)	0

(Continues)

TABLE 1 (Continued)

	Study population N = 398	RA N = 177	AS N = 120	PsA N = 93	JIA N= 8
Serious COVID-19, *n (%)*	279 (70.1)	121 (68.8)	87 (72.5)	64 (68.8)	7 (87.5)
Caused or prolonged hospitalization	53 (13.3)	28 (15.9)	15 (12.5)	9 (9.7)	1 (12.5)
Life-threatening	2 (0.5)	1 (0.6)	1 (0.8)	0	0
Death	13 (3.3)	11 (6.2)	2 (1.7)	0	0
Other medically important conditions	211 (53.0)	81 (46.0)	69 (57.5)	55 (59.1)	7 (75.0)
Outcome					
Unknown	235 (59.1)	98 (55.7)	79 (65.8)	51 (54.8)	6 (75.0)
Not recovered	42 (10.7)	21 (11.9)	10 (8.3)	11 (11.8)	0
Recovering	64 (16.2)	20 (11.4)	11 (9.2)	12 (12.9)	1 (12.5)
Recovered	42 (10.7)	26 (14.8)	18 (15.0)	19 (20.5)	1 (12.5)
Death, *n (%)*	13 (3.3)	11 (6.2)	2 (1.7)	0	0

Abbreviations: AS, ankylosing spondylitis; DMARD, disease-modifying antirheumatic drug; JIA, juvenile idiopathic arthritis; PsA, psoriatic *arthritis; RA, rheumatoid arthritis.*

#only available for 171 patients.

have an important role in infection, albeit independent of TNF activity [23,24]. Furthermore, it is well known that anti-TNF agents promote viral infections [25]. In clinical studies, etanercept does not appear to be more strongly associated than anti-TNF monoclonal antibodies with serious infections in RA patients – including viral infections [25]. However, the two subsets of TNF inhibitor have not been compared directly [26].

A recent clinical study showed that the COVID-19 hospitalization rate for patients with IRD was significantly lower among those treated with a TNF inhibitor [8]. Thus, the use of anti-TNF agents might not only promote the onset of COVID-19 but also reduce the severity of the disease by inhibiting the cytokine storm, as suggested in the literature [27]. Indeed, it is known that monocytes and macrophages are infected by SARS-CoV2; this induces the secretion of the proinflammatory cytokines (including TNF) responsible for moderate-to-severe forms of COVID-19 and (in some cases) cytokine release syndrome [12,28]. Further studies are needed to clarify these hypotheses.

In patients with RA, significantly lower RORs were found for tocilizumab and JAK inhibitors in the main analyses and the sensitivity analyses. These results suggest that tocilizumab and JAK inhibitors have a better safety profile with regard to the risk of COVID-19 in patients with RA, especially since the use of these drug classes in an indication of RA is not negligible [19,29]. Moreover, the use of anti-IL-6 agents and JAK inhibitors is potentially associated with less severe COVID-19 [12,30,31]. On the same lines, some experts have recommended continuing immunomodulatory treatments (including tocilizumab and baricitinib) in patients with COVID-19 [32]. Elevated blood IL-6 levels in hospitalized subjects with severe COVID-19 trigger an uncontrolled activation cascade that impairs the T-cell response and leads to a "cytokine storm" with low blood pressure, acute respiratory distress syndrome, and multiple organ failure [12,13].

Regardless of the indication for use, we found significant disproportionality for tocilizumab. This biologic DMARD was indicated for "COVID-19," "coronavirus infection," "hypercytokinemia," or "acute respiratory distress syndrome" in 8 of the 11 ICSRs, which might explain the high ROR.

Lastly, we also found significant disproportionality for JAK inhibitors in general and tofacitinib in particular (regardless of the indication for use) in the group of patients with IBD but not in those with RA. We hypothesize that the requirement for immunosuppression is greater in patients with IBD than in patients with RA. Moreover, patients with IBD are more likely to develop COVID-19, even in the absence of immunosuppressive treatment [33].

