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COVID-19 and immune-mediated inflammatory diseases: effect of disease and treatment on COVID-19 outcomes and vaccine responses

Filippo Fagni, David Simon*, Koray Tascilar, Verena Schoenau, Michael Sticherling, Markus F Neurath, Georg Schett*

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*Contributed equally

Department of Internal Medicine 3 (F Fagni MD, D Simon MD, K Tascilar MD, V Schoenau MD, Prof G Schett MD), **Deutsches Zentrum Immuntherapie** (F Fagni, D Simon, K Tascilar, V Schoenau, Prof M Sticherling MD, Prof M F Neurath MD, Prof G Schett), **Department of Dermatology** (Prof M Sticherling), **and Department of Internal Medicine 1** (Prof M F Neurath) **Friedrich–Alexander University Erlangen–Nuermberg, Erlangen, Germany**

Correspondence to: Prof Georg Schett, Department of Internal Medicine 3, Friedrich–Alexander University Erlangen–Nuremberg, 91054 Erlangen, Germany **georg.schett@uk-erlangen.de**

At the beginning of the COVID-19 pandemic, patients with immune-mediated inflammatory diseases were considered to be at high risk for SARS-CoV-2 infection and the development of severe COVID-19. Data collected over the past year, however, suggest that a diagnosis of inflammatory arthritis, psoriasis, or inflammatory bowel diseases does not increase risk for SARS-CoV-2 infection or severe COVID-19 compared with people without these diseases. Furthermore, substantial data suggest that certain medications frequently used in patients with immune-mediated inflammatory diseases, in particular cytokine inhibitors, might even lower the risk for severe COVID-19. Conversely, glucocorticoids and potentially B-cell-depleting treatments seem to worsen COVID-19 outcomes. Additionally, the first data on SARS-CoV-2 vaccination in patients with these diseases suggest that tolerability of vaccination in patients with immune-mediated inflammatory diseases is good, although the immune response to vaccination can be somewhat reduced in this patient group, particularly those taking methotrexate or CD20-targeted treatment.

Introduction

In December, 2019, SARS-CoV-2 became the third zoonotic coronavirus to have human-to-human transmission and the first to cause a pandemic.[1] Although the majority of patients with COVID-19 have a self-limiting upper respiratory tract infection, a small but relevant proportion of patients develops acute respiratory distress syndrome that can rapidly lead to multiorgan failure and death. Severe COVID-19 is characterised by an excessive host immune response with overproduction of proinflammatory cytokines such as tumour necrosis factor (TNF), interleukin (IL)-6, growth factors such as granulocyte-macrophage colony-stimulating factor, and chemokines such as IL-8, a response known as cytokine storm (figure 1).[2,3] Some proinflammatory cytokines induced in COVID-19 are therapeutic targets in the treatment of patients affected by immune-mediated inflammatory diseases.[4] Such cytokine inhibitors are widely used in the treatment of inflammatory arthritis, psoriasis, inflammatory bowel disease, and connective tissue disorders. Therefore, the question has arisen whether cytokine blockade and immunomodulatory therapy might affect SARS-CoV-2 infection and its outcomes. In this Review, we summarise data on the risk for SARS-CoV-2 infection and severe COVID-19 in patients with immune-mediated inflammatory diseases of the joints, skin, and gut, as well as systemic diseases.

Risk of SARS-CoV-2 infection

Several datasets have shown that patients with immune-mediated inflammatory diseases are at an increased risk for infections;[5–11] hence, these patients constitute a potentially susceptible population in the COVID-19 pandemic. However, the situation is complicated and evidence directly supporting this concept is scarce. Patients with immune-mediated inflammatory diseases usually receive immune-modulating therapies and often have comorbidities, such as cardiovascular, pulmonary, and metabolic disease, which affect susceptibility to infection[12,13] and are themselves major drivers for infections in these patients. Although the higher prevalence of comorbidities represents a consistent factor for increasing risk of infection, including respiratory tract infections, the effect of treatments cannot necessarily be generalised. Glucocorticoids, for example, are associated with a general increase in risk for infections, suggesting that they lead to broad immunosuppressive effects that impair the function of the innate immune system but also profoundly inhibits adaptive immune cells, such as T cells.

By contrast, targeted immunomodulatory drugs, such as cytokine blockers, seem to have more distinct effects on infection risk, such as the reactivation of intracellular bacteria with TNF inhibitors, higher risk for *Candida* infection with IL-17 inhibitors, and the reactivation of herpes zoster with Janus Kinase (JAK) inhibitors.[7,14–16] Notably, data from large registries suggest that targeting TNF, IL-6, IL-17, and IL-23 does not increase risk of viral infection[17] or worsen influenza outcomes.[8] Hence, cytokine inhibitors seem to act more selectively on specific immune pathways by comparison with a state of general immune suppression. Evidence on the course of respiratory infections in patients with immune-mediated inflammatory diseases, and the effect of immunomodulatory treatments, is scarce. The COVID-19 pandemic provides an unprecedented opportunity to study the effect of these diseases and their treatments on the response of a host that is susceptible to a new virus and to profile the risk of SARS-CoV-2 infection and COVID-19 outcomes.[18]

At the onset of the pandemic most physicians considered patients with immune-mediated inflammatory diseases as a potentially highly susceptible population for SARS-CoV-2 infection and at risk for developing a severe course of COVID-19. However, a substantial amount of data has now been collected, not only in rheumatology but also in

