SARS-CoV-2 vaccination for patients with inflammatory bowel diseases: recommendations from an international consensus meeting

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BACKGROUND

The COVID-19 pandemic has claimed the lives of nearly 2 million people worldwide.[1] Following rapid sequencing of SARS-CoV-2, pharmaceutical companies and academic institutions rapidly generated vaccine candidates on the back of a variety of both established and novel vaccine platforms.[2–4] Vaccines accelerated at unprecedented pace to phase 3 development, and in December 2020, two mRNA vaccines and one inactivated vaccine were authorised for use in a number of countries. Additional vaccine platforms and candidates are in late stages of phase 3 testing.[5] Prioritisation of vaccine access is generally determined by regional health authorities on the basis of risk of SARS-CoV-2 exposure and risk of developing complications from COVID-19 in order to equitably protect and promote global public well-being.[6–8]

IBD, including Crohn's disease and ulcerative colitis, are characterised by chronic intestinal inflammation due to immune dysregulation. IBD is often treated with immune-modifying therapies including corticosteroids, immunomodulators, biologic agents including monoclonal antibody inhibitors of tumour necrosis factor (TNF) alpha, interleukin 12/23, integrins and small molecules such as Janus kinase (JAK) inhibitors. Prior studies have evaluated the safety and effectiveness of various vaccines in patients with IBD, with specific focus on the impact of immune-modifying therapies on serologic responses. In general, non-live vaccines are considered safe in patients with IBD regardless of IBD therapy, although those on specific types of immune-modifying treatments at the time of vaccination may have reduced vaccine immune responses.[9–12] In spite of decreased efficacy associated with immune-modifying medication, most vaccines are broadly recommended for those with IBD.[13–15] Patients with immune conditions (including IBD) were excluded from the SARS-CoV-2 vaccine clinical development programmes,[16] and novel vaccine platforms not previously studied in IBD populations are now authorised in many countries. Therefore, many questions regarding the safety and effectiveness of SARS-CoV-2 vaccination in patients with IBD have emerged with urgent clinical relevance.

The International Organization for the Study of Inflammatory Bowel Disease (IOIBD) is a global organisation of clinician researchers dedicated to the study and management of IBD. There are currently 60 active members and 32 senior members of IOIBD representing 27 countries. In March 2020, IOIBD rapidly developed recommendations for the clinical management of patients with IBD during the COVID-19 pandemic.[17] Now that vaccinations are available, this group reconvened to develop specific recommendations pertaining to the use of SARS-CoV-2 vaccines in IBD populations.

METHODS

We used the modified Delphi method to develop consensus statements regarding SARS-CoV-2 vaccination for patients with IBD.[18] The main characteristics of this technique include expert opinion with anonymous voting on statements, iteration with controlled feedback of group opinion and statistical aggregation of the group response.[19]

A consensus meeting was planned for 18 December 2020. The invitees for this meeting included the membership of IOIBD and additional content experts including an IBD specialist with expertise in vaccinations (GM) and a vaccinologist (FK) with expertise in vaccine development and immune responses to vaccines. Prior to this planned meeting, a questionnaire was developed by authors (CS, GM, MD, DM, MA, DR) to include statements in domains that impact clinical decisions around vaccination for the IBD population. The domains included general issues of vaccines and IBD; risk of COVID-19 to patients with IBD and need for SARS-CoV-2 vaccination; efficacy and safety of the various SARS-CoV-2 vaccines for patients with IBD; timing of when to receive SARS-CoV-2 vaccination; the influence of IBD medications on the decision and timing for SARS-CoV-2 vaccination and prioritisation of patients with IBD for SARS-CoV-2 vaccination. Forty-four statements were created and participants were asked to respond to each statement on a scale from 1 to 10 (1=do not agree at all and 10=agree completely). A priori rules determined that a statement would be accepted if at least 75% of participants scored the statement between 7 and 10. If a 75% consensus was not achieved, it would be discussed during the live meeting, followed by a second round of voting. Statements that were accepted in the first round but had a SD ≥2 or had a proportion of responses between 75% and 77% were also reviewed and voted on a second time if there was particular concern from the participants. If the second round of voting during the live meeting did not achieve consensus of 75% or higher of the respondents, then the statement was not accepted.