None of the ICSRs for patients with IRDs treated with DMARDs mentioned corticosteroids. Nevertheless, 77 of the 1702 reports of COVID-19 mentioned glucocorticoids as suspect drugs (22 were indicated for prophylaxis against transplant rejection, with 16 for a hematologic malignancy, 5 for a respiratory infection, 5 for an unknown indication, 4 for IBD, 3 for RA [in the latter cases, no DMARDs were associated; glucocorticoid was the sole suspect drug], 3 for multiple sclerosis, 3 for granulomatosis with polyangiitis, 3 for polymyalgia rheumatica, 2 for COVID-19, 2 for solid tumors, and 1 each for graft-versus-host

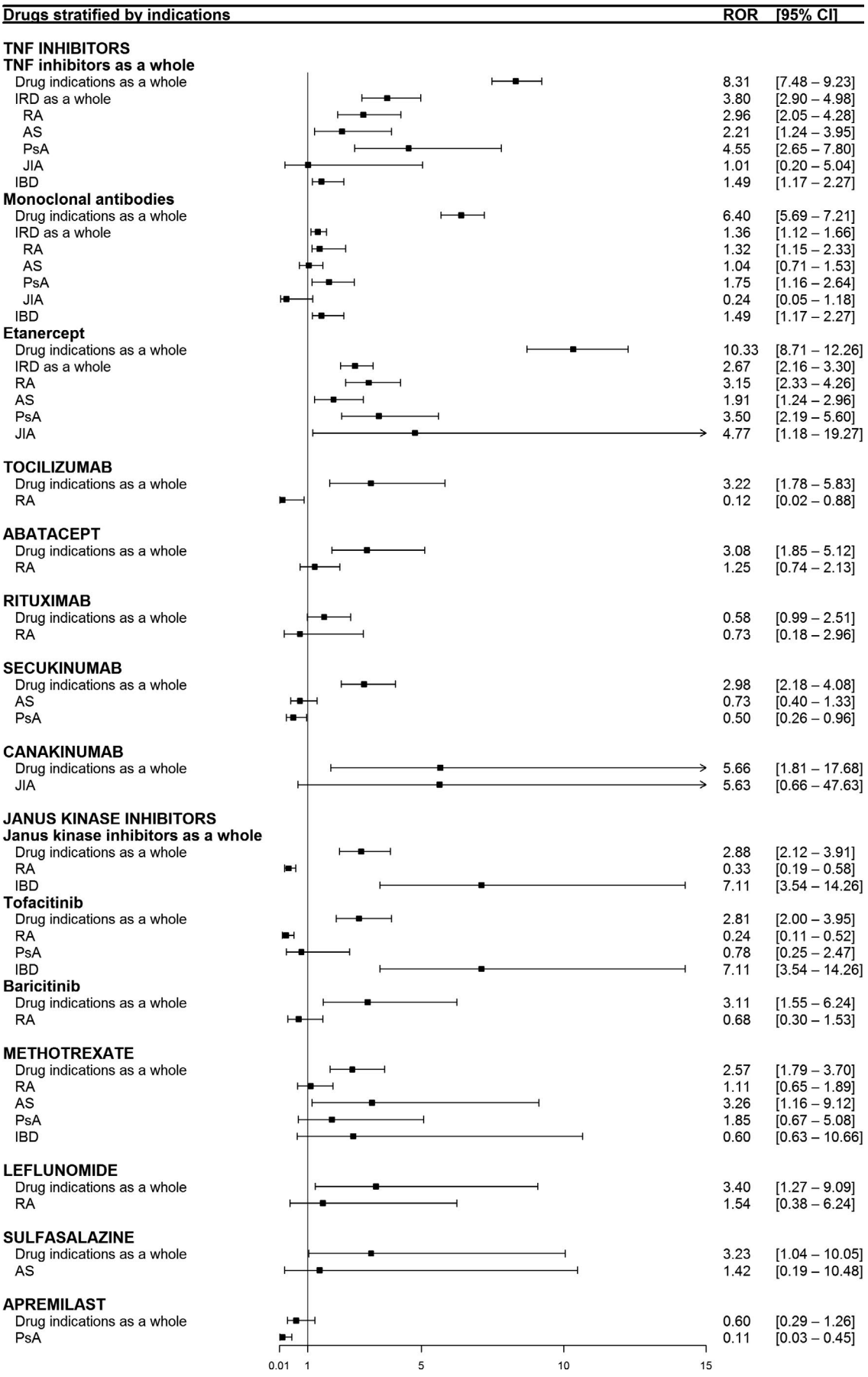

FIGURE 2 RORs for COVID-19 in patients taking DMARDs, by indication. AS, ankylosing spondylitis; DMARD, disease-modifying antirheumatic drug; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis