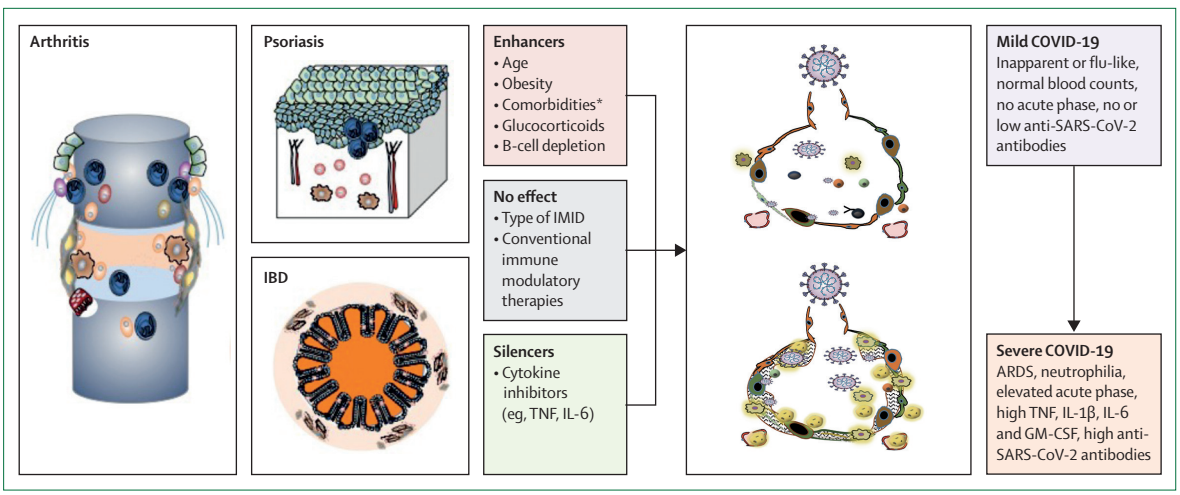

Figure 1: **Factors with immune-mediated inflammatory diseases that influence the risk for the development of severe COVID-19**
ARDS=acute respiratory distress syndrome. IBD=inflammatory bowel disease. IMID=immune-mediated inflammatory diseases. TNF=tumour necrosis factor. IL=interleukin. GM-CSF=granulocyte-macrophage colony-stimulating factor. *Comorbidities such as cardiovascular, pulmonary, and metabolic diseases.

gastroenterology and dermatology, that provide a reassuring message.

Risk of severe COVID-19 and adverse outcomes

COVID-19 is heterogeneous and ranges from asymptomatic infection to severe illness and death. Although detection of asymptomatic and mild infection is notoriously challenging and subject to bias, severe illness can be evaluated by more stringent means such as hospitalisation, mechanical ventilation, and COVID-19-related death—endpoints that have been widely assessed in studies. However, data collected in such studies must be reviewed to assess the reliability and potential for selection bias or confounding. For example, SARS-CoV-2 infection risk depends on several intrinsic and extrinsic variables, including local virus incidence, proportion of people immunised, social behaviour, shielding practices, access to testing, and the accuracy of diagnostic methods; this complexity could cause measurement error and bias in the results. Furthermore, inclusion of appropriate comparison cohorts is particularly important for SARS-CoV-2 infection studies. Hospitalisation rates might not necessarily be interpreted univocally as an indicator for COVID-19 severity, as the frequency of hospital admission is also affected by indirect factors such as the local SARS-CoV-2 incidence, general health state of the community, access to hospital care, and guidelines from the local health authorities. Ultimately, COVID-19-related death might be the most straightforward outcome to determine the severity of the disease course. Even for COVID-19-related death, however, normalisation of results with regard to demographics, comorbidities, treatment, socioeconomic factors, and possible colliders are essential to avoid misinterpretation, a striking example of which was the apparently protective effect of current smoking on COVID-19 mortality.[19,20]

Inflammatory arthritis

Evidence from large cohorts of patients with inflammatory arthritis, including rheumatoid arthritis and spondyloarthritis, has not shown strong associations between these diseases and risk of SARS-CoV-2 infection or adverse COVID-19 outcomes such as hospitalisation, intensive care unit (ICU) admission, need for mechanical ventilation, or COVID-19-related death.[21,22] A cross-sectional study of 2050 patients with inflammatory arthritis in a high-incidence region of Italy during the first phase of the pandemic[21] showed that hypertension and glucocorticoid use, but not the specific diagnosis of inflammatory arthritis, affected the risk of developing COVID-19. Two cross-sectional studies from France (n=655)[22] and Italy (n=955)[23] of patients with rheumatic diseases (mostly inflammatory arthritis) reported no COVID-19 deaths and only eight hospitalisations with mild disease courses (table).

There have also been conflicting findings. Increased risk of COVID-19-related death among patients with rheumatoid arthritis relative to healthy people was reported in a study of 473139 UK Biobank participants.[25] However, despite the large sample size, the analysis was restricted to patients aged older than 50 years, data collection was limited to the first phase of the pandemic, and hospitalisation rates, disease activity, and concomitant therapies were not considered. Therefore, mild COVID-19 cases might have been underestimated, potentially leading to overestimated risk. The most notable methodological issue in this study was the absence of a causal model to identify the relevant covariates to adjust for, resulting in risk of a so-called table-2 fallacy (meaning that effect estimates of secondary exposures are presented in the same manner as the primary exposure estimated from the same model),[39] which is common in studies where full

adjustments are made for all covariates regardless of their causal relationships with the exposure and outcome and all regression effect estimates for covariates are reported. A similarly large (n=33886) and robust matched cohort study using administrative US Veterans Affairs data also found similar results for the aggregated risk of hospitalisation or death in patients with rheumatoid arthritis (hazard ratio [HR] 1·35, 95% CI 1·10–1·66) even after adjusting for demographics and comorbidities.[40] However, the generalisability of these data is unknown because the mean age of the study population was 67·8 years and most patients (84·5%) were men. Additionally, hospitalisation and COVID-19-related death were assessed together. Increased rates of COVID-19-related hospitalisation is not necessarily related to increased odds of death in patients with immune-mediated inflammatory diseases.[28]

Psoriasis

Up to 37% of patients with psoriasis in high-income countries are receiving cytokine inhibitors.[41] Data on COVID-19 risk and outcomes for patients with psoriasis convincingly suggest a comparable risk profile as observed in the general population, with no increase in susceptibility to SARS-CoV-2 infection or severe COVID-19 reported in several cohort studies.[28,30,32,42] A prospective study of 1830 patients with psoriasis taking biologics found comparable incidence of COVID-19 diagnosis (9·7 *vs* 11·5 cases per 10000 person-months), hospitalisation (6·5 *vs* 9·6), and death (0·0 *vs* 1·16) compared with reference values for the local population.[29] Among 5206 patients with chronic plaque psoriasis from high-incidence areas treated with cytokine inhibitors, no deaths were reported and only four patients (all with comorbidities and older age) were admitted to the hospital with COVID-19 pneumonia,[30] despite the high prevalence of comorbidities in this population (25% obesity, 31% hypertension).

