Autoimmune Gut Diseases and COVID-19 Vaccines

Subjects: Immunology

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The SARS-CoV-2 pandemic raised many challenges for all patients with chronic conditions and those with autoimmune diseases, both adults and children. Autoimmune diseases are characterized by hyperreactivity of the immune system and loss of immune tolerance, which damage and destroy healthy tissues, cells, and organs.

autoimmune gut disease autoimmune liver disease COVID-19 vaccine

1. Introduction

The culpable agent for the coronavirus disease 2019 (COVID-19) pandemic is the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1]. It causes acute respiratory distress syndrome (ARDS) in a large number of individuals with severe pulmonary injury [2]. However, the pandemic has raised significant concerns about managing immunocompromised patients. Recent research reveals that these patients have more severe disease courses due to their underlying changed immunological status and immunosuppressive medicines [3]. Furthermore, Kim et al. reported a 40% additional risk for in-hospital mortality and 30% for intensive care unit (ICU) admission among these patients [4].

In response to the high mortality rate and casualties of the COVID-19 pandemic globally, pharmaceutical companies have produced effective vaccines against the SARS-CoV-2 infection. Therefore, immunization against SARS-CoV-2 is considered the most suitable tool in the hands of physicians. Several vaccine candidates and tactics were developed shortly after the onset of SARS-CoV-2 pandemic [5]. However, they were not fully successful in managing or controlling the COVID-19 pandemic. The spread of COVID-19 is mostly influenced by the appearance of novel viral variants brought on by the acquisition of genetic alterations in SARS-CoV-2 in various regions of the world and subsequent rapid transmission across the continents [5].

Additionally, depending on the population and variations, the efficacy of the approved vaccinations against the newly emerging SARS-CoV-2 mutations varied. This highlights the need for a broad-spectrum vaccine that could elicit a more effective immune response toward all new variants [6].

Different types of COVID-19 vaccines have been developed, including live-attenuated vaccines, protein-based vaccines, and gene vaccines (mRNA, vector-based, and VLPs) [5][6]. Nevertheless, the hastened course of vaccine development raises several concerns, especially in particular groups of patients, such as those with an altered

immune system. Moreover, many individuals with immune-mediated chronic diseases, including autoimmune liver and gut diseases, have been excluded from vaccine clinical trials [7]. This resulted in an evidence gap for the long-term safety and efficacy of COVID-19 vaccines in patients with autoimmune diseases.

Some of the theoretical concerns are related to the complex pathogenesis of autoimmune diseases, including liver and gut conditions, immunosuppressive therapy, and the cumulative risk of flare [8]. Researchers rely on real-world data from vaccination after vaccine approval for these patients.

Nevertheless, autoimmune disease patients still experience high levels of COVID-19 vaccine hesitancy. Some concerns are stopping immunosuppression before vaccination and minimizing the risk of relapse and adverse effects. The COVID-19 Vaccination in Autoimmune Diseases (COVAD) study, a long-term ongoing global self-reported study that includes patients with autoimmune disease, collected data on short and long-term adverse effects and disease flares in patients following COVID-19 vaccines [9][10].

A questionnaire-based study among Chinese people with IBD also showed COVID-19 vaccination hesitancy, mostly related to the history of immune-modifying therapies, potential adverse reactions, and effectiveness [11].

2. Autoimmune Gut Diseases and COVID-19 Vaccines

Autoimmune diseases are characterized by hyperreactivity of the immune system and loss of immune tolerance, which damage and destroy healthy tissues, cells, and organs [12].

Patients diagnosed with inflammatory bowel disease (IBD), especially those who have undergone biological or immunosuppressive therapy, are a subject of interest due to the risk factors that arise from the illness regarding COVID-19 morbidity [13]. Currently, risk factors associated with a higher risk of infection due to IBD morbidity are nutrition status, age, comorbidity, and pharmacotherapy. The most enduring hypothesis is that malnutrition and food deficiency lead to a compromised immune response. Food deficiency relates to decreased phagocyte function and abnormal cell-mediated immunity [13]. Additionally, patients suffering from IBD often have vitamin D deficiency, increasing the severity of COVID-19 infection [14]. Going further down the road, researchers reviewed the role of vitamin D in deficient patients not only for COVID-19 severity but as a potential adjuvant for COVID-19 vaccination, as seen for other vaccines [15].

Many previously described studies underline that treating IBD patients with immunomodulators (TNF-antagonists, non-TNF targeted biologics), immunosuppressive therapy, or corticosteroids can increase the risk of infections, or the complications associated with various infections [16]. On the other hand, managing the activity of IBD is also of paramount importance because it plays a risk factor for infections or associated complications. That is why IBD treatment should be as optimal as possible and the treatment course uninterrupted [17][18].

Up to now, there are some clinical studies that involve patients with autoimmune gut diseases and assess the safety and effectiveness of COVID-19 vaccines. Thus, researchers conducted a literature research and summarize

their findings in **Table 1**.

Table 1. Summarized COVID-19 vaccine studies on safety profile, efficacy, and adverse effects rate in patients with inflammatory bowel disease.