The questionnaire was sent electronically using Google Forms (Menlo Park, California, USA) to all voting participants on 11 December 2020. A literature review was provided to the participants prior to the meeting including evidence directly relevant for proposed statements. These included Grading of Recommendations, Assessment, Development and Evaluations

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(GRADE) evidence tables on published vaccine response trials in IBD and key articles addressing specific statements,[20–23] systematic reviews and large cohorts on COVID-19 outcomes in IBD,[17 24–26] societal and national positions on SARS-CoV-2 vaccination in pregnancy[27–30] and reviews and published phase 3 data on SARS-CoV-2 vaccines including potential relevance for IBD.[5 12 16 31–33] Results from round 1 of voting were analysed using simple descriptive statistics to include the proportion of respondents voting in the 7–10 range for each statement, mean and SD.

The live virtual meeting took place using Zoom Video Communications (San Jose, California, USA). The meeting commenced with a presentation by the vaccinologist and focused on immunity related to vaccination, various platforms being used to develop SARS-CoV-2 vaccines and efficacy and safety based on available data. All participants had an opportunity to ask questions during a discussion period. Next, results from round 1 of voting were presented and all discussions and revoting occurred based on the a priori rules described above. Three new statements were added related to pregnancy and lactation based on feedback from the participants and these went through one round of voting during the live meeting.

RESULTS

In the first round of voting, there were 64 respondents. This included 54 (84%) adult gastroenterologists, 4 (6%) paediatric gastroenterologists, 5 (8%) surgeons and 1 (1%) pathologist. Respondents represented North America (25), South America (2), Europe (27), Israel (4), Asia (5) and New Zealand (1). Of the 44 statements, 32 were accepted and 12 statements were not accepted in the first round of voting. For the 32 statements that were accepted the mean proportion of votes within the 7–10 range was 89.2% (mean 8.52, SD 1.57). This is in contrast to the

Table 1 Accepted statements related to general issues with vaccines, need for SARS-CoV-2 vaccination, timing, and prioritisation for patients with IBD by the IOIBD

Accepted statements	Proportion agreement	Strength of agreement (Mean)	SD
General issues of vaccines in IBD			
Vaccinations are not associated with the onset of IBD.	95.3%	9.22	1.53
Vaccinations are not associated with exacerbation of IBD.	95.3%	9.16	1.31
Patients with IBD, irrespective of whether they are receiving immune-modifying therapies, can safely receive all non-live vaccinations for vaccine-preventable illnesses.	100%	9.47	0.76
Patients with IBD who are receiving immune-modifying therapies should not receive live virus vaccines while they are receiving their immune-modifying therapies.	85.9%	8.27	1.95
Patients with IBD are able to mount an immune response to various vaccines, although immune-modifying therapies partially blunt that response.	98.4%	8.79	1.08
Patients with IBD receiving infliximab infusions can receive non-live vaccinations on the day of their infusion or in mid-cycle without reduction in efficacy and safety.	87.5%	8.22	1.65
Risk of COVID-19 to patients with IBD and need for SARS-CoV-2 vaccination			
Patients with IBD are at the same risk of infection with SARS-CoV-2 as compared with the general population.	90.6%	8.55	1.61
Patients with IBD should be vaccinated against SARS-CoV-2.	98.4%	9.20	1.12
Timing of when to receive SARS-CoV-2 vaccination			
The best time to administer SARS-CoV-2 vaccination in patients with IBD is at the earliest opportunity to do so.	95.3%	8.91	1.27
Disease activity of IBD should not impact the timing of SARS-CoV-2 vaccination.	90.0%	8.50	1.55
Vaccination against SARS-CoV-2 is unlikely to cause a flare of IBD.	89.1%	8.31	1.38
SARS-CoV-2 vaccination can be administered to patients with IBD during induction with biologic therapies irrespective of timing within the treatment cycle.	97.5%	8.33	1.14
SARS-CoV-2 vaccination can be administered to patients with IBD on maintenance biologic therapies irrespective of timing within the treatment cycle.	100%	8.93	1.00
The prioritisation of patients with IBD for SARS-CoV-2 vaccination			
Healthcare/essential workers with IBD should be vaccinated in the same prioritisation tier as healthcare/essential workers without IBD.	92.2%	8.84	2.00
Individuals who are not healthcare/essential workers and have no risk factors for complications of COVID-19 but have IBD should be vaccinated in the same prioritisation tier as those who are non-healthcare/essential workers and have no risk factors for SARS-COV2.	82.5%	8.02	2.03
Individuals at increased risk for complications of COVID-19 based on age or comorbidities who also have IBD should be vaccinated in the same prioritisation tier as individuals at increased risk for complications of COVID-19 without IBD.	96.8%	9.13	1.07
Individuals with IBD who are on immune-modifying therapies but are not otherwise at risk for complications of COVID-19 should be vaccinated in the same prioritisation tier as those who are 'immunocompromised'.	81.3%	8.09	1.80
Once SARS-CoV-2 vaccinations are authorised for children, guidance for vaccination of children with IBD will be the same as for children without IBD.	100%	8.90	1.03
Household contacts of patients with IBD are encouraged to receive SARS-CoV-2 vaccination.	97.4%	9.08	1.34
Household contacts of patients with IBD should avoid live, replication-competent SARS-CoV-2 vaccination.	81.6%	7.71	2.04
Women with IBD planning pregnancy should be encouraged to receive the SARS-CoV-2 vaccine prior to attempting conception, but not delay conception solely to wait for vaccination.	100%	8.87	1.03
SARS-CoV-2 vaccines should be offered to pregnant women with IBD in accordance with regional recommendations for pregnant women without IBD.	100%	8.97	1.07
SARS-CoV-2 vaccines should be offered to lactating women with IBD in accordance with regional recommendations for lactating women without IBD.	100%	8.81	1.08

