Safety of drugs during previous and current coronavirus pandemics: Lessons for IBD.

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Abstract

The Coronavirus 2019 (COVID-19) pandemic has posed challenges in the routine care of patients with inflammatory bowel disease. One of the key challenges needing addressing is the quantification of the risks of immunosuppressive and biologic therapies in IBD patients during the pandemic. The similarities and differences between the previous coronavirus outbreaks and the pathobiology of the infections can give useful information in understanding the risks, and perhaps potential beneficial aspects of drugs used in IBD. Although clinical, immunological and pharmacological data from the experience with the previous coronavirus outbreaks cannot be automatically translated to predict the safety of IBD therapies during COVID-19 pandemic, the signals so far from these outbreaks on IBD patients who are on immunomodulators and biologics are reassuring to patients and clinicians alike.

Introduction

The 21st century has seen the worldwide spread of three previously unrecognized coronaviruses, the severe acute respiratory syndrome coronavirus (SARS-CoV-1) and Middle East respiratory syndrome coronavirus (MERS-CoV), and more recently SARS -COV-2 (1) . Starting from 2002 in China, The SARS-CoV-1 produced, then unprecedented, nosocomial transmission resulting in nearly 9000 deaths across 29 countries (2). Exactly a decade later another coronavirus MERS-CoV emerged with 2254 laboratory positive cases with at least 800 deaths over 27 countries (3). The current pandemic SARS-CoV2 originated in Hubei province in China, and was declared a pandemic by World Health Organisation on March 11 2020 (4).

Understandable concerns have been raised on the safety of steroids, immunosuppressive drugs, and biologics used in patients for a variety of indications including immune mediated inflammatory disease such as inflammatory bowel diseases (IBD), which do increase the risk of opportunistic bacterial, viral and fungal infections (5). The magnitude of the infection-risk in general with the therapies used in IBD is small and vary based on the patient, disease, and drug characteristics (6). Equally, another aspect needing consideration if patients discontinue their IBD therapies is the potential risk of IBD flares needing hospitalization which will increase the risk of acquiring SARS-CoV-2. Several consensus guidelines recommend continuation of IBD therapies, primarily with the aim of reducing the risk of a flare needing hospitalization or surgery (7, 8, 9).

Two studies recently showed that IBD patients are not at increased risk of being infected with COVID-19 (10, 11). By contrast, there is scarce data so far on the risk of SARS-CoV-2 infection in IBD patients who are on therapies which potentially alter the immune response to pathogens (12). Therefore, continuing concerns remain both from IBD patients and the

clinicians managing them, regarding the potential of IBD related drugs causing more frequent infections by SARS-CoV2, and increased risk of severe complications from COVID-19 (13).

In this review we discuss the immune-pathological aspects of previous and ongoing coronaviruses (SARS-CoV-1, MERS-CoV and SARS-CoV-2) outbreaks and describe the pharmacological and clinical aspects relevant to the drugs used in IBD.

Genealogy and immunopathology of coronavirus – implications to drug safety

SARS-COV, MERS-COV and SARS-COV2 belong to the same beta coronavirus genus and have many similar structural characteristics. They share the single positive stranded RNA genome which has 14 open reading frames (ORFs) which encodes for four structural proteins named membrane (M), nucleocapsid (N), envelope (E) and spike (S) at the 3` terminal end of the genome, and 15 non-structural proteins encoded at the 5` terminal end (14,15) (Figure 1). The S protein is responsible for viral entry and thus plays a pivotal functional role in viral entry to the host cells, and the non-structural proteins are the key players in viral replication (16). The SARS-CoV-2 virus enters cells via the same mechanism as SARS-CoV, which is by binding of the surface spike glycoprotein (S protein) on the surface of the virus to angiotensin-converting enzyme 2 (ACE2), a receptor on the cell surface controlling the cleavage of several peptides. ACE2 is expressed in type 2 pneumocytes in the lung, blood vessels, oropharyngeal mucosa, small intestine, colon, and kidneys (17, 18) with remarkably high expression in the epithelial cells of the proximal and distal intestines, and this is also a portal for viral entry **(Figure 2)**. Single cell RNA sequencing analysis showed that ACE2 expression in colon cells was positively correlated with the regulation of viral infection and congenital cellular immunity and was negatively correlated with viral transcription, protein translation, phagocytosis, and complement activation [19]. Recently, Garg et al. have described differences in the ACE2 between inflamed and non-inflamed biopsies in patients

with IBD, but the mucosal expression or activity was not associated with the use of therapies in IBD (20). Furthermore, their study indicated that the level of circulating ACE is upregulated in patients with IBD. In addition, a more recent elegant study Maria Abreu and colleagues (21) reported that the expression of ACE2 and TMPRSS2, which are the entry portals for SARS-CoV-2, are not increased in inflamed colon and ileum of patients with IBD and some medical therapies are associated with lower levels of ACE2. Therefore, ACE2-mediated SARS-CoV-2 infection may be a double-edged sword in respect to susceptibility and immunity, and this may be relevant to the risks of viral acquisition and progressive pathology in patients with IMIDs (22).

Effective immune response of the host's innate and adaptive immune systems to the infection is essential in control of viral replication in SARS-CoV-1, MERS and SARS-CoV-2, but it can also result in exaggerated immune response including recruitment of macrophages, activation of T- lymphocytes and B lymphocytes resulting in overproduction of pro-inflammatory cytokines.(23) Pathological investigation into patients with severe SARS-CoV-1, MERS and SARS-CoV-2 reveals extensive inflammatory cell infiltration with lung and systemic inflammation [24]. This severe inflammation is shown to be due to exuberant and dysregulated cytokine response following infection with the coronaviruses resulting in increased levels of cytokines such as TNF-a, IL1, IL-6, IL-8 and IL13 (24, 25). Such an exuberant innate cytokine response is attributed to hyper-activation of macrophage/monocyte lineage cells (26). Additionally, increased levels of type I interferon (IFN) and a dysregulated interferon-stimulated gene response were observed in patients with severe SARS (27). This concept of immune-pathogenesis from coronavirus infections was first raised with the observation that the severe manifestations in SARS-COV and MERS was seen when the viral loads were decreasing simultaneously with up- regulation of cytokines and chemokines called the `cytokine storm` resulting in the clinical picture seen in acute respiratory distress

syndrome (ARDS) (28,29,30) Most patients with severe COVID-19 requiring intensive unit care and ventilation exhibit similar exaggerated immune response seen with SARS-CoV-1 and MERS-CoV with substantially elevated serum levels of pro- inflammatory cytokines including IL-6 and IL-1β, as well as IL-2, IL-8, IL-17, G- CSF, GM- CSF, IP10, MCP1, MIP1α TNF characteristic of cytokine storm (31,32,33).

Overall, it is becoming increasingly apparent. that the tug of war between coronaviruses and host antiviral defences are at the core of the pathogenic potential of all coronaviruses determining the clinical course and outcome, and this gives insights on the relative risks of drugs and also opens a window for exploring therapeutic options (34) **(Figure 3)**

Immunosuppressive drugs and severity of coronavirus infections: opportunity in the face of adversity?

The impact of drugs, in particular, steroids, immunosuppressive and biologics were brought in to sharp focus during the three coronavirus pandemics despite the wide variation in the severity of the outbreaks and the mortality rates. These drugs remain the cornerstones of therapies in IBD and have revolutionised IBD care. The lack of prospective data specific to the SARS-CoV-2 infection to date means that our understanding of the genealogy and immunopathology need to be integrated to the pharmacological aspects of these drugs to shed some light into this challenging conundrum.

Corticosteroids and coronaviruses

Corticosteroids are thought to have a divergent effect on viral infections including SARS COV viruses; on one hand they inhibit host immune response acting on migration and chemokines production leading to impaired viral clearance and the resultant prolonged viremia (35), while on the other hand reducing the expression of pro-inflammatory cytokines such as IL-1, IL-2, IL-6, TNF- α and IFN- γ and inhibiting leukocyte migration (36) and thereby supressing the exuberant systemic inflammatory response which account for the lung pathology including ARDS. Because of the overlapping genetic, immunopathologic and clinical features of SARS-CoV-1, MERS-CoV and SARS-CoV-2 infections, it is reasonable to assess the impact of corticosteroids on these viruses together.

Most of the data on the use of corticosteroids come from observational databases during SARS-CoV-1 (37,38,39,40,41) , MERS-CoV (42,43) and the published data so far on SARS-CoV-2 (44,45,46,47). Hence, it is challenging to come to a firm conclusion on their benefit

and risk as they have inherent selection bias, as corticosteroids are likely to be given to patients with severe disease, heterogeneity on the type, dose and duration of the use of steroids and the confounding aspect that some of these patients may have received multiple other adjunctive treatments.