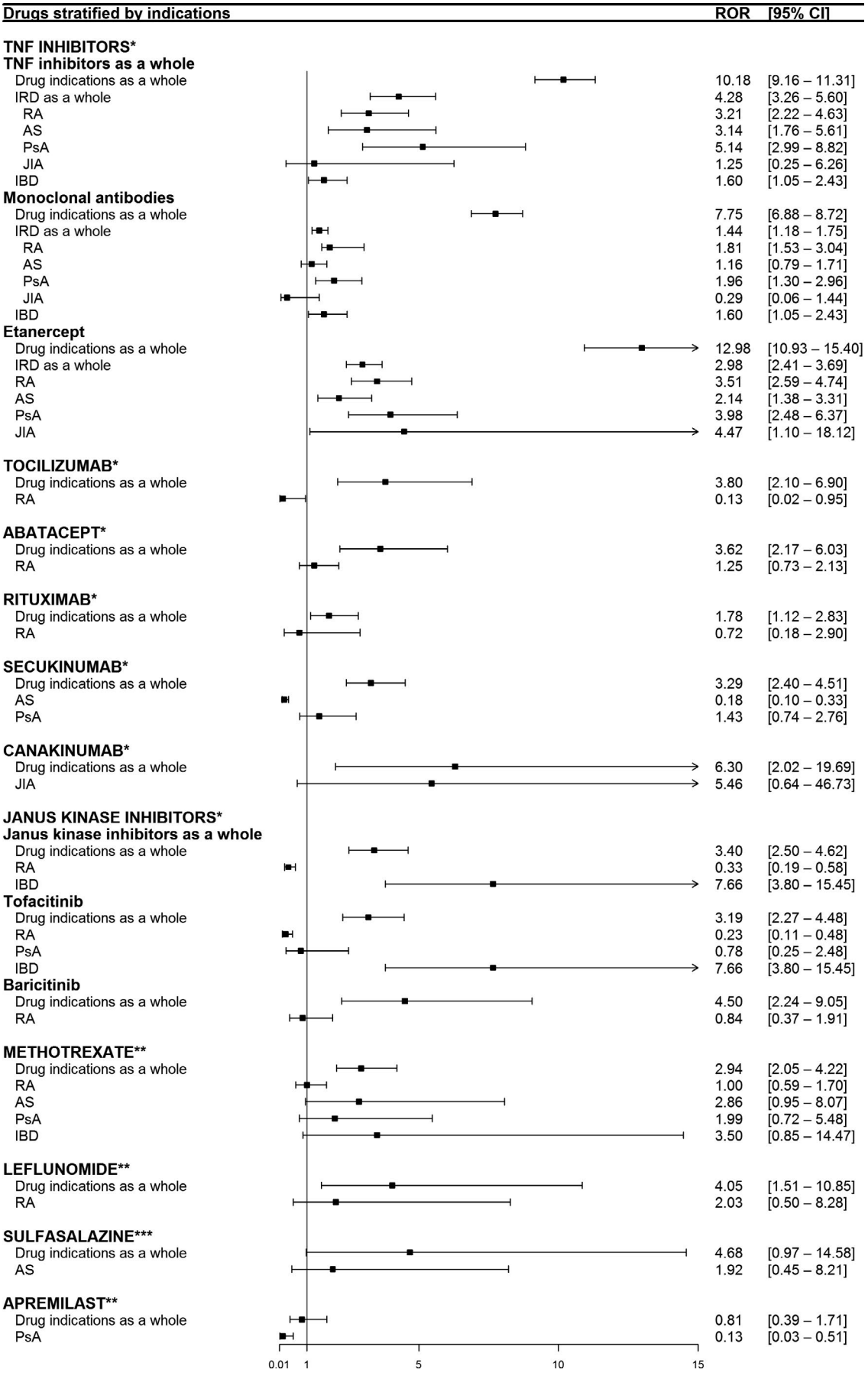
Drugs stratified by indications
ROR
[95% CI]
TNF INHIBITORS*
TNF inhibitors as a whole
Drug indications as a whole 10.18 [9.16 – 11.31]
IRD as a whole 4.28 [3.26 – 5.60]
RA 3.21 [2.22 – 4.63]
AS 3.14 [1.76 – 5.61]
PsA 5.14 [2.99 – 8.82]
JIA 1.25 [0.25 – 6.26]
IBD 1.60 [1.05 – 2.43]
Monoclonal antibodies
Drug indications as a whole 7.75 [6.88 – 8.72]
IRD as a whole 1.44 [1.18 – 1.75]
RA 1.81 [1.53 – 3.04]
AS 1.16 [0.79 – 1.71]
PsA 1.96 [1.30 – 2.96]
JIA 0.29 [0.06 – 1.44]
IBD 1.60 [1.05 – 2.43]
Etanercept
Drug indications as a whole 12.98 [10.93 – 15.40]
IRD as a whole 2.98 [2.41 – 3.69]
RA 3.51 [2.59 – 4.74]
AS 2.14 [1.38 – 3.31]
PsA 3.98 [2.48 – 6.37]
JIA 4.47 [1.10 – 18.12]
TOCILIZUMAB*
Drug indications as a whole 3.80 [2.10 – 6.90]
RA 0.13 [0.02 – 0.95]
ABATACEPT*
Drug indications as a whole 3.62 [2.17 – 6.03]
RA 1.25 [0.73 – 2.13]
RITUXIMAB*
Drug indications as a whole 1.78 [1.12 – 2.83]
RA 0.72 [0.18 – 2.90]