For the **SECURE-IBD database** see https://covidibd.org/

These results suggest no strong association between psoriasis and infection, hospitalisation, ICU admission, and death due to COVID-19. So far, only one study reported increased odds of SARS-CoV-2 infection (OR 3·43, 95% CI 2·25–5·73]) and hospitalisation (OR 3·59, 1·49–8·63) among patients with psoriasis, but ICU admission rates and mortality risk were comparable with those of the general population.[28] In all available studies, COVID-19 death risk in psoriasis cohorts was similar to that of reference populations (table).[28,29,31,32] It is important to note, however, that patients with psoriasis are likely to carry a heavier burden of cardiovascular, metabolic, and pulmonary comorbidities compared with the general population, thus potentially increasing the risk of severe COVID-19 despite good disease control by treatments.[43]

Inflammatory bowel diseases

Patients with Crohn's disease and ulcerative colitis can be at increased infection risk because of gut barrier dysfunction and intensive immune-modulatory treatments.[44] At the onset of the COVID-19 pandemic, there was an intensified discussion about whether the integrity of the intestinal barrier might be associated with worse outcomes of SARS-CoV-2 infection. An increased expression of SARS-CoV-2 receptor ACE2 in the terminal ileum and colon of patients with inflammatory disease was observed in experimental settings, and increased gut leakage biomarkers were found in patients with severe COVID-19.[45,46] Yet despite a high prevalence of gastrointestinal symptoms in patients with COVID-19, these factors do not seem to have clinically relevant effects on the COVID-19 disease course. Although early reports showed no cases of SARS-CoV-2 among patients with inflammatory bowel disease,[33,47] subsequent research has identified COVID-19 cases among such patients;[48] however, no studies have found an association between SARS-CoV-2 infection and inflammatory bowel disease diagnosis (table).[33,49] In one single-centre study of 168 patients with inflammatory bowel disease, the prevalence of SARS-CoV-2 infection was 3·0% (comparable with the population-weighted prevalence), and infection was associated with age, obesity, hypertension, and diabetes.[50] The most recent available analysis of the international SECURE-IBD database, published in 2020, suggests that people with inflammatory bowel disease have similar severe COVID-19 outcomes to that seen in the general population.[49] Nevertheless, consistent with previous findings on infectious risk in patients with inflammatory bowel disease,[51] higher disease activity and flares lead to increased susceptibility to SARS-CoV-2 infection and worse COVID-19 outcomes.[34] A 10-fold increase in risk of COVID-19-related pneumonia was found among patients with active inflammatory bowel disease (OR 10·25, 95% CI 2·11–49·73) in a study of 79 patients, however, the same study also reported an almost 5-fold increase in patients taking glucocorticoids (OR 4·94, 0·95–22·55).[34] In conclusion, evidence suggests that the risk profile for SARS-CoV-2 infection and severe COVID-19 outcomes in patients with inflammatory bowel disease is likely to be similar to the general population if patients have good disease control and do not use glucocorticoids; however, caution is advised in patients with poor disease control needing glucocorticoid treatment or those with comorbidities.

Connective tissue diseases

Patients with connective tissue diseases, such as systemic lupus erythematosus, primary Sjögren's syndrome, systemic sclerosis, and polymyositis and dermatomyositis have an increased morbidity and mortality attributed to infectious diseases.[52] Data on SARS-CoV-2 infection rate in patients with these diseases have produced conflicting results. Several reports have suggested an increased risk of SARS-CoV-2 infection in patients with connective tissue diseases when compared with the general population and to patients with other immune-mediated

	Patient population, n	Ongoing therapies	Design	SARS-CoV-2 infection		Hospitalisation		Death	
				Study population	General population	Study population	General population	Study population	General population
Inflammatory arthritis									
Fernandez-Gutierrez et al (2021)[24]	3951 (61·7% patients with inflammatory arthritis)	Glucocorticoids 45·6%; cIMD 49·6%; cytokine inhibitors 20·9%	Prospective cohort study	0·09%	NA	1·5%* (glucocorticoids RR 1·7, 95% CI 1·01–2·9;* TNFi RR 0·3, 0·6–1·1)†	0·3%	NA	NA
Topless et al (2021)[25]	5409	NA	Retrospective cohort study	RR rheumatoid arthritis ns†	NA	NA	NA	Rheumatoid arthritis RR 1·90 (1·20–3·00)*	NA
Haberman et al (2020)[26]	103	Glucocorticoids 12·6%; cIMD 34%; cytokine inhibitors 70·9%	Prospective cohort study	All patients with symptomatic COVID–19	NA	26% (glucocorticoids RR 26·22 95% CI 3·82–180·19;* JAKi RR 10·23, 1·88–55·51;* cIMD RR ns;† cytokine inhibitors RR ns;† TNFi RR ns;† IL-17i RR ns†	NA	4%	NA
Costantino et al (2021)[22]	655	Glucocorticoids 16·4%; cIMD 24·1%; cytokine inhibitors 61·7%	Cross sectional	1·8%† (glucocorticoids RR ns;† cIMD RR ns;† cytokine inhibitors RR ns)†	4·4%	0·8%	NA	0%†	NA
Ferri et al (2020)[27]	1641 (57·2% with inflammatory arthritis)	cIMD 60·6%; cytokine inhibitors 51·7%	Cross-sectional	1·5%* confirmed RR for both groups: (RR IMID 1·93, 95% CI 1·05–3·52;* RR connective tissue disease 2·35, 0·68–8·05)	0·8%	NA	NA	0·06%†	NA
Psoriasis									
Damiani et al (2020)[28]	1193	Cytokine inhibitors 100%	Retrospective cohort study	0·2%† (cytokine inhibitors RR 3·43, 2·25–5·73)*	0·5%	0·4% (cytokine inhibitors RR 3·59, 1·49-8·63)	0·1%	0%† (cytokine inhibitors RR ns)†	0·2%
Piaserico et al (2020)[29]	1830	Cytokine inhibitors 100%	Retrospective cohort study	0·097%†	0·12%	0·065%†	0·09%	0%†	0·097%
Gisondi et al (2020)[30]	5206	Cytokine inhibitors 100%	Retrospective cohort study	NA	NA	0·056%†	0·059%	0%†	NA
Gisondi et al (2020)[31]	980	Cytokine inhibitors 100%	Retrospective cohort study	NA	NA	0%†	0·2%	0%†	NA
Lima et al (2020)[32]	104	cIMD 9·6%; cytokine inhibitors 26%	Retrospective cohort study,	NA	NA	Cytokine inhibitors RR ns†	NA	Cytokine inhibitors RR ns†	NA
Inflammatory bowel disease									
Norsa et al (2020)[33]	522	cIMD 17%; cytokine inhibitors 16%	Prospective cohort study	0%†	4%	0%†	NA	0%†	NA
Bezzio et al (2020)[34]	79	Glucocorticoids 11%; cIMD 9%; cytokine inhibitors 63%	Prospective cohort study	All had COVID–19	NA	28%	NA	8% (active IBD RR 8·45, 1·26–56·56)	NA
Lukin et al (2020)[35]	119	Glucocorticoids 29·4% Cytokine inhibitors 70·6%	Matched cohort + prospective cohort study	All had COVID–19	All had COVID–19	All hospitalised	All hospitalised	0%†	5·9%