Systemic corticosteroids have long been used among critically ill patients presenting with ARDS well before the first SARS COV-1 outbreak (48). A meta-analysis of individual patient level data from four RCTs evaluating prolonged methylprednisolone therapy for ARDS reported a significant reduction in mortality and an increase in ventilator-free days (49). Low to moderate doses of corticosteroids were used in patients with ARDS complicating H1NI, and were reported to reduce both 30 and 60 day mortality (50). Hydrocortisone, when given to patients with bacterial pneumonia in intensive care units, showed some benefit in mortality (51). In a recent study, administration of methylprednisolone reduced the risk of death (hazard ratio, 0.38; 95% CI, 0.20–0.72; P = 0.003) in subjects having ARDS from SARS-CoV-2 (48). In vitro studies have previously shown reduction in post viral inflammatory cytokine production, although this has not been replicated in influenza (52).

A number of recent meta-analyses (53, 54, 55, 56, 57, 58, 59, 60) have assessed the impact of corticosteroids in viral infections, and more specifically, on their use during the three major coronavirus outbreaks, including the most recent pandemic. An early systematic review of studies on patients with SARS-CoV-1, including 29 studies documenting glucocorticoid use, found 25 studies that were inconclusive, and four studies that suggested possible harm (53). Moreover, a prospective, randomized double-blinded, placebo-controlled trial compared early hydrocortisone treatment (before day seven of the illness) with a placebo and found that early hydrocortisone therapy was associated with a higher subsequent plasma viral load (61). In the setting of MERS-CoV, use of corticosteroids for critically ill patients did not improve the 90

day mortality and was associated with delayed MERS-CoV RNA clearance (62), a data replicated more recently for SARS-CoV-2 (63). In a recent systematic review of 4 studies including 542 Chinese patients with SARS-CoV-2 treated with systemic steroids was inconclusive; with 2 studies showing deleterious effect, one showing no benefit and another showing significant reduction in mortality (56). A further meta-analysis, combing all the studies of steroid use during the three outbreaks, included 11 studies (10 cohort and one randomised controlled trial) involving 5249 patients showed no corticosteroid use in subjects with SARS-CoV-2, SARS-CoV-1, and MERS-CoV infections did not convincingly improve survival, reduce hospitalization duration nor ICU admission rate and/or use of mechanical ventilation (55). Corticosteroid use was associated with delayed virus clearing with a mean difference of 3.78 days (55).

Corticosteroids also impair the induction of anti-viral type-I interferon responses to a range of respiratory viruses (64). Early corticosteroid use did not benefit critically ill patients with ARDS but was independently associated with higher mortality in the setting of severe influenza pneumonia (65). Overall, the current data does not support the use of corticosteroids in the coronavirus infections (59) and randomised controlled trials are needed before routine use.

There is data suggesting that doses above 20 mg of prednisolone are associated with increased risk of bacterial and viral infections in IBD and even with increased hospitalization suggesting a lower dosing strategy (66,6760). In a recent Italian series of IBD patients with COVID-19, a trend towards adverse outcome with concomitant corticosteroids was reported (68). In a more recent series from New York, the use of steroids appears to predict COVID-19 (OR 1.38, 95% CI 1.07-1.77) (69). Locally acting steroids such as budesonide and beclomethasone theoretically have some advantages in relation to side effect profile (70, 71), but no data is available in the setting of coronaviruses. Hence overall, while there is no data

on whether current use of steroids increases the risk of severe COVID-19, it seems prudent to minimise the use of systemic steroids, think of alternatives to steroids, and if used, taper to the lowest possible dose quickly.

Immunomodulators and coronaviruses

Broad immunosuppression has the potential to increase susceptibility, persistence, and reactivation of viral infections in patients (72). Acute respiratory viruses implicated in causing severe disease in immunocompromised patients include respiratory syncytial virus (RSV), influenza viruses A and B, parainfluenza viruses and adenovirus, and immunocompromised patients are generally considered at increased risk of influenza and at higher risk of complicated infection (73,74). There is also risk of opportunistic viral infection with thiopurines, but these are mainly DNA viruses such as Hepatitis B and C, Epstein Barr Virus and Human Papilloma Virus. (74)

Partial assessment regarding whether immunosuppression is a relevant risk factor for COVID-19 infection and severe course can be guided by the findings of SARS-CoV-1 and MERS-CoV outbreaks (75). On review of large published cohorts of SARS-CoV1 and MERS-CoV infections (76, 77, 78, 79, 80) , the risk factors for both infections included advanced age and presence of one or more co-morbidities such as diabetes, heart disease ,hypertension, lung disease and obesity. Although there were no specific studies on immunosuppressed individuals including IBD, no fatality was reported in patients undergoing chemotherapy or other immunosuppressive treatments, at any age (76, 78, 79). Although transplant patients were expected to have poorer outcomes following acquisition of SARS CoV1, at the end of the outbreak no mortality or graft loss had been recorded (75, 77, 79)

Atypical presentation of MERS-CoV was reported from Korea in 3 patients on immunosuppressants, all of whom made full recovery without the need for invasive ventilation (81). In another series of 45 patients with serious MERS-CoV infection, there was a single patient who was on prolonged immunosuppression who also made an uneventful recovery (78). In a hospital outbreak of MERS-CoV in Jordan, immunosuppressive individuals did not have additional risks (77). In an analysis of 1253 cases from the epicentre of MERS in Saudi Arabia from 2012- 2015, immunosuppressant use was not associated with increased risk for MERS-CoV infection (80). In another study, with a cohort of 114 patients, one of the patients was on immunosuppressants for double transplant (kidney and liver) and, while requiring intensive unit care, did not die (76). In a retrospective cohort study of host susceptibility in South Korean MERS outbreak, 3 patients of solid organ transplantation were included but none developed MERS-CoV infection, but 2 out of the 3 patients with autologous cell transplantation did, without any mortality (79). In an animal model of MERS-CoV using immunosuppressed rhesus macaques, despite increased viral replication, pathology in the lungs was significantly lower in immunosuppressed animals (82).

Available early data from the current SARS-CoV-2 pandemic is also showing similar results. Guan et al included 399 patients with at least one co-morbidity, including three patients with immunodeficiency, in their retrospective analysis of 1590 patients, and reported no increase in the probability to reach the composite end point of admission to ICU, ventilation and death in those with immunodeficiency (83). In an Italian study from Bergamo (84), which was the epicentre of the outbreak in Italy, no cases of clinical pulmonary disease were recorded among immunosuppressed transplant recipients (n=200) and those who were on immunosuppression for autoimmune liver disease (n=100) and recorded positive RT-PCR for SAS-CoV-2 in only 3 patients although asymptomatic carriage in this Pediatric population was possibleAs reported with SARS-CoV-1, atypical presentation with predominantly

gastrointestinal symptoms in a renal transplant patient who also had splenectomy and was on immunosupressants has been reported (85) . The IG-IBD study included 6 patients on thiopurines, 3 of whom developed COVID-19 pneumonia (68). Taxonera et al (11), in their cohort of 1918 patients (21% on immunosuppressant alone and 8% on combo therapy with biologics), reported the incidence figures of COVID-19 similar to the general population. Five of their 12 patients with positive nasopharyngeal swab were on thiopurines or methotrexate and none required ventilation. Another Spanish study included 40 patients, among whom 11(28%) were on immunomosupressants which were stopped at hospitalization, and reported no requirement for intensive care treatment or mortality among those on immunosupressants (86).

Intriguingly some immunosuppressive agents used in treatment, including in IBD, have been found to interfere with viral replication (87). Although the doses used were much higher in comparison to that in treatment of immune disorders such as IBD, thiopurines, when used for haematological malignancies, appeared to be specific inhibitors of SARS CoV-1 virus (88). Furthermore, in the setting of both SARS-CoV-1 and MERS-CoV infection, mercaptopurine and 6-thioguanine was found to selectively inhibit viral replication by targeting papain-like protease and targeting several proteins involved in viral maturation (89, 90). There is increasing amount of literature suggesting the role of calcineurin inhibitors (cyclosporine, tacrolimus) as a potent antiviral in the treatment of human coronaviruses (105-109). Both Cys and TAC inhibit viral replication in a number of strains of CoV, including SARS-CoV, through the inhibition of peptidyl-prolyl cis trans-isomerases, such as cyclophilin A and FK506-binding proteins, that are cellular interaction partners of SARS CoV non-structural protein 1 (91, 92, 93, 94). In a monocentric cross-sectional study of 384 patients, 46 of whom ((12%) were on calcineurin inhibitors alone, the immunosuppression with calcineurin inhibitors did not increase the risk of hospitalisation or mortality (95). Cyclosporine was

successfully used in a pregnant patient with acute severe ulcerative colitis with COVID-19

(96). These promising signals, and the underlying pharmacological basis, have prompted

some to suggest consideration of calcineurin inhibitors for treatment of coronavirus infections

(97, 98). In a study of rheumatoid arthritis patients on methotrexate with resolved HBV

infection, the incidence of HBV reactivation was very low at 1.93/100 person-years (99).