12 statements that were not accepted and had a mean proportion of votes within the 7–10 range of 63.5% (mean 7.01, SD 2.18).

The live virtual meeting included 40 voting participants, all of whom voted in round 1. The invited vaccinologist was a non-voting participant. Participants included 34 (88%) adult gastroenterologists, 2 (5%) paediatric gastroenterologists, 2 (5%) surgeons and 1 (1%) pathologist. Participants represented North America (18), South America (2), Europe (13), Israel (3), Asia (3) and New Zealand (1). Eighteen statements were revoted on in this meeting. Twelve of these statements had previously not been accepted, three were new statements related to pregnancy, two were new statements that allowed further clarification of original statements from round 1, and one had an SD ≥2.

After round 2, there were a total of 49 statements. Forty-four of these 49 statements were accepted. A complete list of all accepted statements is reported in tables 1 and 2. Highlighted themes of the accepted statements are included in box 1.

DISCUSSION

The approval of SARS-CoV-2 vaccinations in many regions worldwide creates an urgency to develop recommendations for patients with IBD and other immune-mediated diseases. The IOIBD membership is an international representation of IBD specialists and created these consensus statements to help guide the highly engaged IBD community.

The panel recommends vaccinating all patients with IBD as soon as they are able to receive the vaccine, regardless of immune-modifying therapies. The exception is for any live-attenuated virus vaccines or replication-competent viral vector vaccines that come to market. There are many nuances that were addressed with the 44 accepted statements. The statements address the safety and efficacy of emerging vaccine types, the impact of different classes of IBD therapies on vaccination safety and response and priority of patients with IBD as compared with people without IBD. The overarching theme of these statements is that people with IBD should be vaccinated according to their overall risk of exposure to and risk of complications from SARS-CoV-2. These risks continue to be explored in registries such as Surveillance Epidemiology of Coronavirus Under Research Exclusion (SECURE) and other population-based studies.[24]

Table 2 Accepted statements related to SARS-CoV-2 vaccination for patients with IBD by the IOIBD