(Table continues on next page)

	Patient population, n	Ongoing therapies	Design	SARS-CoV-2 infection		Hospitalisation		Death	
				Study population	General population	Study population	General population	Study population	General population
(Continued from previous page)									
Connective tissue disease									
Fasano et al (2020)[36]	268	Glucocorticoids 58%; cIMD 37%	Cross sectional	Suspected COVID-19‡ 19%	NA	0%	NA	0%†	NA
Favalli et al (2020)[37]	123	Glucocorticoids 64·2%; cIMD 60%; cytokine inhibitors 20%	Cross sectional	0·81%;* suspected COVID-19‡ 11·3%*	0·62%	0·8%	NA	0·8%†	NA
Bozzalla Cassione et al (2020)[38]	165	NA	Retrospective cohort study	2·5%*	0·76%	0·65%	NA	0%†	NA
Ferri et al (2020)[27]	1641 (42·8% with connective tissue disease)	cIMD 60·6%; cytokine inhibitors 51·7%	Cross sectional	1·5%* confirmed RR for both groups: (IMID RR 1·93, 1·05–3·52;* connective tissue disease RR 5·46, 2·04–14·63)*§	0·8%	NA	NA	0·06%†	0·07%

Risk is measured in terms of relative risk and in terms of prevalence (for cross-sectional studies) or incidence (for prospective and retrospective studies) in comparison to a reference population. NA=not available. ns=not significant. RR=relative risk. IMID=immune-mediated inflammatory arthritis. cIMD=conventional-immunomodulatory drugs. TNFi=tumour necrosis factor inhibitors. IL17i=interleukin-17 inhibitors. JAKi=JAK inhibitors. *Increased risk for IMID. ‡Patients with COVID-19-compatible symptoms but not having a definite diagnostic test. †Reduced risk for IMID. §RR referred to definite and highly suspected COVID-19 cases with connective tissue disease in comparison to inflammatory arthritis.

Table: **Risk of SARS-CoV-2 infection and adverse COVID-19 outcomes in inflammatory arthritis, psoriasis, inflammatory bowel diseases, and connective tissue diseases**

inflammatory diseases.[27,38] A meta-analysis that included 319025 patients from 62 studies[53] showed that patients with connective tissue diseases had the highest prevalence of COVID-19 compared with other immune-mediated inflammatory diseases. This group also had a higher proportion of glucocorticoid usage (60·3%), which might have contributed to this result.[53]

Evidence is also conflicting regarding COVID-19 outcomes in patients with connective tissue diseases. A comparative cohort study of 456 patients with immune-mediated inflammatory diseases and COVID-19 and healthy participants found that connective tissue disease, but not inflammatory arthritis, confers higher risk of severe COVID-19 (OR 1·82, 95% CI 1·00–3·30),[54] after adjustment for sex, age, and comorbidities. By contrast, another matched cohort study of 123 patients with connective tissue diseases found opposite results, with only one patient undergoing rituximab treatment dying from COVID-19.[37] Similar favourable results also emerged from an Italian observational cohort of 268 patients with systemic lupus erythematosus.[36] Data are scarce about the effect of therapy on SARS-CoV-2 infection in patients with these diseases, particularly B-cell depleting therapies, but could partly explain these findings. Moreover, fewer studies are available in patients with connective tissue diseases by comparison with other immune-mediated inflammatory diseases and COVID-19. Thus, while awaiting larger studies, the question about an increased susceptibility to SARS-CoV-2 infection in these patients remains open (table).

In our opinion, the vast majority of available data shows that diagnosis with an immune-mediated inflammatory disease does not itself increase the risk for SARS-CoV-2 infection or adverse COVID-19 outcomes, suggesting that the immune dysfunction in these patients does not necessarily affect their risk of SARS-CoV-2 infection.

Immunomodulatory therapies and COVID-19 outcomes

Glucocorticoids

The risk for infectious mortality and morbidity related to chronic and high-dose therapeutic regimens with glucocorticoids is long-known, including for viral infections.[14] Consequently, the relative risk associated with glucocorticoids is consistently higher than that of other drugs used for immune-mediated inflammatory diseases, often linear to daily dosage.[16,35] Regarding COVID-19, the RECOVERY trial[55] found that the use of systemic dexamethasone in patients without immune-mediated inflammatory diseases resulted in lower mortality; however, this effect was only observed in severely ill patients requiring ventilator support, with potential evidence for harm in patients with mild COVID-19. The unfavourable effect of glucocorticoids in patients with mild COVID-19 was confirmed in another study, in which mortality and progression to ventilation