The patients on concomitant methotrexate in IBD so far has not reported any additional risks

from SARS-CoV-2 (11, 68, 86)

Overall, immunosuppressive therapy does neither seem to have a major impact on infection

with SARS CoV-1, MERS-CoV and SARS-CoV-2 nor does it seem to lead to a severe

disease course in many cases. However, it must be kept in mind that reported case numbers

are exceedingly small overall and continued vigilance is needed.

Biologic agents, small molecules, and coronaviruses

Bacterial, fungal, and viral infections have been reported with use of all classes of biologics

to a varying degree. In general, the reported rates of viral infection and serious viral infection

are relatively low in the various licencing trials of biologic agents and small molecules

(**Table 1**). The majority of the biologics and small molecules had not been in routine use

during the earlier outbreaks, particularly during MERS-CoV, and the epicentres of those

SARS-CoV1 and MERS-CoV did not have high usage of these agents during the outbreaks.

Therefore there is limited, if any, clinical data on the impact of biologics and small molecules

in any of the coronavirus infections, hence the approach based on the characteristic of the

particular agent in conjunction with the immuno-pathological features of SARS-CoV-2

infection may need guide risk stratification **(Figure 3).**

Anti TNFs and coronaviruses

Marked elevations of TNF alpha is found in patients with SARS-CoV-1, MERS-CoV and SARS-CoV-2. (23, 25, 26). Anti TNFs may increase the risk of reactivation of opportunistic DNA viruses such as hepatitis B, CMV, EBV, Herpes simplex and HPV (73, 7 4). Furthermore, anti TNF treatment may diminish the degree of protective immunity resulting from vaccination, but levels achieved appear adequate with other viruses (100).

Paradoxically, it is plausible that the use of biologics may have a beneficial effect in reducing the inflammatory immune responses following COVID-19 by reduction of cytokines, including TNF. TNFα has been implicated in the severe immune-based pulmonary injury caused by SARS-CoV-, suggesting that TNFα inhibitors could be a potential treatment for the acute respiratory disease syndrome caused by coronavirus (101). Coronavirus viral spike protein is able to induce a TNF-α-converting enzyme (TACE)-dependent shedding of the ACE2 ectodomain, and this process, which appears to be strictly coupled to TNFα, is essential for the penetration of the virus into the cell. This means TNF inhibitors might be effective in blocking viral entry and the detrimental effects of exuberant TNF-α (102). Anti TNF agents, as an option for therapeutic modulation, were proposed during the SARS-CoV-1 outbreak although no human studies were performed (103). Following this, in a study on 22 piglets to assess the efficacy of an anti-TNFα) therapy for endotoxin respiratory diseases, the investigators observed that TNFα blockade was not associated with decrease in disease severity(104) Subsequently, anti TNF for therapy of viral infections caused by respiratory syncytial virus or influenza virus was studied again in animal models and showed that TNF depletion reduced pulmonary recruitment of inflammatory cells, cytokine production by T cells resulting in amelioration of the severity of virus-specific lung immunopathology without preventing virus clearance. (105). Hence it has been postulated that the use of TNFα

inhibitors may be effective in reducing both SARS-CoV-2 infection rates and the consequent organ damage, and early clinical trials of Anti TNF agents in COVID-19 are awaited (106).

However, it is important to recognise that it is equally plausible that theoretical possibility of increased viral burden resulting from inability of immune response may result in increases severity of inflammation (107). Hence some concerns have been raised by some authors in relation to broad immunosuppression in the presence of an overwhelming infective illness (108). Nevertheless, there is no evidence indicating that TNFα blockade is harmful to patients in the context of severe infections including septic shock (109). A randomised controlled trial of anti TNF agents with septic shock in intensive care units showed no evidence of increased infections in the anti TNF treated patients (110).

No patients on anti TNF agents have been recorded in any of the series reported during the SARS-CoV-1 or MERS outbreaks, but there is an increasing amount of literature suggesting that TNFα blockade is not harmful to patients in the context of COVID-19 (111,112,113). These opinions are supported by the case series of patients on anti TNFs for immune mediated inflammatory disorders such as arthritis and inflammatory bowel diseases (10,11, 68, 86,114). In a report of 320 rheumatology patients on disease modifying drugs, half of whom were on anti-TNF agents at the height of the pandemic in northern Italy, Monti et al (114) reported only 2 cases of swab positive COVID-19 on anti TNF agents. In the Nancy-Milan cohort of 14 swab positive IBD patients (10), 8 of whom were on anti TNF (2 in combination with immunomodulators), but none required intensive care stay and there was no mortality. Two of the 12 patients in the report from Taxonera et al (11) were on anti TNF agents (1 combo therapy) and neither required intensive care treatment. Eleven of the 50 patients (28%) in another Spanish study (86) had positive swab test for COVID-19, but only four needed hospitalizations with COVID-19 pneumonia. One patient with COVID-19 and acute severe colitis was treated with infliximab with successful outcome. TNF inhibitor use

was not associated with swab positive or suspected cases of COVID-19 in a recent series of 86 patients with IMIDs of whom 3 needed hospitalization (69). The latest review (accessed on 15th May 2020) of the SECURE-IBD registry (115) with 314 patients on anti TNF monotherapy shows a 19% hospitalisation rate (2% in ICU) with mortality rate of 1%. However, the hospitalisation rates, intensive care treatment and mortality appears to be higher in the 106 patients who are on combination therapy with anti TNF and immunomodulators (36%, 5% and 3% respectively), and therefore further data is required.

Anti-integrins and coronaviruses

Vedolizumab selectively inhibits the interaction of α4β7 with mucosal adhesion molecule -1 preventing the entry of T lymphocytes across the endothelium to the inflamed gastrointestinal mucosa (116). The receptors are present in GI tract, nasopharyngeal mucosa, and biliary epithelium. The gut-selective mode of action of vedolizumab should theoretically be associated with a lower risk of infections. No increase in viral infections including nasopharyngitis was noted in vedolizumab treated patients in a meta-analysis (117). Higher, but statistically insignificant, rates of enteric infections occurred in vedolizumab-exposed patients (7.4/100 PYs; 95% CI: 6.6-8.3) to placebo (6.7 PYs; 95% CI: 3.2-10.1) in this meta-analysis (117). No reactivation of hepatitis B or C was noted in 29 patients with history of Hepatitis B or C in a post marketing surveillance study of the licencing trials (118). In SIV-infected animals, combination of anti-retroviral therapy and vedolizumab resulted in sustained virologic response (119), and further Phase 1 studies in HIV patients did not show any increase in viral replication (120).

Vedolizumab was not available for clinical use during SARS-CoV1 or at the outset of MERS-CoV outbreaks and no reports of patients on vedolizumab with these infections are reported in literature. The Nancy-Milan cohort, the series from Taxonera et al and Rodríguez-Lago et al, had one ulcerative colitis patient each on vedolizumab with COVDI-19 and none of these patients required hospitalisation (10,11,86). The IG-IBD study included 15 patients on vedolizumab, five of whom needed admission but reported no association with risk for COVID-19 pneumonia (68). The SECURE IBD registry (Accessed on 15th May 2020) has included data from 107 patients on vedolizumab with a 29% hospitalisation rate; (6% in ICU) and 4% mortality (115).

JAK Inhibitors and coronaviruses

Therapies targeting JAKs may interfere with normal anti-viral response including inhibition of IFN-γ activity (121), and may potentially increase the risk of infection and/or reactivation of several viral infectious diseases including a dose dependent risk for VZV observed for Tofacitinib (122). In some studies the use of higher dose of Tofacitinib along with corticosteroids was associated with serious infections (123).

JAK inhibitors also have anti-viral potential since they lower the pro-inflammatory response mediated by viruses and block many pro-inflammatory cytokines involved in cytokine storm such as IL1-, IL6, IL-8 and TNF (1124). Of relevance would be the IL-6 or IL6_R blockade with JAKs or specific anti IL-6R antibody Tocilizumab (125). Baricitinib, currently not used in IBD but approved for rheumatoid arthritis, blocks viral endocytosis and assembly of virus particles into pneumocytes, and has shown promising results in clinical trials in SARS-CoV-2 (126,127). This potential beneficial effect is not seen with Tofacitinib. Fedratinib, a selective

JAK2 inhibitor which inhibits TH17 mediated immune hyperstimulation, is also proposed for treatment of severe COVID-19 infection (128).