SECUKINUMAB*
Drug indications as a whole 3.29 [2.40 – 4.51]
AS 0.18 [0.10 – 0.33]
PsA 1.43 [0.74 – 2.76]
CANAKINUMAB*
Drug indications as a whole 6.30 [2.02 – 19.69]
JIA 5.46 [0.64 – 46.73]
JANUS KINASE INHIBITORS*
Janus kinase inhibitors as a whole
Drug indications as a whole 3.40 [2.50 – 4.62]
RA 0.33 [0.19 – 0.58]
IBD 7.66 [3.80 – 15.45]
Tofacitinib
Drug indications as a whole 3.19 [2.27 – 4.48]
RA 0.23 [0.11 – 0.48]
PsA 0.78 [0.25 – 2.48]
IBD 7.66 [3.80 – 15.45]
Baricitinib
Drug indications as a whole 4.50 [2.24 – 9.05]
RA 0.84 [0.37 – 1.91]
METHOTREXATE**
Drug indications as a whole 2.94 [2.05 – 4.22]
RA 1.00 [0.59 – 1.70]
AS 2.86 [0.95 – 8.07]
PsA 1.99 [0.72 – 5.48]
IBD 3.50 [0.85 – 14.47]
LEFLUNOMIDE**
Drug indications as a whole 4.05 [1.51 – 10.85]
RA 2.03 [0.50 – 8.28]
SULFASALAZINE***
Drug indications as a whole 4.68 [0.97 – 14.58]
AS 1.92 [0.45 – 8.21]
APREMILAST**
Drug indications as a whole 0.81 [0.39 – 1.71]
PsA 0.13 [0.03 – 0.51]
0.01
1
5
10
15