increased after glucocorticoid therapy.[56] The adverse effects of glucocorticoids in the context of COVID-19 have also been confirmed in patients with inflammatory arthritis and inflammatory bowel disease, where chronic glucocorticoid intake was associated with higher risk of SARS-CoV-2 infection, increased hospitalisation, ICU admission rates, and mortality.[22,26,57–59] In a large cross-sectional study on 600 patients with immune-mediated inflammatory diseases from 40 countries (using data from the COVID-19 Global Rheumatology Alliance [GRA]), the main clinical and demographical variables associated with COVID-19-related hospitalisation were older age (>65 years), cardiovascular, pulmonary, and renal comorbidities, and the intake of 10 mg or more of prednisone daily, which was associated with a doubled risk of hospitalisation (OR 2·05, 95% CI 1·06–3·96).[57] Similar results emerged in another large, multicentre study of 2050 patients with inflammatory arthritis in a high-incidence area during the first stages of the pandemic; use of 2·5 mg or more of prednisone daily was associated with a significantly higher probability of symptomatic SARS-CoV-2 infection (RR 2·89, 95% CI 1·26–6·62; figure 2).[21] Nonetheless, since glucocorticoid intake usually reflects increased disease activity, disentangling the two factors is difficult. For instance, an analysis of 3729 patients from the GRA registry initially revealed that a prednisolone-equivalent dose of more than 10 mg per day (OR 1·69, 95% CI 1·18–2·41]) and moderate-to-high disease activity (OR 1·87, 1·27–2·77) were associated with higher odds of death.[60] However, reanalysis of the same data later showed that moderate-to-severe disease activity alone (OR 1·81, 95% CI 1·14–2·86), but not glucocorticoids alone, resulted in increased risk of death by COVID-19.[61] Nevertheless, the strength of association between disease activity and death increased when higher dosages of glucocorticoids (ie, more than 10 mg per day) were taken. Altogether, glucocorticoid use and disease activity are highly overlapped and current data do not allow identification of which of the two variables is the major contributor to risk. Yet, identification of the relevant variable would have a minor effect on clinical practice, as ensuring sufficient disease control also leads to a reduced use of glucocorticoids.

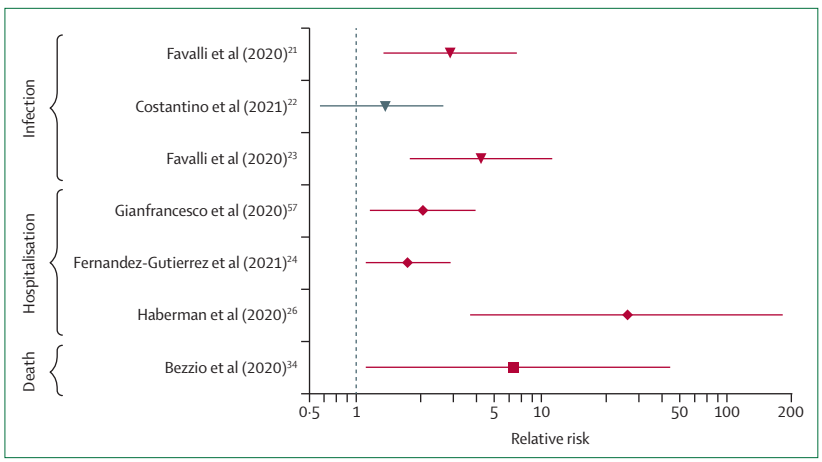

Figure 2: **Relative risk of SARS-CoV-2 infection and COVID-19-related hospitalisation and death in patients with immune-mediated inflammatory disease receiving glucocorticoids compared with patients with immune-mediated inflammatory disease not receiving glucocorticoids**
Significant results (p<0·05) are reported in red, non-significant results are reported in grey. Only studies that reported relative risk values for glucocorticoids exposure were included.[21–24,26,34,37]

Conventional immunomodulatory drugs

Data on the specific effect of conventional immunomodulatory drugs on SARS-CoV-2 infection and COVID-19 disease course are scarce and, to some extent, contrasting. One analysis of the GRA database found an association between sulfasalazine (OR 3·60, 95% CI, 1·66–7·78) and other immunosuppressant drugs (eg, cyclophosphamide, mycophenolate, tacrolimus, ciclosporin, or azathioprine; RR 2·22, 1·43–3·46) with poorer COVID-19 outcomes.[60] Sulfasalazine was also associated with an increased risk of adverse COVID-19 outcomes in patients treated for inflammatory bowel disease.[49] In a cohort of 1439 patients with inflammatory bowel disease and COVID-19,[49] thiopurine monotherapy (RR 4·08, 1·73–9·61) and combination therapy (RR 4·01, 1·65–9·78) resulted in an increased risk of severe COVID-19—defined as ICU admission, need for mechanical ventilation, and death—compared with patients treated with TNF inhibitors. However, previous data from several patient cohorts show no increased risk associated with any conventional immunomodulatory drugs.[21,22,27] Additionally, patients treated with conventional-synthetic disease-modifying anti-rheumatic drugs had similar rates of IgG seroconversion to SARS-CoV-2 compared with healthy participants.[62] The available evidence suggests caution with sulfasalazine, and potentially some other immunomodulatory drugs, but further studies are required to comprehensively evaluate the effects of individual immunomodulatory drugs on COVID-19.

Cytokine inhibitors

Evidence gathered throughout all phases of the pandemic suggest cytokine inhibitors are safe. That said, a single report has described an increased risk of SARS-CoV-2 infection (OR 3·43, 95% CI 2·25–5·73) and hospitalisation (3·59, 1·49–8·63) in patients with psoriasis treated with cytokine inhibitors.[28] Notably, however, odd ratios were not adjusted for confounding exposures, and the population studied was predominantly men with high prevalence of risk factors for COVID-19 (eg, older age, high body-mass index [BMI], high smoking prevalence) who were from a high-incidence region, and these factors might have led to an overestimation of risk. By contrast, other studies have shown no increase in the rates of COVID-19 in cohorts of patients with immune-mediated inflammatory diseases receiving continued anticytokine therapy (figure 3).[13,23,24,57,64] Additionally, significantly lower anti-SARS-CoV-2 seroconversion rates