The New York series on IMIDs had 4 patients on Tofacitinib, one among them needing hospitalisation but not ventilation (86). Two patients on Tofacitinib with COVID-19 have been reported in rheumatology literature, both without severe outcomes (114). In a case report from Washington (129), a young patient on Tofacitinib continued the treatment uninterrupted following diagnosis of COVID-19 and had complete recovery without the need for hospitalisation. Seventeen patients on vedolizumab have been reported so far to the SECURE IBD registry (115), five of whom needed hospitalisation, with one mortality (Accessed on 15th May 2020).

IL12, IL-23 antagonists and coronaviruses

Hypothetically, blocking IL12 and IL23 which are involved in cytokine storm may have a beneficial effect in ameliorating the cytokine storm in COVID-19 (130,131). Ustekinumab blocks IL-12 and IL-23 is used in management of both IBD and psoriatic arthritis. There is no data on this agent in relation to any of the coronavirus infections including COVID- 19. Reassuringly, studies so far have not reported to be associated with increase in viral infections (132,133,134). Whether there is an effect on the coronavirus infection outcome with IL12.IL-23 blockade is currently uncertain. In the NANCY-Milan cohort, 2 patients were on ustekinumab, and in both COVID-19 infection resolved without complications (10). One patient was on ustekinumab along with mercaptopurine in the Taxonera et al series (11) with no severe complications. None of the 4 patients on ustekinumab in the Rodríguez-Lago et al (86) study had complications from COVID-19 infection. Both patients on ustekineumab in the New York IMID series (69) with COVID-19 recovered without hospitalisation. In the

102 patients so far included (Accessed on 15th May 2020) in the SECURE IBD registry (115) on ustekinumab, 13(13%) required hospitalisation, with one mortality.

Conclusions:

Currently there is no data to indicate that therapies used in IBD will result in more severe outcomes in patients. Whether drug-induced immunosuppression will prevent the cytokine storm in patients infected with COVID-19 will require further investigation. Until we have more data, a risk versus benefit grid based approach (Table 2) may be useful. Data from prospective observational studies, coupled with increased understanding of the interaction between viral immunopathology and immunosuppressive and biologic drugs, will aid in accurate risk stratification for IBD patients. In the interim, IBD patients should continue their therapies as recommended by their physicians and adopt all the necessary public health measures, as recommended, to combat the spread of this deadly virus.

References:

1. Petrosillo N, Viceconte G, Ergonul O et al. COVID-19, SARS and MERS: are they closely related? Clin Microbiol Infect. 2020 Mar 28. pii: S1198-743X(20)30171-3. doi: 10.1016/j.cmi.2020.03.026

2. World Health Organization. WHO Guidelines for the Global Surveillance of Severe Acute Respiratory Syndrome (SARS). Updated Recommendations. October 2004. Available online: http://www.who.int/mediacentre/factsheets/mers-cov/en/ (accessed on 8 October 2018).

3. Salamatbakhsh M, Mobaraki K,Sadeghimohammadi S, et al. The global burden of premature mortality due to the Middle East respiratory syndrome (MERS) using standard expected years of life lost, 2012 to 2019. BMC Public Health (2019) 19:1523.https://doi.org/10.1186/s12889-019-7899-2

4. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports

5. Singh S, Facciorusso A2, Dulai PS, et al. Comparative Risk of Serious Infections with Biologic and/or Immunosuppressive Therapy in Patients with Inflammatory Bowel Diseases: A Systematic Review and Meta-Analysis. Clin Gastroenterol Hepatol. 2020 ;18(1):69-81.e3. doi: 10.1016/j.cgh.2019.02.044. Epub 2019 Mar 12

6. Rahier JF, Magro F, Abreu C, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohns Colitis. 2014; 8(6):443-68. doi: 10.1016/j.crohns.2013.12.013.

7. Rubin DT, Abreu MT, Rai V, Siegel CA, on behalf of the International Organization for the Study of Inflammatory Bowel Disease, Management of Patients with   Crohn's Disease and

Ulcerative Colitis during the COVID-19 Pandemic: Results of an International Meeting, Gastroenterology (2020), doi: https://doi.org/10.1053/j.gastro.2020.04.002.

8. Kennedy NA, Jones GR, Lamb CA et al. British Society of Gastroenterology guidance for management of inflammatory bowel disease during the COVID-19 pandemic Gut 2020;0:1–7. doi:10.1136/gutjnl-2020-321244

9. Rubin, D., Feuerstein, J., Wang, A., & Cohen, RAGA Clinical Practice Update on Management of Inflammatory Bowel Disease During the COVID-19 Pandemic: Expert Commentary. Gastroenterology.2020, 4:10-14

10. Allocca M, Fiorino G, Zallot C, et al. Incidence and patterns of COVID-19 among inflammatory bowel disease patients from the Nancy and Milan cohorts. Clin Gastroenterol Hepatol. 2020 Apr 30. pii: S1542-3565(20)30616-9. doi: 10.1016/j.cgh.2020.04.071. [Epub ahead of print] No abstract available

11. Taxonera C , Sagastagoitia I, Alaba C, et al. 2019 novel corona virus disease (COVID-19) in patients with inflmaamatory owel disease . Aliment Pharmacol ther 2020 doi:10.1111/apt.1504.

12. Higgins PDR, Ng S, Danese S, Rao K. The Risk of SARS-CoV-2 in Immunosuppressed IBD Patients. Crohn's & Colitis 360 2020; 2 (2),1-4.

13. D`Amico F, Danese S, Peyrin-Biroulet L, on behalf of the ECCO-COVID task force. Inflammatory bowel disease management during the COVID-19 outbreak: a survey from the European Colitis and Crohns Organization (ECCO) . Gastroenterology 2020. Doi:10.53/j.gastro.2020.04.059.

14. Chen Y, Liu Q, Guo D. Emerging coronaviruses: genome structure, replication, and pathogenesis. J Med Virol 2020; 92: 418e23. https://doi.org/10.1002/jmv.25681. jmv.25681.

15. Kumar S, Maurya VK, Prasad AK, Bhatt MLB, Saxena SK. Structural, glycosylation and antigenic variation between 2019 novel coronavirus (2019-nCoV) and SARS coronavirus(SARS-CoV). Virus Disease 2020; 31 (1): 13-21. doi: 10.1007/s13337-020-00571-5.

16. Ou X, Liu Y, Lei X, Li P, Mi D et al. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nature Communications 2020; 11 (1): 1620. doi: 10.1038/s41467-020-15562-9

17. Hamming I., Timens W., Bulthuis MLC Lely AT, Navis G.J., van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631–637

18. Zou X., Chen K., Zou J.W., Han P.Y., Hao J., Han Z.G. The single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to Wuhan 2019-nCoV infection. Fronts of Medicine. 2020.

19. Wang J, Zhao S, Liu M, et al. ACE2 expression by colonic epithelial cells is associated with viral infection, immunity and energy metabolism. medRxiv preprint doi: https://doi.org/10.1101/2020.02.05.20020545.

20. Garg M, Royce SG, Tikellis C, et al. Imbalance of the renin-angiotensin system may contribute to inflammation and fibrosis in IBD: a novel therapeutic target? Gut 2020;69:841–51.

21. Burgueño JF, Reich A ,Hazime H,et al Expression of SARS-CoV-2 Entry Molecules ACE2 and TMPRSS2 in the Gut of Patients With IBD. Inflamm Bowel Dis. 2020 Apr 25 doi: 10.1093/ibd/izaa085

22. Garg M, Christensen B, Lubel JS. Letter: Gastrointestinal ACE2, COVID-19 and IBD - opportunity in the face of tragedy? Gastroenterlogy 2020. doi:10.1053/j.gastro.2020.04.051.

23. Li G, Fan Y, Lai Y, Han T, Li Z et al. Coronavirus infections and immune responses. Journal of Medical Virology 2020; 92 (4):424-432.

24. Kong SL, Chui P, Lim B, et al. Elucidating the molecular physiopathology of acute respiratory distress syndrome in severe acute respiratory syndrome patients. Virus Res. 2009; 145:260–9.

25. Wong CK, Lam CW, Wu AK, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome Clin Exp Immunol. 2004; 136:95–103

26. Perlman S, Dandekar AA. Immunopathogenesis of coronavirus infections: implications for SARS. Nat Rev Immunol. 2005 Dec;5(12):917-27.

27. Baas T, Taubenberger JK, Chong PY, Chui P, Katze MG. SARS-CoV virus-host interactions and comparative etiologies of acute respiratory distress syndrome as determined by transcriptional and cytokine profiling of formalin-fixed paraffin embedded tissues. J Interferon Cytokine Res. 2006; 26:309–17.