Accepted statements	Proportion agreement	Strength of agreement (Mean)	SD
Efficacy and safety of the various SARS-CoV-2 vaccines for patients with IBD			
SARS-CoV-2 vaccination will be effective in patients with IBD to prevent COVID-19.	82.8%	8.13	1.46
Patients with IBD should receive the same vaccine dosing regimen as patients without IBD.	85.9%	8.44	1.62
Patients with IBD receiving SARS-CoV-2 vaccination should be referred to registries tracking vaccination effects.	95.3%	9.05	1.25
Messenger RNA vaccines are safe to administer to patients with IBD.	82.5%	7.92	1.74
Replication-incompetent vector vaccines are safe to administer to patients with IBD.	95.2%	8.81	1.02
Inactivated SARS-CoV-2 vaccines are safe to administer to patients with IBD.	89.1%	8.16	1.78
Recombinant SARS-CoV-2 vaccines are safe to administer to patients with IBD.	90.2%	8.18	1.61
SARS-CoV-2 vaccines that contain whole or fragments of coronavirus proteins combined with an adjuvant to enhance immune response are safe to administer to patients with IBD.	76.6%	7.55	1.89
Live attenuated vaccines for SARS-CoV-2 are not considered safe for patients with IBD who are receiving immune-modifying therapies or expected to receive immune-modifying therapies within the next 8 weeks.	84.1%	8.37	1.71
IBD specialists should trust national and international regulatory bodies for appropriate review and authorisation of SARS-CoV-2 vaccinations.	95.3%	8.69	1.22
The influence of IBD medications on the decision and timing for SARS-CoV-2 vaccination			
SARS-CoV-2 vaccination should not be deferred because a patient with IBD is receiving oral or topical 5-ASA medications.	96.9%	9.41	1.00
SARS-CoV-2 vaccination should not be deferred because a patient with IBD is receiving systemic corticosteroids.	87.5%	8.20	1.65
Patients with IBD vaccinated with SARS-CoV-2 vaccine should be counselled that vaccine efficacy may be decreased when receiving systemic corticosteroids.	92.5%	8.53	1.99
SARS-CoV-2 vaccination should not be deferred because a patient with IBD is receiving thiopurine or methotrexate monotherapy.	88.9%	8.32	1.83
SARS-CoV-2 vaccination should not be deferred because a patient with IBD is receiving monotherapy with an anti-TNF agent.	95.3%	8.86	1.31
SARS-CoV-2 vaccination should not be deferred because a patient with IBD is receiving monotherapy with an anti-IL12/23 or anti-IL23 agent.	90.3%	8.69	1.53
SARS-CoV-2 vaccination should not be deferred because a patient with IBD is receiving monotherapy with an anti-integrin agent.	93.8%	9.08	1.34
SARS-CoV-2 vaccination should not be deferred because a patient with IBD is receiving a biologic in combination with a thiopurine or methotrexate.	82.8%	8.11	2.05
SARS-CoV-2 vaccination should not be deferred because a patient with IBD is receiving monotherapy with a JAK inhibitor.	76.2%	7.83	2.21
SARS-CoV-2 vaccination should not be deferred because a patient with IBD is receiving monotherapy with an S1P receptor agonist.	75.0%	7.72	1.89
SARS-CoV-2 vaccination should not be deferred because a patient with IBD is in a clinical trial for an IBD medication, as permitted per protocol.	87.5%	8.53	1.52

ASA, aminosalicylic acid; JAK, janus kinase; S1P, sphingosine-1-phosphate.; TNF, tumour necrosis factor.

Box 1 Highlighted themes of accepted statements related to SARS-CoV-2 vaccination for patients with IBD by the International Organization for the Study of Inflammatory Bowel Disease (IOIBD)

- Patients with IBD should be vaccinated against SARS-CoV-2.
- The best time to administer SARS-CoV-2 vaccination in patients with IBD is at the earliest opportunity to do so.
- SARS-CoV-2 vaccines including messenger RNA vaccines, replication-incompetent vector vaccines, inactivated vaccines and recombinant vaccines are safe to administer to patients with IBD.
- SARS-CoV-2 vaccination should not be deferred because a patient with IBD is receiving immune-modifying therapies.
- Patients with IBD vaccinated with SARS-CoV-2 should be counselled that vaccine efficacy may be decreased when receiving systemic corticosteroids.

There was debate around the language of statements regarding pregnancy. Due to discrepant guidance from different regions of the world,[27 28 30] a decision was made to add the phrase 'in accordance with regional recommendations'. Our statements convey that if SARS-CoV-2 vaccinations are considered safe for pregnant women without IBD, then they should be considered safe for pregnant women with IBD.

A significant proportion of the live virtual meeting focused on the expected immune response to a SARS-CoV-2 vaccine while a patient is receiving immune-modifying medications. The participants endorsed the statement that people with IBD are able to mount an immune response to various vaccines, although immune-modifying therapies may partially blunt that response. This was felt not to be a reason to delay vaccination or stop immune-modifying therapies, but rather a reason to recommend counselling patients receiving systemic corticosteroids that efficacy may be decreased.