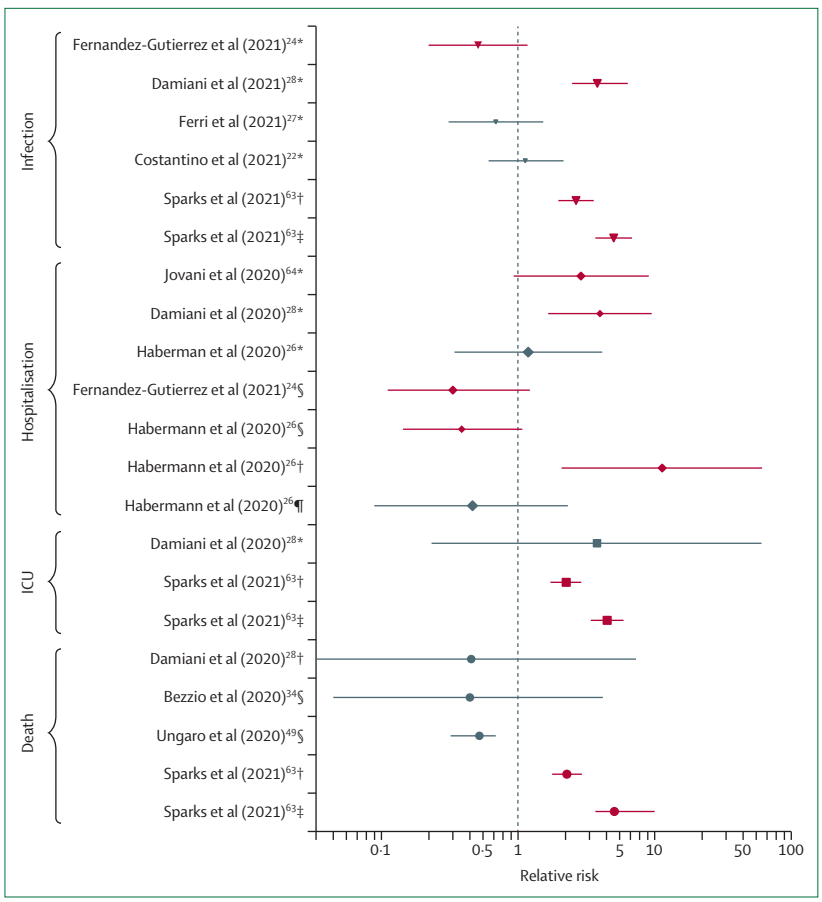

Figure 3: **Relative risk of SARS-CoV-2 infection and COVID-19-related hospitalisation, ICU admission, and death in patients with immune-mediated inflammatory diseases receiving cytokine inhibitors compared with patients with immune-mediated inflammatory disease not receiving cytokine inhibitors**
Significant results (p<0·05) are reported in red, non-significant results are reported in grey. Only studies that reported relative risk values for biological and targeted synthetic DMARD exposure were included in the figure.[22,24,26-28,34,49,63,64] DMARD=disease modifying anti-rheumatic drug. ICU=intensive care unit. *DMARDs. †JAK inhibitors. ‡Rituximab. §TNF inhibitors. ¶IL-17 inhibitors.

(a proxy for infection rates) were reported in a large cohort study of 534 patients treated with cytokine inhibitors compared with participants from the general population and health-care workers.[62] Only 0·75% of the patients treated with anticytokine drugs had developed anti-SARS-CoV-2 IgG (risk ratio [RR] 0·32, 95% CI 0·11–0·99), whereas patients not receiving cytokine blockade showed a prevalence of anti-SARS-CoV-2 IgG responses comparable to healthy participants (3·09%; RR 1·21, 0·50–2·90). This result aligns with previous observations from the 2003 SARS-CoV and the 2012 Middle East respiratory syndrome epidemics, which reported no increased risk of infection, morbidity, and mortality for patients affected by conditions requiring immunomodulatory treatment.[65] It's worth noting that studies that use seroconversion as evidence of SARS-CoV-2 infection have some limitations; for example, not all participants exposed to SARS-CoV-2 mount humoral immunity against the virus leading to seroconversion, and patients with underlying illnesses might take extra precautions (eg, shielding) and thus have lower exposure to the virus. Nevertheless, seroprevalence studies allow estimations of infection prevalence in a population.

Pathogenic similarities between severe COVID-19 and immune-mediated inflammatory diseases might also explain the favourable safety profile of cytokine inhibitors.[66] Notably, the trials on the use of the anti-IL-6 receptor inhibitor tocilizumab[67–69] and JAK inhibitors baricitinib and tofacitinib[70–72] in severe COVID-19 have shown positive, albeit small, effects on progression to ventilation, survival, and time to recovery in patients without underlying immune diseases. However, data on COVID-19 in patients receiving stable therapy with JAK inhibitors are currently scarce. One study reported that JAK inhibitor treatment in patients with rheumatoid arthritis might be associated with severe COVID-19,[63] suggesting that, similar to glucocorticoids, the timing of immunomodulation might affect the disease course.

In inflammatory arthritis, the risk of COVID-19 death was higher only for patients with rheumatoid arthritis receiving maintenance therapy with glucocorticoids, whereas no difference in disease course was found for cytokine inhibitors (table).[21,22,26] A European multicentre study investigated the clinical and serological prevalence of SARS-CoV-2 in 3028 patients with diverse immune-mediated inflammatory diseases, predominantly inflammatory arthritis, and found that those treated with cytokine inhibitors showed an almost 50% reduction in symptomatic COVID-19 (OR 0·51, 0·32–0·82),[73] suggesting that cytokine inhibitors (eg, TNF inhibitors) can alleviate the course of COVID-19. In a prospective study of 103 patients with inflammatory arthritis from the USA, in which the use of oral glucocorticoid was associated with a significant increase in the risk of hospital admission, even after adjustment for age and comorbidities (OR 26·22, 3·82–180·19), whereas cytokine inhibitors were not.[26] In that study, patients who were hospitalised were more likely to be older than 65 years and have hypertension.

A protective effect of cytokine inhibitors in patients with symptomatic COVID-19 was also reported among 2050 patients with inflammatory arthritis (adjusted OR 0·47, 0·46–0·48).[21] A trend for safety of cytokine inhibitors was also reported in a study of 2869 patients with rheumatoid arthritis; however, rituximab (OR 4·15, 3·16–5·44) and JAK inhibitors (OR 2·06, 1·60–2·65) were both associated with severe COVID-19, including hospitalisation, oxygen therapy, mechanical ventilation, or death,[63] and these associations persisted after adjustment for demographics and comorbidities. Altogether, these data support continuing cytokine inhibitors for the treatment of inflammatory arthritis. However, closer attention and more specific studies on SARS-CoV-2 infection in patients receiving JAK inhibitors and rituximab are needed, as these drugs can potentially interfere with the antiviral response.[63,74]