28. Peiris, J. S. et al. Clinical progression and viral loading in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet 361, 1767–1772 (2003).

29. Faure, E. et al. Distinct immune response in two MERS-CoV-infected patients: can we go from bench to bedside? PLoS ONE 9, e88716 (2014).

30. Kong, S. L., Chui, P., Lim, B. & Salto-Tellez, M. Elucidating the molecular physiopathology of acute respiratory distress syndrome in severe acute respiratory syndrome patients. Virus Res. 145, 260–269 (2009).

31. Shi, Tan M, Chen X ,et al. Immunopathological characteristics of coronavirus disease 2019 cases in Guangzhou, China. medRxiv https://doi.org/10.1101/2020.03.12.20034736.

32. Qin C, Zhou L, Hu Z, Zhang S, Yang S et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clinical Infectious Diseases: an official publication of the Infectious Diseases Society of America 2020. doi: 10.1093/ cid/ciaa248.

33. Qin, C. Zhou L, Hu Zet al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin. Infect. Dis. https://doi.org/10.1093/cid/ciaa248 (2020).

34. Mehta P, McAuley, D, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet, 395(10229), 1033-1034.

35. . C. Tullar, F. Issa, Immune regulation by glucocorticoids can be linked to cell type dependent transcriptional responses, Transplantation 103 (2019) 651.

36. Schäcke H, Schottelius A, Döcke WD, et al Dissociation of transactivation from transrepression by a selective glucocorticoidreceptor agonist leads to separation of therapeutic effects from side effects, Proc.Natl. Acad. Sci. U.S.A. 101 (2004) 227–232.

37. Wang G, Li N, Wu Y, et al. The Cox regression analysis on the use of corticosteroids in the treatment of SARS. Natl Med J China. 2004;84: 1073–78.

38. Chen RC, Tang XP, Tan SY, et al. Treatment of severe acute respiratory syndrome with glucosteroids: the Guangzhou experience. Chest. 2006;129:1441–52.

39. Yam LY, Lau AC, Lai FY, et al. Corticosteroid treatment of severe acute respiratory syndrome in Hong Kong. J Infect. 2007; 54:28–39.

40. Lee N, Allen Chan KC, et al. Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients. J Clin Virol. (2004) 31:304– 9. doi: 10.1016/j.jcv.2004.07.006.

41. Auyeung TW , Lee JSW , Lai WK , et al. The use of corticosteroid as treatment in SARS was associated with adverse outcomes: a retrospective cohort study. J Infect 2005; 51 (2):98–102 PubMed PMID: 16038758.

42. Arabi YM, Mandourah Y, Al-Hameed F,et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. Am J Respir Crit Care Med. (2018) 197:757–67. doi: 10.1164/rccm.201706-1172OC.

43. Alfaraj SH , Al-Tawfiq JA , Assiri AY , et al. Clinical predictors of mortality of middle east respiratory syndrome coronavirus (mers-cov) infection: a cohort study. Travel Med Infect Dis May-Jun 2019; 29 :48–50 PubMed PMID: 30872071. Epub 2019/03/11.

44. Huang C , Wang Y , Li X , et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England) 2020 ; 395 (10223):497–506 PubMed PMID: 31986264. Epub 2020/01/28.

45. Wang D, Hu B, Hu C, et al. Clinical characteristics of138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020:e201585 PubMed PMID: 32031570.

46. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med.2020. doi: 10.1001/jamainternmed.2020.0994

47. Liu K, Fang YY, Deng Y, LiuW,WangMF,Ma JP, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin Med J. (2020). doi: 10.1097/CM9.0000000000000744

48. Meduri GU, Tolley EA, Chrousos GP, et al. Prolonged methylprednisolone treatment suppresses systemic inflammation in patients with unresolving acute respiratory distress syndrome: evidence for inadequate endogenous glucocorticoid secretion and inflammation-induced immune cell resistance to glucocorticoids. Am J Respir Crit Care Med. 2002; 165:983–91. doi: 10.1164/ajrccm.165.7.2106014.

49. Meduri GU, Bridges L, Shih MC, et al. Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: analysis of individual patients' data from four randomized trials and trial-level meta-analysis of the updated literature. Intensive Care Med 2016; 42:829–40. doi: 10.1007/s00134-015-4095-4.

50. Li H, Yang SG , Gu L, et al,. Effect of low-to moderate-dose corticosteroids on mortality of hospitalized adolescents and adults with influenza A(H1N1) pdm09 viral pneumonia, Influenza Other. Resp. Viruses 11 (2017) 345–354.

51. Confalonieri, R. Urbino, A. Potena, et al., Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study, Am. J. Respir. Crit. Care Med. 171 (2005) 242–248.

52. T. Homma, Y. Fukuda, Y. Uchida, T. Uno, M. Jinno, Y. Kishino, et al., Inhibition of virus-induced cytokine production from airway epithelial cells by the late addition of budesonide, Medicina (Kaunas) 56 (2020).

53. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med. (2006) 3:e343. doi: 10.1371/journal.pmed.0030343.

54. Yang Z, Liu J ,Zhou Yet al., The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis, Journal of Infection, https://doi.org/10.1016/j.jinf.2020.03.062.

55. Li H1, Chen C, Hu F, et al. Impact of corticosteroid therapy on outcomes of persons with SARS-CoV-2, SARS-CoV, or MERS-CoV infection: a systematic review and meta-analysis. Leukemia https://doi.org/10.1038/s41375-020-0848-3.

56. Veronese N, Demurtas J, Yang L,et al. Use of Corticosteroids in Coronavirus Disease 2019 Pneumonia: A Systematic Review of the Literature. Front. Med. 7:170. doi: 10.3389/fmed.2020.00170.

57. Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. Cochrane Database Syst Rev. 2016;3:Cd010406.

58. Ni YN, Chen G, Sun J, Liang BM, Liang ZA. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. Crit Care. 2019; 23(1):99.

59. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020; 395 (10223): 473-475. doi: 10.1016/s0140-6736(20)30317-2.

60. Sun S, Liu D, Zhang H, Zhang X, Wan B. Effect of different doses and time-courses of corticosteroid treatment in patients with acute respiratory distress syndrome: a meta-analysis. Exp Ther Med. 2019;18:4637–44.

61. Lee N, Allen Chan KC, Hui DS, Ng EK, Wu A, Chiu RW, et al. Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients. J Clin Virol. (2004) 31:304– 9. doi: 10.1016/j.jcv.2004.07.006.

62. Hui DS. Systemic corticosteroid therapy may delay viral clearance in patients with middle east respiratory syndrome coronavirus infection. Am J Resp Crit Care Med 2018;197(6):700-701.

63. Ling Y, Xu SB, Lin YX, Tian D, Zhu ZQ, Dai FH, et al. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. Chin Med J. (2020). doi: 10.1097/CM9.0000000000000774

64. Brun-Buisson C, Richard JM , Mercat A , et al. Early Corticosteroids in Severe Influenza A/H1N1 Pneumonia and Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 2011; 183; 1200–1206.

65. Singanayagam A, Glanville N, Girkin JL, et al. Corticosteroid suppression of antiviral immunity increases bacterial loads and mucus production in COPD exacerbations. Nat Commun 2018; 9: 2229.

66. Dorrington AM, Selinger CP, Parkes GC, Smith M, Pollok RC, Raine T. The historical role and contemporary use of corticosteroids in inflammatory bowel disease. J Crohns Colitis. 2020 Mar 14. pii: jjaa053. doi: 10.1093/ecco-jcc/jjaa053

67. Tinsley A, Navabi S, Williams ED, et al. Increased Risk of Influenza and Influenza-Related Complications Among 140,480 Patients With Inflammatory Bowel Disease. Inflamm Bowel Dis. 2019; 25(2):369-376.

68. Bezzio C, Saibeni S, Variola A, et al. Inflammatory bowel disease Outcomes of COVID-19 in 79 patients with IBD in Italy: an IG-IBD study. Gut 2020; 0: 1–5.

69. Haberman R, Axelrad J, Chen A, et al. Covid-19 in Immune-Mediated Inflammatory Diseases — Case Series from New York. N Engl J Med 2020; : NEJMc2009567.

70. Bonovas S, Nikolopoulos GK, Lytras T,et al. Comparative safety of systemic and low-bioavailability steroids in inflammatory bowel disease: Systematic review and network meta-analysis. Br J Clin Pharmacol. 2018;84(2):239-251.

71. Manguso F, Bennato R, Lombardi G, et al. Efficacy and Safety of Oral Beclomethasone Dipropionate in Ulcerative Colitis: A Systematic Review and Meta-Analysis. PLoS One. 2016; 11(11):e0166455.