Type of Vaccine	Type of Study	Subjects	Data on Efficacy (% Protection, Other)	Data on Safety (Main Side Effects)	Reference
mRNA	Prospective study design	All patients included n = 246 (67% Crohn's disease, 33% ulcerative colitis)	N/A	After the first dose (injection site reactions in 38%; fatigue/malaise 23%, headaches 14%, fever/chills 5%); After the second dose (injection site reaction 56%; fatigue, malaise 45%, headaches 34%, fever/chills 29%)	Botwin et al. [19]
mRNA, adenoviral	A prospective, observational cohort study	All patients included n = 3316 with IBD (n = 1908, Pfizer/BioNTech; n = 1272 Moderna, n = 161, Janssen)	N/A	No severe systemic reactions require emergency room visits. After the first dose: adverse reaction injection site (66%); fever (6%), fatigue (46%), headaches (32%), muscle aches (20%); After the second dose: adverse reaction injection site (65%); fever (25%), fatigue (46%), headaches (32%), muscle aches (12%); Low flare rate (2%)	Weaver et al. [20]
mRNA	Self-reported study	84 IBD patients (23-with Crohn's disease, 25 with ulcerative colitis) on anti-TNF therapy	Biologic therapy associated with lower anti-RBD antibodies	N/A	Wong et ICARUS-IBD Working Group [21]
mRNA	Multicenter, UK prospective, case-control study	352 IBD patients on immunosuppressive therapy (thiopurine, infliximab, ustekinumab, vedolizumab, tofacitinib) and 72 healthy controls	No significant differences in anti-SARS-CoV-2 S1 RBD antibody concentrations between the healthy control group and patients treated with thiopurine, ustekinumab, or	N/A	Alexander et al. [22]

Type of Vaccine	Type of Study	Subjects	Data on Efficacy (% Protection, Other)	Data on Safety (Main Side Effects)	Reference
			vedolizumab, lower anti-SARS-CoV-2 S1 RBD antibody concentrations independently associated with infliximab, tofacitinib, and thiopurine, but not with ustekinumab or vedolizumab (0.84 [0.54–1.30]; p = 0.43)		
mRNA	Multicenter Israeli population-based cohort study	12,109 IBD patients, 4946 non-IBD controls, 707 unvaccinated IBD patients	99.7% protection; patients on TNF inhibitors and/or corticosteroids did not have a higher incidence of infection; risk of exacerbation was 29% in vaccinated vs. 26% in unvaccinated IBD (p = 0.3)	N/A	Lev-Tzion et al. [23]
mRNA and adenoviral	Prospective, CLARITY IBD multicenter cohort study	1293 vaccinated IBD patients	anti-SARS-CoV-2 antibody concentrations reduced in patients treated with infliximab than vedolizumab	N/A	Kennedy et al. [24]
mRNA	Retrospective	7321 vaccinated IBD, 7376 unvaccinated IBD patients	Full vaccination associated with 69% reduced risk for COVID-19 and 80.4% effectiveness	N/A	Khan and Mahmud [25]
mRNA	Retrospective	5562 vaccinated IBD, 859,017 vaccinated non-IBD patients	N/A	2.2% adverse events in IBD patients on biologics/immunomodulatory therapy vs. 1.67 without such treatment; special adverse events	Hadi et al. [26]

Type of Vaccine	Type of Study	Subjects	Data on Efficacy (% Protection, Other)	Data on Safety (Main Side Effects)	Reference
mRNA	Retrospective cohort	12,231 vaccinated IBD, 36,254 vaccinated non-IBD patients	0.19% breakthrough infections after the second dose (7 days) and 0.14% (14 days)	N/A	Ben-Tov et al. [27]
mRNA, adenovirus vector	Prospective	33 vaccinated IBD—children and young adults	15 times higher levels of IgG antibodies compared to natural infection, all participants developed neutralizing antibodies	For mRNA vaccine—sore arm, chills, fever, etc.; vector vaccine—the same; no one has contracted COVID-19 2–6 months following vaccination	Dailey et al. [28]
mRNA	Prospective single-center	317 vaccinated IBD patients	Detectable antibodies in 300/317 IBD patients; 85% in patients on corticosteroids	N/A	Kappelman et al. [29]
mRNA	Prospective, multicenter	84 patients with immune-mediated disease, 8 vaccinated IBD patients	90.5% of all patients with immune-mediated diseases develop IgG antibodies to SARS-CoV-2	Less frequent mild adverse effects (injection site pain, headache, chills, arthralgia)	Simon et al. [30]
mRNA	Prospective, multicenter	133 patients with chronic inflammatory disease, 42 vaccinated IBD patients	N/A	Incidence rate of overall adverse events—0.55; local—0.64; mainly fatigue, headache, myalgia, fever and chills; severe adverse reactions incidence rate 0.02, requiring hospitalization—0.00 and IBD flares—0.01	James et al. [31]
mRNA, adenovirus vector	Prospective, multicenter	353 vaccinated IBD patients	Higher quantitative log10 antispike IgG after mRNA vs. adenovirus	N/A	Pozdnyakova et al. [32]
mRNA	International web-based	3272 IBD patients	N/A	72.4% local symptoms, 51.4% systemic symptoms	Ellul et al. [33]