Pre-pandemic era reports on cytokine inhibitor-related risk of infection in patients with psoriasis linked TNF inhibitors, but not IL-17 and IL-23 inhibitors, to an increase of the risk of upper respiratory tract infection;[17] however, meta-analyses did not find differences in the rate of serious infections for any cytokine inhibitor used in psoriasis.[75] Data from a global registry of COVID-19 in patients with psoriasis showed that hospitalisations were more frequent in those using non-biologic systemic therapy than with biologics (OR 2·84, 1·31–6·18).[76] Also, anecdotal reports of patients with psoriasis who continued IL-17 inhibitors or IL-23 inhibitors despite having COVID-19 have been reported. In such cases, patients had an asymptomatic to mild disease course with normal resolution of the infection. Data on cytokine inhibitors and COVID-19 in patients with inflammatory bowel disease are consistent. Multiple studies on inflammatory bowel disease cohorts confirmed that cytokine inhibitors are not associated with an increased risk of SARS-CoV-2 infection or susceptibility to severe COVID-19 (table).[36,48,51]

In connective tissue diseases, the use of targeted immune modulatory drugs is almost exclusively restricted to B-cell-targeted drugs, which are known to impair humoral immune responses. Treatment with the anti-CD20 drug rituximab was previously associated with increased susceptibility to viral infections, including hepatitis B virus, cytomegalovirus, and human polyomavirus 2 (commonly known as JC virus).[77–78] The effect of B-cell depletion on SARS-CoV-2 infection remains to be clarified. Two patients with systemic vasculitis and multiple comorbidities were reported to have mild COVID-19 despite rituximab treatment.[79,80] Also, an analysis of the GRA registry had found no evidence of significantly poorer outcomes in the first 37 patients treated with rituximab, who were pooled with other cytokine inhibitors-treated patients.[57] However, as the pandemic has progressed, contrasting evidence from COVID-19 registry data and cohorts of patients with connective tissue diseases, reported long-persisting SARS-CoV-2 viraemia, delayed humoral response, and higher rates of hospitalisation, severe COVID-19 and death in patients taking B-cell depleting therapies.[77,78,81] A French cohort study found a negative effect of rituximab on severe COVID-19 outcomes (pooled risk of ICU admission or death) but not on the risk of death in patients with immune-mediated inflammatory diseases.[82] The 63 patients treated with rituximab were more likely to develop severe COVID-19 (effect size 3·26, 1·66–6·40) even after correcting for other risk factors including age, BMI, comorbidities, and glucocorticoid use.[82] Patients with a shorter interval (<50 days) between rituximab infusion and COVID-19 progressed to severe disease more often than those with a longer interval. Additionally, an analysis of the GRA registry reported higher odds of deaths due to COVID-19 in 159 patients treated with rituximab (OR 4·04, 2·32–7·03).[60] Therefore, further research on whether, when, and how to discontinue B-cell depleting therapies in COVID-19 is needed before a definite statement on the safety of B cell depletion is possible (table).

Response to SARS-CoV-2 vaccination

mRNA and vector-based vaccines lead to robust humoral and cellular immune responses in healthy individuals,[83,84] but data on vaccine responses in patients with immune-mediated inflammatory diseases are currently scarce. A small study of 26 such patients suggested development of anti-SARS-CoV-2 IgG antibodies in response to vaccination[85] with no effect on underlying disease activity. Larger studies have suggested that mRNA vaccination responses might be impaired in a proportion of patients with immune-mediated inflammatory diseases. In an observational study on mostly young (median age 44 years), female patients with immune-mediated inflammatory diseases, 94% developed anti-SARS-CoV-2 antibodies, but no control group was included.[86] An initial signal of reduced vaccine immunogenicity came from a prospective cohort study of 84 patients with immune-mediated inflammatory diseases and 182 healthy participants, which showed delayed and reduced antibody responses, with one in ten patients not having sufficient neutralising antibody responses, compared with one in 100 healthy participants.[87] Patients with immune-mediated inflammatory diseases not taking immunomodulatory drugs were shown to respond less efficiently to the vaccine than healthy participants, suggesting impairment related to disease activity rather than to a role for particular therapies.

A decreased humoral immune response to vaccines in patients with these diseases seems to be evident after the first vaccine. Among 120 patients with immune-mediated inflammatory diseases who received either mRNA or viral vector-based vaccines, 15% of participants receiving immunomodulatory drugs, and particularly patients taking conventional medications such as methotrexate, did not develop detectable concentrations of anti-SARS-CoV-2 antibodies.[88] Another study, published as a preprint, of 133 patients reported a 3-fold reduction in antibody titres among patients receiving anti-metabolite therapies, and a 10-fold reduction in antibody titres among patients treated with prednisone, independently of the daily dose.[89] Attenuated vaccination responses in patients taking conventional immunomodulatory drugs was confirmed in another multi-centre study of 82 patients with immune-mediated inflammatory diseases (compared with 208 healthy participants), with patients treated with methotrexate showing reduced rates of adequate immunogenicity to mRNA vaccination and reduced $CD8^+$ T-cell responses. Patients on anticytokine or non-methotrexate oral medications had similar immunogenicity compared with healthy participants.[90] These latter findings are in accordance with previous vaccine studies done in patients with inflammatory arthritis,

in which cytokine inhibitors seem to have no effect on vaccination response.[91] For inflammatory bowel disease, a large vaccination study showed that patients treated with infliximab and vedolizumab usually responded well to the mRNA and viral vector-based vaccines, although responses were blunted by a factor of 0·29 for mRNA-based vaccines and 0·39 for viral vector-based vaccines in those receiving TNF inhibitors as compared with vedolizumab.[92,93] Thus, patients receiving TNF blockers might require monitoring of appropriate vaccination responses.[94]

Another small study in patients with systemic autoinflammatory syndromes treated with IL-1 inhibitors reported good responses and safety after COVID-19 vaccinations, with no evidence for vaccine-induced disease flares.[92] Studies of influenza vaccination showed that anti-CD20 therapies blunt the humoral immune response to vaccines. This response has been confirmed for SARS-CoV-2 vaccines with one study showing that none of the patients treated with B-cell targeted therapies developed a serological response to at least one dose of vaccination.[95–97] A longer delay time period between the last rituximab infusion and vaccination, which allows partial reconstitution of B cells, was associated with increased odds of seroconversion. Despite the absence of an assessment after the completion of the vaccine cycle for all patients and insufficient data on specific vaccination types, these findings that specific studies on the timing of rituximab treatment will be necessary to develop an individualised vaccination strategy. Furthermore, although humoral immune responses to SARS-CoV-2 vaccines are impaired or absent in patients with depleted B-cell concentrations, evidence so far suggests that T-cell responses are not impaired, suggesting that SARS-CoV-2 vaccination can and should be also done in patients taking these medications.[96,97] Further studies will be needed to determine the importance of T-cell responses against SARS-CoV-2 to address the management of people who are humoral non-responders. However, the ideal time for SARS-CoV-2 vaccination seems to be during the phase of B-cell repopulation, just before receiving the next course of CD20 targeted therapy.