72. Memoli MJ, Athota R, Reed S, et al. The natural history of influenza infection in the severely immunocompromised vs non-immunocompromised hosts. Clin Infect Dis 2014; 58:214–24.

73. Wisniewski A, Kirchgesner J, Seksik P, et al. Increased incidence of systemic serious viral infections in patients with inflammatory bowel disease associates with active disease and use of thiopurines. United Eur Gastroenterol J 2019. DOI:10. 1177/2050640619889763.

74. Kirchgesner J, Lemaitre M, Carrat F, et al. Risk of Serious and Opportunistic Infections Associated with Treatment of Inflammatory Bowel Diseases. Gastroenterology 2018; 155: 337-346.e10.

75. D'Antiga L. Coronaviruses and immunosuppressed patients. The facts during the third epidemic. Liver Transpl. (2020). doi: 10.1002/lt.25756. [Epub ahead of print].

76. Arabi YM, Arifi AA, Balkhy HH, et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. Ann Internal Med. (2014) 160:389–97. doi: 10.7326/M13-2486

77. Al-Abdallat MM, Payne DC, Alqasrawi S, et al. Hospital-associated outbreak of Middle East respiratory syndrome coronavirus: a serologic, epidemiologic, and clinical description. Clin Infect Dis. (2014) 59:1225–33. doi: 10.1093/cid/ciu359

78. Assiri A, Al-Tawfiq JA, Al-Rabeeah AA,et al. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. Lancet Infect Dis. (2013) 13:752–61. doi: 10.1016/S1473-3099(13)70204-4.

79. Ko JH,Seok H, Park GE et al. /Host susceptibility to MERS-CoV infection, a retrospective cohort study of the 2015 Korean MERS outbreak. J Infect Chemother 24 (2018) 150e152.

80. Aleanizy FS, Mohmed N, Alqahtani FY , et al Outbreak of Middle East respiratory syndrome coronavirus in Saudi Arabia: a retrospective study. FYBMC Infect Dis. 2017;17(1):23. doi: 10.1186/s12879-016-2137-3.

81. Kim SH, Ko JH, Park GE, et al Atypical presentations of MERS-CoV infection in immunocompromised hosts. J Infect Chemother 2017 ; 23 (2017) 769e773. http://dx.doi.org/10.1016/j.jiac.2017.04.004.

82. Prescott J, Falzarano D, de Wit E, et al. Pathogenicity and Viral Shedding of MERS-CoV in Immunocompromised Rhesus Macaques.Front. Immunol.2018 9:205.doi: 10.3389/fimmu.2018.00205.

83. Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med [Internet]. 2020;1–13. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/32109013.

84. D`Antiga L. Coronaviruses and immunosuppressed patients. The facts the third epidemic. Liver Transpl 2020; doi 10.1002/lt.25756.

85. Guillen E, Pineiro GJ, Revuelta I, et al. Case report of COVID-19 in a kidney transplant recipient: Does immunosuppression alter the clinical presentation? Am J Transplant. 2020;00:1–4. https://doi.org/10.1111/ajt.15874.

86. Rodríguez-Lago I, Ramírez de la Piscina P, Elorza A, et al Characteristics and prognosis of patients with inflammatory bowel disease during the SARS-CoV-2 pandemic in the Basque Country (Spain), Gastroenterology (2020), doi: https://doi.org/10.1053/j.gastro.2020.04.043.

87. Zhou Y, Hou Y, Shen J, et al. Network-based drug repurposing for noval coronavirus 1019-nCoV19 SARS-CoV-2. Cell Discov 2020; 6:14-15.

88. Milano F, Campbell AP, and Guthrie KA, et al (2010) Human rhinovirus and coronavirus detection among allogeneic hematopoietic stem cell transplantation recipients Blood 115(10) 2088–2094 https://doi.org/10.1182/blood-2009-09-244152 PMID: 20042728 PMCID: 2837322.

89. Chen X, Chou CY, Chang GG. Thiopurine analogue inhibitors of severe acute respiratory syndrome-coronavirus papain-like protease, a deubiquitinating and deISGylating enzyme. Antivir. Chem. Chemother. 2009;19:151–156. doi: 10.1177/095632020901900402. [PubMed] [CrossRef] [Google Scholar]

90. Cheng KW, Cheng SC, Chen WY et al. Thiopurine analogs and mycophenolic acid synergistically inhibit the papain-like protease of Middle East respiratory syndrome coronavirus. Antivir. Res. 2015;115:9–16. doi: 10.1016/j.antiviral.2014.12.011.

91. Pfefferle S, Schöpf J, Kögl M, et al. The SARS-coronavirus-host interactome: identification of cyclophilins as target for pan-coronavirus inhibitors. PLoS Pathog, 2011; 7:e1002331.

92. Ma-Lauer Y, Zheng Y, Malešević M, et al. Influences of cyclosporin A and non immunosuppressive derivatives on cellular cyclophilins and viral nucleocapsid protein during human coronavirus 229E replication. Antiviral Res, 2020; 173:104620

93. de Wilde AH, Zevenhoven-Dobbe JC, van der Meer Y, et al. Cyclosporin A inhibits the replication of diverse coronaviruses. J Gen Virol 2011; 92: 2542–8.

94. Carbajo-Lozoya J, Müller MA, and Kallies S, et al (2012) Replication of human coronaviruses SARS-CoV, HCoV-NL63 and HCoV-229E is inhibited by the drug FK506 Virus Res 165(1) 112–117 https://doi.org/10.1016/j.virusres.2012.02.002 PMID: 22349148.

95. Cavagna L, Bruno R ,Zanframundo G, et al. Clinical presentation and evolution of COVID-19 in immunosuppressed patients. Preliminary evaluation in a North Italian cohort on calcineurin-inhibitors based therapy. doi: https://doi.org/10.1101/2020.04.26.20080663.

96. Rosen MH, MD, Axelrad A, Hudesman D et al. Management of Acute Severe Ulcerative Colitis in a Pregnant Woman With COVID-19 Infection: A Case Report and Review of the Literature. Inflamm Bowel Dis • Volume XX, Number XX, XXXX 2020. doi: 10.1093/ibd/izaa109

97. Russell CD, Haas J. Cyclosporine has a potential role in the treatment of SARS. J Infect. 2013;67(1):84–85.

98. Rudnicka L, Goldust M, Glowacka P,et al. Cyclosporine therapy during the COVID-19 pandemic is not a reason for concern., Journal of the American Academy of Dermatology (2020), doi: https://doi.org/10.1016/ j.jaad.2020.04.153.

99. Fukuda W, Hanyu T, Katayama M,et al. Incidence of hepatitis B virus reactivation in patients with resolved infection on immunosuppressive therapy for rheumatic disease: a multicentre, prospective, observational study in Japan. Ann Rheum Dis 2017;76:1051–1056.

100.   Cullen G, Bader C, Korzenik JR, Sands BE. Serological response to the 2009 H1N1

influenza vaccination in patients with inflammatory bowel disease. Gut. 2012; 61:385–391.

101.   Feldmann M, Maini RN, Woody JN, Holgate ST, Winter G et al. Trials of anti-tumour

necrosis factor therapy for COVID-19 are urgently needed. The Lancet 2020. doi:

10.1016/S0140- 6736(20)30858-8

102.   Haga S, Yamamoto N, Nakai-Murakami C, Osawa Y, TokunagaK et al. Modulation of

TNF-alpha-converting enzyme by the spike protein of SARS-CoV and ACE2 induces TNF-alpha

production and facilitates viral entry. Proceedings of the National Academy of Sciences of

the United States of America 2008; 105 (22): 7809-7814. doi: 10.1073/pnas.0711241105.

103.   Tobinick E (2004) TNF-alpha inhibition for potential therapeutic modulation of SARS

coronavirus infection Curr Med Res Opin 20(1)39–40

https://doi.org/10.1185/030079903125002757

104.   Atanasova K, Van Gucht S, and Van Reeth K (2010) Anti-TNF-alpha therapy does not

ameliorate disease in a model of acute virus-endotoxin mediated respiratory disease in pigs

Vet Immunol Immunopathol 137(1–2) 12–9

https://doi.org/10.1016/j.vetimm.2010.04.003PMID: 20466438 PMCID: 2922464

105.   Hussell T , Pennycook A, Openshaw PJM. Inhibition of tumor necrosis factor

reduces the severity of virus-specific lung immunopathology .Eur. J. Immunol. 2001. 31:

2566–2573.

106.   Chinese Clinical Trial Register (ChiCTR) - The world health organization international

clinical trials registered organization registered platform.

http://www.chictr.org.cn/showprojen.aspx?proj=49889 (accessed 13 May 2020).