Several questions emerge in vaccinating patients with IBD against COVID-19. Will the vaccines' effectiveness be affected by IBD medications? Will the vaccines be as safe on a background of immunosuppression? Efficacy of the vaccines has been measured as cases of COVID-19 following immunisation (generally a week or two after the booster dose).[16 34] Immunogenicity is measured as neutralising antibodies and/or T-cell responses to the spike protein.[5] Prospective registries of patients with IBD receiving SARS-CoV2 vaccines are urgently needed to measure the amplitude and duration of immune responses across different vaccine platforms. However, experience with previous vaccines in this patient population can edify a strategy now.

Corticosteroid, immunomodulator and/or anti-TNF treatment are associated with suboptimal vaccine response. Patients with IBD on infliximab or adalimumab have decreased antibody titers and lower seroconversion rates compared with controls in response to the inactivated influenza virus,[21] subunit pneumococcal pneumonia[9 12] and HBV vaccines.[35] This response may be further blunted by thiopurines and methotrexate either given alone or in combination with anti-TNF therapy.[36] Depending on the antigen, higher dose influenza vaccine was associated with higher antibody levels in patients with IBD on anti-TNFs compared with the standard dose,[37] suggesting that patients on these medications may benefit from vaccine regimen modification strategies. Patients with rheumatoid arthritis on the JAK inhibitor tofacitinib mounted a normal antibody response against the influenza vaccine and a diminished response to the pneumococcal vaccine, which was not improved on temporary drug discontinuation.[38] IL12/23 blockade with ustekinumab does not seem to alter vaccine response to either the influenza[39] or pneumococcus vaccine[40] and may show higher antibody responses in the case of the HBV vaccine.[41] Similarly, patients with IBD treated with vedolizumab did not have altered immune responses to the influenza vaccine.[37] However, vedolizumab treatment did result in diminished vaccine efficacy in response to an oral cholera vaccine[42] and may reduce efficacy of mucosally delivered vaccines, which may be relevant for some SARS-CoV-2 vaccines currently in development.[5] Because of the size of these IBD cohorts, the actual efficacy of vaccines to prevent disease even in patients who did not achieve threshold titres is not known.

The current vaccines in phase 2/3 studies for SARS-CoV-2 have achieved high levels of antibody responses (IgG) and T cell responses (mRNA, AdV) against the spike protein. It is not currently known what the threshold titres should be to achieve protection. While most current vaccines given to patients with IBD use recombinant proteins, several of the leading COVID-19 vaccines use mRNA-based technology (Pfizer, Moderna) or non-replicating adenoviral vectors expressing the spike protein (AstraZeneca/Oxford, J&J, Sinovac, Sputnik V). These vaccines are reported to elicit robust spike protein-specific antibody responses as well as CD4+ and CD8+T cell response.[43] Evidence suggests that both B and T cell-mediated immunity are needed for optimal protection against COVID-19.[31 44–46] There are also several inactivated (Sinopharm, Sinovac) and protein subunit vaccines (Novavax) either in phase 3 studies or recently authorised for use in several countries. In terms of immunogenicity, inactivated and vector-based vaccines seem to have the lowest immunogenicity, with mRNA and protein-based vaccines (with adjuvants) having higher antibody titres.[31]

Live attenuated as well as replication-competent viral vector vaccine candidates are in preclinical testing or entering phase 1/2. There is concern that replication-competent vaccines may cause illness in immunocompromised hosts. At present, vaccine studies have excluded immunocompromised adults, children and pregnant women, although some women became pregnant during the trials. Because the leading vaccine candidates elicit strong antibody responses, it is expected that patients with IBD will develop protective immunity from any of these vaccine strategies in spite of immune-modifying medications. The role of checking titres or providing booster doses for low titres has yet to be determined.

The panel recognises that both the development of the statements as well as the consensus responses were limited by the lack of available data and based on expert opinion, including guidance from a vaccinologist. Despite data gaps, the global IBD patient and professional communities need guidance in the face of such uncertainty. These consensus statements are meant to inform clinical decision-making but should not replace individualised management decisions. Real-world data from registries will help generate data on vaccine outcomes in patients with IBD to inform future recommendations.

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