Type of Vaccine	Type of Study	Subjects	Data on Efficacy (% Protection, Other)	Data on Safety (Main Side Effects)	Reference
	survey				
mRNA	Cohort study	122 IBD patients and 60 controls, on immunomodulating therapy	97% of IBD patients developed antibodies, lower in patients than in controls, higher after Moderna vs. Pfizer; lower when on immunosuppressive therapy;	OR = 0.97 significant side effects associations after full vaccination	Caldera et al. [34]
mRNA, adenovirus vector	Prospective single-tertiary study	602 IBD patients on immunosuppressive therapy	Lower Ig concentrations in patients on treatment; 97.8% seropositivity in IBD patients	N/A	Cerna et al. [35]
mRNA, adenovirus vector	Retrospective observational	72 IBD patients;	100% antibody response in patients group; reduced antibody levels in IBD vs. controls, no differences between vaccines; all IBD patients developed an immune response	Local and systemic mild reactions	Classen et al. [36]
mRNA	Prospective controlled	185 IBD patients, 73 healthy controls	100% response following vaccination, lower in older and on anti-TNF therapy	Local pain, headache	Edelman-Klapper et al. [37]
mRNA, adenovirus vector	Cohort/ real-life survey: telephone questionnaire	239 IBD patients on biologics	N/A	High acceptance rate and mild and transitory adverse reaction	Garrido et al. [38]
mRNA	Prospective study	19 IBD patients on biologics	95% immune response rate	N/A	Levine et al. [39]
mRNA	Prospective study	19 patients on biologics	21.13-fold increase of total IgG antibodies after 1st	N/A	Rodriguez-Martino et al. [40]

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However, they also exerted decreased antibody production while on infliximab and vedolizumab [21][24]. Thus, Botwin et al.'s findings are helpful for physicians and patients by confirming the similar safety profile for mRNA vaccines for IBD patients [19]. Furthermore, the authors observed a difference in adverse reactions following the first and second doses. Higher rates of adverse reactions were found after the second dose [18][19]. However, patients who recovered from COVID-19 had more reactions than patients with no previous antispike response after the first dose but not the second one. Nevertheless, more studies are needed to confirm this observation.

Type of Vaccine	Type of Study	Subjects	Data on Efficacy (% Protection, Other)	Data on Safety (Main Side Effects)	Reference
			dose, and 90-fold after second dose; % virus neutralizing antibodies was lower in IBD patients [43]		
mRNA, adenovirus vector	Prospective study	126 IBD patients on biologics	74.5–81.2% immune response in patients on anti-TNF vs. 92.8–100% on vedolizumab and ustekinumab, resp.; fewer virus-neutralizing antibody titers in patients treated with anti-TNF	N/A	[44][45] Shehab et al. [41]

However, solid organ transplantation patients may not receive sufficient protection after vaccination.

D'Amico et al. suggested more pros than cons for SARS-CoV-2 vaccination in IBD patients. However, despite insufficient data, it can be extrapolated information from data reported in patients with other autoimmune diseases [46]. This is why the American College of Rheumatology recommends COVID-19 vaccines for patients with autoimmune inflammatory diseases based on the previously available data for other vaccines [47].

The recently published systemic review and meta-analysis by Sung et al. focused on efficacy, seroconversion rate (antibody titer against SARS-CoV-2 S protein), and the adverse effects in 27,454 IBD patients from 11 studies. As expected from the data from other studies, COVID-19 incidence was comparable in IBD and non-IBD patients and 8.63 times lower than observed in unvaccinated IBD patients. However, the reported adverse event rate after vaccination was 69%, the severe adverse rate was 3%, and mortality was 0% [48].

Doherty et al. published similar results in their paper—reduced immune responses after vaccination in IBD patients on anti-TNF therapy and other immunomodulators. However, the overall conclusion is that patients with IBD still benefit from COVID-19 vaccination, and recommendations included minimizing corticosteroid doses before vaccination if possible [49].

Jena et al. in their systematic review and meta-analysis on effectiveness and durability of COVID-19 vaccination in IBD patients confirmed the lower pooled seroconversion rate. However, the pooled relative risk of infection breakthrough was similar to control subjects [50]. Tabesh et al. also conducted a systematic scoping review of 15 studies, concluding that COVID-19 vaccines are effective and safe for patients with IBD on different therapeutic regimens [51].

One of the most significant limitations of the published studies so far is that they cover effectiveness or adverse effects solely, but rarely both. Additionally, adapted immunization techniques may be appropriate in some IBD patients to maximize immunogenicity, according to prior experience [52][53].

Still, the main concerns for patients with IBD remain a lack of immune protection after vaccination (17.6% of respondents), worsened adverse effects (24.6%) due to IBD, and flare following vaccination (21.1%), according to an international web-based survey [33].

Duong et al. also reported that 2/3 of surveyed IBD patients were willing to get vaccinated against COVID-19 [54], which was also reported by Hudhud et al. [55].

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