107. Lee N, Chan MC, Lui GC, et al. High viral load and respiratory failure in adults hospitalized for respiratory syncytial virus infections. J Infect Dis 2015; 212: 1237–40.

108. Ritchie AI , Singanayagam A .Immunosuppression for hyperinflammation in COVID-19: a double edged sword? Lancet. 2020;395(10230):1111. doi: 10.1016/S0140 6736(20)30691-7.

109. Lv S, Han M, Yi R, Kwon S, Dai C, Wang R. Anti-TNF-alpha therapy for patients with sepsis: a systematic meta-analysis. Int J Clin Pract. 2014;68(4):520-528.

110. Cohen J, Carlet J. INTERSEPT: an international, multicenter, placebo-controlled trial of monoclonal antibody to human tumor necrosis factor-alpha in patients with sepsis. International Sepsis Trial Study Group. Crit Care Med 1996; 24: 1431–40.

111. Möhn N, Pul R, Kleinschnitz C,et al. Implications of COVID-19 Outbreak on Immune Therapies in Multiple Sclerosis Patients—Lessons Learned From SARS and MERS.Front. Immunol. 11:1059. doi: 10.3389/fimmu.2020.01059

112. Grassia R, Soro S, Conti CB. Inflammatory Bowel Diseases and Biological Treatment in SARS-CoV-2 Era. Why Not? Inflamm Bowel Dis 2020; doi: 10.1093/ibd/izaa110.

113. Ceribellia A, Mottab F, De Santisa M, et al. ,Recommendations for coronavirus infection in rheumatic diseases treated with biologic therapy. Journal of Autoimmunity 109 (2020) 102442

114. Monti S, Balduzzi S, Delvino P, et al .   Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies Ann Rheum Dis 2020;0:1–2. doi:10.1136/annrheumdis-2020-217424.

115.   SECURE-IBD. SECURE-IBD Registry: Surveillance Epidemiology of Coronavirus (COVID-19) Under Research Exclusion. 2020. https://covidibd.org/updates-and-data/. Accessed 12th May 2020.

116.   Wyant T, Fedyk E, Abhyankar B. An Overview of the Mechanism of Action of the Monoclonal Antibody Vedolizumab. J Crohns Colitis. 2016 ;10(12):1437-1444.

117.   Bye WA, Jairath V, Travis SPL. Systematic review: the safety of vedolizumab for the treatment of inflammatory bowel disease. Aliment Pharmacol Ther. 2017; 46:3–15.

118.   Ng SC, Hilmi IN, Blake A, et al. Low frequency of opportunistic infections in patients receiving vedolizumab in clinical trials and post-marketing setting. Inflamm Bowel Dis, 24(11): 2431–2441, https://doi.org/10.1093/ibd/izy153.

119.   Byrareddy SN, Arthos J, Cicala C, et al. Sustained virologic control in SIV+ macaques after antiretroviral and 4 7 antibody therapy. Science 2016;354:197–202.

120.   Sneller MC, Clarridge KE, Seamon C, et al. An open-label phase 1 clinical trial of the anti-α4β7 monoclonal antibody vedolizumab in HIV-infected individuals. Sci Transl Med 2019;11: eaax3447.

121.   Jamilloux, T. El Jammal, L. Vuitton, et al, JAK inhibitors for the treatment of autoimmune and inflammatory diseases, Autoimmun. Rev. 18 (2019) 102390, https://doi.org/10.1016/j.autrev

122.   Colombel JF. Herpes zoster in patients receiving JAK inhibitors for ulcerative colitis: mechanism, epidemiology, management, and prevention, Inflamm. Bowel Dis. 24 (2018) 2173–2182

123.   Weisshof R, Aharoni Golan M, Sossenheimer PH, et al. Real-World Experience with Tofacitinib in IBD at a Tertiary Center. Dig Dis Sci. 2019;64(7):1945-1951

124.   Boor PPC, de Ruiter PE, Asmawidjaja PS,et al .JAK-inhibitor tofacitinib suppresses

interferon alfa production by plasmacytoid dendritic cells and inhibits arthrogenic and

antiviral effects of interferon alfa. Transl Res 2017; 188: 67–79.

125.   Zhang C, Li JW, Zhao H, et al. The cytokine release syndrome (CRS) of severe COVID-

19 and interleukin-6 receptor (IL-6R) antagonist Tocilizumab my be the key to reduce the

mortality. International Journal of Antimicrobial Agnets 2020; 11;54.

Htttps://doi.org/10/1016.j.ijantimicag.2020.105954.

126.   Richardson P, Griffin I, Tucker C, Smith D, Oechsle O etal. Baricitinib as potential

treatment for 2019-nCoV acute respiratory disease. Lancet (London, England) 2020; 395

(10223): e30-e31. doi: 10.1016/s0140-6736(20)30304-4.

127.   P. Richardson, I. Griffin, C. Tucker, et al. Baricitinib as potential treatment for 2019-

nCoV acute respiratory disease, Lancet 395 (2020) e30–e31.

128.   D. Wu, X.O. Yang, TH17 responses in cytokine storm of COVID-19: an emerging

target of JAK2 inhibitor Fedratinib, J. Microbiol. Immunol. Infect. (2020), https://

doi.org/10.1016/j.jmii.2020.03.005.

129.   141. Jacobs J, Calrk-Snustad K, Lee S. Case report of a SARS-CoV -2 infection in a

patient with ulcerative colitis on Tofacitnib . Inflmm Bowel Dis 2020;

doi:10.1093/ibd/izaa093.

130.   Moschen AR, Tig H, Raine T. IL-12, IL-23 and IL-17 in IBD: immunobiology and

therapeutic targeting. Nat Rev Gastroenterol Hepatol 2019; 16:185-96.

131.   Neurath M. Covid-19 and immunomodulation in IBD. Gut 2020; 0:1–8.

doi:10.1136/gutjnl-2020-321269

132.   Ritchlin CT, Stahle M, Poulin YS et al. Serious infections in patients with self-reported

psoriatic arthritis from the Psoriasis Longitudinal Assessment and Registry (PSOLAR) treated

with biologics. BMC Rheumatol. 2019 Nov 28; 3:52. doi: 10.1186/s41927-019-0094-3.

133.   Singh S, Facciorusso A, Dulai PS. Et al Comparative Risk of Serious Infections with

Biologic and/or Immunosuppressive Therapy in Patients With Inflammatory Bowel Diseases:

A Systematic Review and Meta-Analysis. Clin Gastroenterol Hepatol. 2020 Jan;18(1):69-

81.e3. doi: 10.1016/j.cgh.2019.02.044.

134.   Hanauer SB, Sandborn WJ, Feagan BG, et al. IM-UNITI: Three-year Efficacy, Safety,

and Immunogenicity of Ustekinumab Treatment of Crohn's Disease. J Crohns Colitis. 2020;
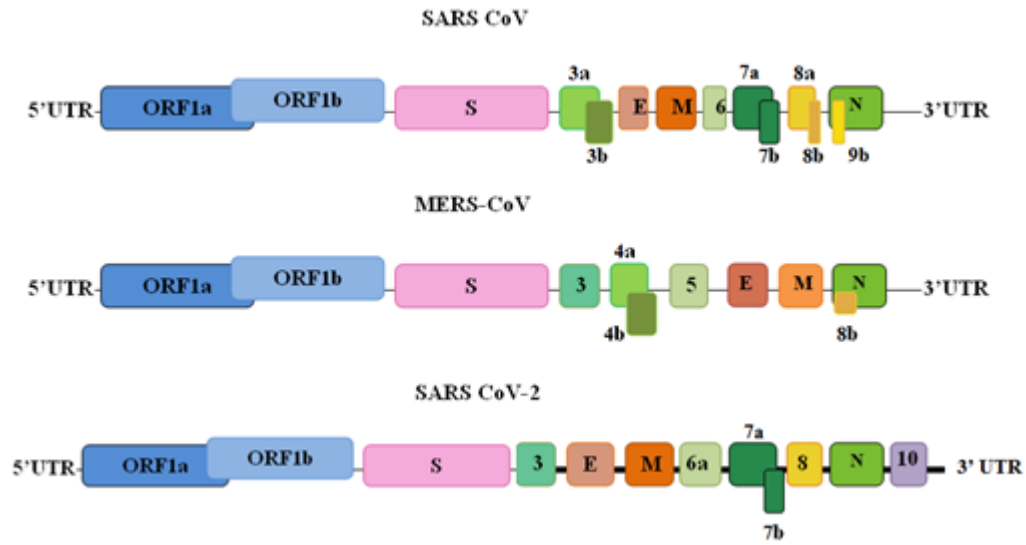
14(1):23-32.