FIGURE 3 RORs for COVID-19 in patients taking DMARDs, by indication and after the removal of reports of the most frequent ADRs (selected as potential competitors) for each of the drug classes studied. *After removal of reports on the SOC "infections and infestations". **After removal of reports on the SOC "gastrointestinal disorders". ***After removal of reports on the SOC "skin and subcutaneous tissue disorders". ADR, adverse drug reaction; AS, ankylosing spondylitis; DMARD, disease-modifying antirheumatic drug; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SOC, system organ class

disease, systemic lupus erythematosus, systemic scleroderma, hydrocephaly, psoriatic arthritis [in the latter case, no DMARDs were associated; the glucocorticoid was the sole suspect drug], tonsillitis, dysphonia, and capsulitis of the shoulder), and 37 were reported with glucocorticoids as concomitant drugs (14 for prophylaxis against transplant rejection, with 5 for hematologic malignancy, 5 for solid tumors, 3 for an unknown indication, 2 for COVID-19, 2 for RA [one combined with infliximab and the other combined with abatacept], 1 for psoriatic arthritis [combined with adalimumab], 1 for multiple sclerosis, 1 for systemic lupus erythematosus, 1 for polymyalgia rheumatica, and 1 for a lung infection). According to the European league against rheumatism (EULAR) guidelines on the clinical management of RA with synthetic and biologic DMARDs, a short course of glucocorticoids should be tapered as rapidly as possible (implying that the disease is stable) [34]. Most of the patients with RA in the present study were taking biologic DMARDs, which also suggests that the disease was stable; however, the absence of detailed clinical data in VigiBase® prevents us from confirming this assumption. This might be why none of the patients with RA in our study population had a corticoid as the suspect drug, and only one case mentioned a corticosteroid as a concomitant drug. According to the EULAR guidelines on the pharmacologic management of psoriatic arthritis, nonsteroidal antiinflammatory drugs may be used to relieve musculoskeletal signs and symptoms, whereas systemic corticosteroids should be used with caution at the lowest effective dose [35]. Lastly, nonsteroidal antiinflammatory drugs (but not corticosteroids) are recommended for the treatment of axial AS [36]. This might explain why only two cases of PsA mentioned corticosteroids (once as a sole suspect drug and once as a concomitant drug) and no cases of AS mentioned corticosteroids. Nevertheless, with regard to corticosteroids, there was a discrepancy between our results and those of observational studies of patients with IRD, probably due to differences in selection of the study population. In an observational analysis of the COVID-19 Global Rheumatology Alliance physician-reported registry [8], all patients with IRD were included; in contrast, we first selected cases of COVID-19 with DMARDs and then stratified by indication. Thus, in the COVID-19 Global Rheumatology Alliance cohort of 600 patients, 32% were being treated with corticosteroids but 16% were not taking a DMARD. Moreover, the COVID-19 Global Rheumatology Alliance cohort included patients with various rheumatic diseases (such as vasculitis and polymyalgia rheumatica) for which corticosteroids treatment is obligatory. In the present study of VigiBase®, a few cases mentioned corticosteroids (regardless of whether or not the indication was an IRD), which is suggestive of underreporting, a major limitation of pharmacovigilance studies, along with missing data.

Our results are reassuring with regard to the severity of COVID-19 in DMARD-treated patients. Even though most cases (70.1%) were considered serious, only 13.3% of the patients were hospitalized and only 3.3% died. These results are consistent with the low reported mortality rate in cohort studies of this population [8,11,29].

Our study had several limitations, most of which are inherent to all pharmacovigilance studies and case/non-case designs (e.g., missing data and event competition bias) [16]. We attempt to reduce this bias by removing the most frequent ADRs from the analyses, using SOCs. Nevertheless, there are no validated methods for the selection of competitive ADRs [18]. Moreover, only cases voluntarily recorded in the database were captured, which creates reporting bias and limits our conclusions. Furthermore, we could not determine the absolute frequency of COVID-19 associated with DMARDs, notably because of underreporting. However, widespread underreporting would not affect the results of a disproportionality analysis [16]. Furthermore, most of the notified cases of COVID-19 came from Europe; none came from Asia, where our results may not therefore be applicable. Lastly, VigiBase® does not contain comprehensive information on the patient's medical history, which prevented us from analyzing other putative risk factors for COVID-19.

However, our study had several major strengths associated with its case/non-case design [16]. Firstly, we studied the world's largest pharmacovigilance database, which reflects medication use in routine clinical practice. Secondly, the case/non-case design is a validated method for investigating disproportionality between reports and drugs [16].

5 | CONCLUSION

Our analysis of reports voluntarily uploaded to VigiBase® suggests that COVID-19 is significantly less frequent in patients treated with TNF inhibitors than in patients treated with other drugs, particularly for patients with IRDs. This signal must now be confirmed in specific case–control or cohort analyses. Significant inverse disproportionality was found for tocilizumab or

JAK inhibitors in patients with RA; our results are therefore consistent with the scarce data published to date in this field.

DISCLAIMER

The interpretation of data in the present study represents the opinions of the authors only and not those of the WHO or the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM, Saint-Denis, France).

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AUTHORS' CONTRIBUTIONS

AD and BB were the major contributors to the study conception and design and acquisition, analysis, and interpretation of the data; drafted the article, and revised it critically for important intellectual content. JS and YB were the major contributors to the analysis and interpretation of the data, drafted the article, and revised it critically for important intellectual content. PD, SL, VGC, and KM were the major contributors to the analysis and interpretation of the data and revised the article critically for important intellectual content. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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