Conclusion

Overall, current data are largely reassuring as they do not strongly suggest that the presence of an immune-mediated inflammatory disease or most medications associated with their treatment (except for glucocorticoids and rituximab) universally puts patients at increased risk for SARS-CoV-2 infection or the development of severe COVID-19. The higher risk of severe COVID-19 reported in some studies[20,57] might be attributed to the accompanying cardiovascular, pulmonary, and metabolic comorbidities associated with these diseases, which have been shown to be the main determinants of poor COVID-19 outcomes.[2,20] Notably, increased rates of hospitalisation in patients with immune-mediated inflammatory disease were not associated with increased rates of death.[28] Consequently, particular attention might be focused on controlling comorbidities and to prioritising vaccination according to comorbidities.

Although abundant evidence shows that glucocorticoid use leads to increased risk of infection and COVID-19-related morbidity and mortality in patients with immune-mediated inflammatory disease, cytokine inhibitors do not seem to interfere with antiviral response or viral clearance; no marked differences in COVID-19 susceptibility have emerged between patients and the general population. On the contrary, protective effects have been reported for cytokine inhibitors, particularly TNF inhibitors.[21,26,57] These effects could be due to better control of the underlying disease, lower use of glucocorticoids, beneficial effects of cytokine blockade on preventing the development of hyperinflammatory states, or a combination thereof. In view of these findings, current recommendations from rheumatologists, dermatologists, and gastroenterologists unanimously recommend continuation of cytokine inhibitors during the pandemic.[98–102] Despite the fact that the continuation of cytokine inhibitors during COVID-19 infection has not been shown to lead to poorer outcomes in several reported cases, patients with evidence of SARS-CoV-2 infection, even if asymptomatic, are currently advised to suspend such drugs.[98–102]

The findings discussed in this Review seem to be consistent across high-income countries with diverse health systems and in patients with different immune-mediated inflammatory diseases (table) but little evidence is available on COVID-19 in patients in low-income countries.[103] In many of these countries, insufficient testing capacity and already strained health-care systems have resulted in barriers to access of medical care. For patients with immune-mediated inflammatory diseases, this issue adds to the challenge of receiving adequate care during the pandemic, especially in rural areas with poor infrastructure. An increase in the risk of relapse and in glucocorticoid use could come as a consequence of the pandemic in low-resource settings, which could potentially expose the patient population to worse COVID-19 outcomes by comparison with their counterparts in high-income countries.

Altogether, immune-mediated inflammatory diseases and cytokine inhibitors do not seem to affect susceptibility to and severity of COVID-19. Conversely, broad spectrum immune suppression (eg, glucocorticoids, B-cell depleting drugs) is linked to worse outcomes, suggesting that the action of modern treatments (ie, cytokine inhibitors) are confined to dampening specific immune pathways without impairing host defence. As control of inflammation is crucial to the overall health of patients with immune-mediated inflammatory diseases, the benefits of cytokine inhibitors seem to outweigh the risks, and these drugs can be and have been continued during this pandemic, although patients should still adhere to preventive

Search strategy and selection criteria

We searched PubMed, medRxiv, bioRxiv, and Google Scholar for articles published from Jan 1, 2020, to May 31, 2020, using the search terms "COVID-19", "SARS-CoV-2", "Glucocorticoids", "DMARD", "csDMARD", "bDMARD", "Biologics", and the comprehended drug classes, "tsDMARD", "Seroconversion", and "arthritis", "Rheumatoid, arthritis", "Psoriatic arthritis", "psoriasis", "Inflammatory bowel diseases" "IBD", "Crohn's disease", "Ulcerative colitis". We also searched for "Infection", "Hospitalisation", "Intensive care unit", "ICU", "Mechanical ventilation", "Morbidity", and "Mortality" risk and rates related to COVID-19 in patients receiving immunomodulatory drugs, and reviewed publications that reported data on these parameters. Finally, we searched for "Vaccine" and "Vaccination" "Response" and "Immunogenicity" related to immunomodulatory drugs. We limited our search to articles that were published in English.

measures against SARS-CoV-2 infection. Furthermore, data from patients with immune-mediated inflammatory diseases undergoing vaccination suggest that COVID-19 vaccines are effective, despite immunomodulatory treatment, except for B-cell depleting therapies, methotrexate, or TNF blockers. Individuals receiving these therapies might require testing to assess whether adequate immune responses are elicited after vaccination and whether booster vaccination is required to generate sufficient protection against SARS-CoV-2 infection in these individuals.

Contributors

FF, VS, KT, DS, MN, and MS made the literature research and analysed the data. FF, DS, and GS wrote the first draft of the manuscript. FF, DS, MN, MS, and GS edited and developed the final version. FF, DS, GS did the literature research and wrote the manuscript. GS, KT, MS, and MN revised the manuscript. FF, DS, and GS had full access to all the data and take the final responsibility to submit the manuscript for publication.

Declaration of interests

KT reports honoraria for lectures from UCB and Gilea. MS reports honoraria for lectures from Abbvie, Amgen, Celgene, Hexal, Jannsen, Leo, Lilly, Pfizer, Merck Sharpe & Dome, Mundipharma, Novartis, Sanofi, UCB; support for attending meetings from Abbvie, Celgene, Hexal, Jannsen, Leo, Lilly, Pfizer, Novartis, UCB; and participation advisory boards from Abbvie, Amgen, Celgene, Hexal, Jannsen, Leo, Lilly, Pfizer, Merck Sharpe & Dome, Mundipharma, Novartis, Sanofi, and UCB. MN reports consulting fees from Boehringer Ingelheim, IFM Therapeutics, Sterna Biologicals, Pentax; and honoraria for lectures from Abbvie, Amgen, Celgene, Falk, Janssen, Merck Sharpe & Dome, and Takeda. GS reports honoraria for lectures from Abbvie, Bristol Myers Squibb, Eli Lilly, Gilead, Janssen, Novartis, Pfizer, UCB; and consulting fees from Eli Lilly, Janssen, Novartis.

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