Figure 1: The similarities and differences in the genome of SARS-CoV-1, MERS-CoV, SARS-CoV-2. There are only 380 aminoacid substitutions mainly in non structural protein genes including 27 in the S-protein

SARS-Cov-1,Severe acute respiratory syndrome coronalvirus 1;,MERS-CoV ,Middle east respiratory syndrome coronavirus; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; ORF ,open reading frames;S ,spike protein;E-envelope protein;M,membrane protein;N,nucleocapsid protein
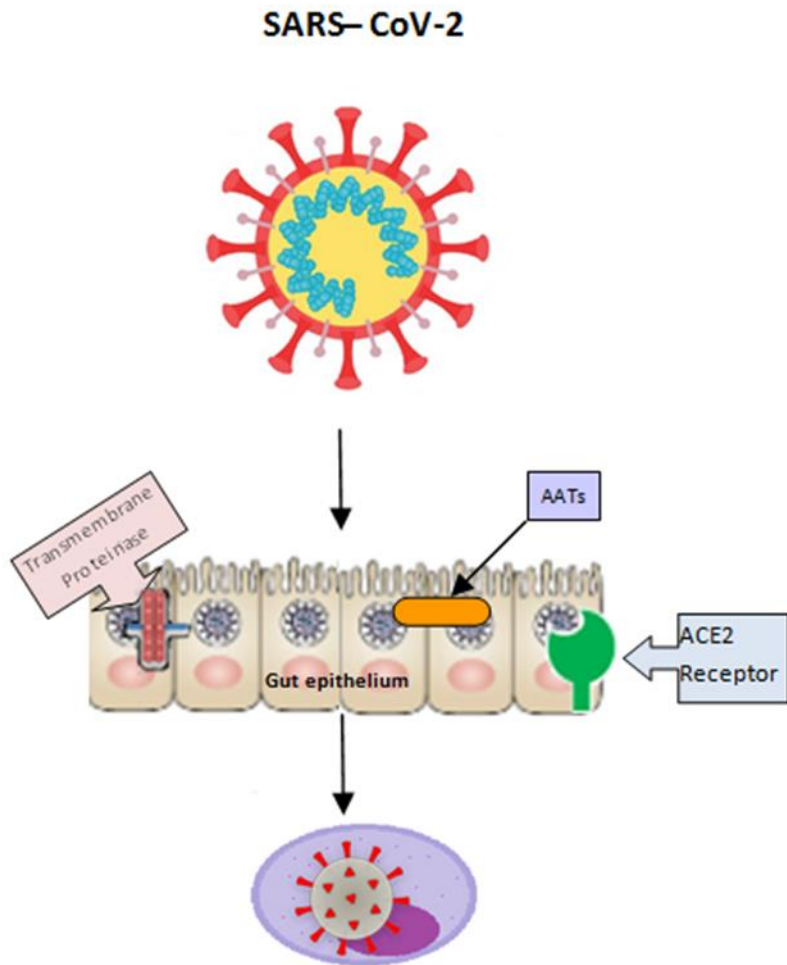
Figure 2: SARS-CoV-2 entry via ACE2 receptor in gut

SARS-CoV-2, Severe adult respiratory syndrome coronavirus 2; ACE2 receptor, angiotensin converting enzyme -2 receptor; AATs aminoacid transporters

	5ASAs	Steroids	Thiopurine	MTX	Anti TNF	Vedolizumab	Ustekinumab	Tofacitinib
Increased rate of SARS CoV-2	Uncertain Risk	Possible Risk	Uncertain Risk	Uncertain Risk	Possibly beneficial	No effect	No effect	Uncertain Risk
Increased rate of COVID-19	Possible Risk	Possible Risk	Uncertain Risk	Uncertain Risk	Possibly beneficial	No effect	Possibly beneficial	Uncertain Risk

Legend:
- Orange = Uncertain Risk
- Red = Possible Risk
- Green = Possibly beneficial
- Light green = No effect

Table 2: Safety and potential utility of IBD drugs during COVID-19

MTX, methotrexate; 5ASAs, 5-aminosalicylates,TNFα- tumour necrosis factor α

Table 1: Viral infections in licencing trials of biologics

Study	Nº patients	Nº (%) infection		Type of Infection
		Placebo	Treatment	
ACT 1	Placebo n=121 Infliximab n=243	1 (0.8)	1 (0.4)	Varicella-zoster virus infection
		0 (0)	1 (0.4)	Herpes zoster
		5 (4.1)	11 (4.5)	Serious infection
ACT 2	Placebo n=121 Infliximab n=243	0	1 (0.4)	Varicella-zoster virus infection
		1 (0.8)	3 (1.2)	Herpes zoster
		1 (0.8)	5 (2)	Serious infection
ACCENT I	Placebo n= 188 Infliximab n=385	8 (4)	14 (3.6)	Serious infection
ACCENT II	Placebo n=13 Infliximab n=15	8 (61.5)	10 (66.7)	≥1 infection
		0 (0)	1 (6.7)	≥1 serious infection
GEMINI I	Placebo n=275 Vedolizumab n=620	26 (9)	80 (13)	Nasopharyngitis
		21 (8)	52 (8)	Upper respiratory tract infection
		6 (2)	30 (5)	Influenza
		12 (4)	24 (4)	Bronchitis
		5 (2)	19 (3)	Gastroenteritis
		8 (3)	15 (2)	Sinusitis
		11 (4)	14 (2)	Urinary tract infection
		8 (2.9)	12 (1.9)	Serious infection
GEMINI II	Placebo n=301 Vedolizumab n=814	56 (19)	184 (23)	Upper respiratory tract infection
		121 (40)	359 (44)	Any infection
		9 (3)	45 (5.5)	Serious infection

|				
UNITI I	Placebo n=245 Ustekinumab n=495	13 (5.3)	22 (4.4)	Nasopharyngitis
		58 (23.7)	121 (24.4)	Any infection
		3 (1.2)	10 (2)	Serious infection
UNITI II	Placebo n=208 Ustekinumab= 419	7 (3.4)	15(3.6)	Nasopharyngitis
		48 (23.1)	76 (18.1)	Any infection
		3 (1.4)	4(0.9)	Serious infection
IM-UNITI	Placebo n=133 Ustekinumab n=263	16 (12)	24 (9.1)	Nasopharyngitis
		66 (49.6)	124 (47.1)	Any infection
		3 (2.3)	10 (3.8)	Serious infection
OCTAVE I	Placebo n=122 Tofacitinib n=476	1 (0.8)	3 (0.6)	Herpes Zoster
		19 (15.6)	111 (23.3)	Any infection
		0 (0)	6 (1.3)	Serious infection
OCTAVE II	Placebo n=112, Tofacitinib n=429	0 (0)	2 (0.5)	Herpes Zoster
		0 (0)	1 (0.2)	CMV colitis
		17 (15.2)	78 (18.2)	Any infection
		0 (0)	1 (0.2)	Serious infection
OCTAVE-SUSTAIN	Placebo n= 198 Tofacitinib n=394	1 (0.5)	4 (1)	Herpes Zoster
		48 (24.2)	149 (37.8)	Any infection
		2 (1)	3 (0.8)	Serious infection
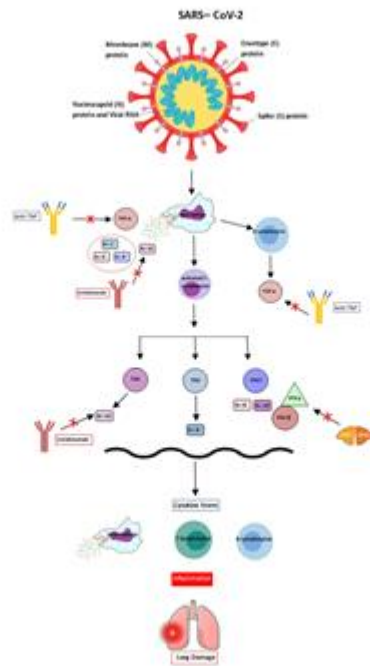
Figure 3: Cytokines in COVID-19 hyper stimulation: Potential sites of actions of drugs used in IBD

SARS-CoV-2, Severe acute respiratory syndrome-coronavirus-2; TNFα,tumour necrosis factor α; IL-1,interleukin-1, IL-4 , interleukin-4; IL-6, interleukin -6; IL-8,interleukin-8, IL-12, interleukin-12; IL-23,interleukin-23; TH1, T helper cell -1, TH2,T helper cell -2; TH17, T helper cell 17; IFNγ, interferon γ; TNFβ, tumour necrosis factor β; JAK1, janus kinase 1;

JAK2 ,janus kinase 2