ABSTRACT

The COVID-19 pandemic, caused by novel coronavirus SARS-CoV-2, has had an enormous impact on public health, medical systems, economies, and social conditions. The pandemic has also greatly influenced medical care systems for patients with inflammatory bowel disease (IBD). Establishment of a global registry system and accumulated experiences have led to consensus for IBD management under the COVID-19 pandemic. IBD itself does not pose an increased risk of SARS-CoV-2 infection or aggravation of COVID-19, and immune-control treatments other than systemic steroids, such as biologics, are unlikely to increase this risk. The importance of suppressing disease activity has not changed since before the pandemic. The effects of the COVID-19 pandemic on behavioral changes and psychological states among patients have various results and differ by country or region as well as between adult and pediatric patients. In future, information-sharing tools that can widely and correctly disseminate the views of experts will be very important. Vaccination remains in its infancy, but the impact of immunoregulatory therapy on antibody titers must be investigated. Information about COVID-19 is constantly being updated, and new and accurate medical care updates are needed. In Japan, the Japan COVID-19 Taskforce contributes to information dissemination, patient registries, and clinical research.

1. Introduction

Symptomatic infection with the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is denoted coronavirus disease 2019 (COVID-19). Asymptomatic infection with SARS-CoV-2 has also been identified. SARS-CoV-2 is an RNA virus and genomic sequencing has revealed that SARS-CoV-2 has approximately 79% homology with SARS coronavirus and approximately 50% homology with Middle East respiratory syndrome (MERS) coronavirus. SARS-CoV-2 binds to angiotensin-converting enzyme II (ACE2) receptor to infect the host, and intestinal tract organs have high expression of the ACE2 receptor [1].

Upper respiratory tract infection, fever, pneumonia, dysosmia, and dysgeusia are clinical symptoms of COVID-19. However, 17.6% of patients with COVID-19 report gastrointestinal symptoms, with 10.2% experiencing nausea or vomiting and 12.5% experiencing diarrhea. Viral RNA has also been detected in feces among 48.1% of patients with COVID-19; viral RNA has been detected in feces in 70.3% of these patients, even when no viral RNA is detected in respiratory samples [2]. One report puts forth the possibility of fecal-oral transmission of SARS-CoV-2 [3]. It remains unclear whether viral RNA detected in intestinal juice or feces is infectious. However, it has been reported that patients with gastrointestinal symptoms have more severe clinical symptoms and more cases of family onset [4].

The COVID-19 pandemic has had a major impact on clinical practice in the management of inflammatory bowel disease (IBD). Medical care began in a confused state at the start of the pandemic, but evidence has gradually been accumulating and a certain consensus has been formed. Herein, I would like to review the current status of IBD management during the COVID-19 pandemic.

2. Trends among patients with IBD and COVID-19 globally and in Japan

The Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD) (https://covidibd.org/) database is a global database of SARS-CoV-2 infections reported in patients with IBD. SECURE-IBD provides country-specific trends regarding the number
of patients with IBD who develop COVID-19. Furthermore, information is available in the database on the relationship between the treatment background of IBD and data of COVID-19 severity and mortality.

As of 10 April 2020, a total of 457 patients worldwide were registered in the SECURE-IBD database; this number reached 798 on May 1 and 1074 on May 15 in 2020. On 27 October 2020, the total was 2797 registered patients, with eight patients from Japan registered for the first time. On 26 January 2021 when the third epidemic wave began in Japan, the number of registered patients increased to 4735 globally, and the number of registered patients from Japan increased to 25. Since the establishment of SECURE-IBD, the highest number of registrations has overwhelmingly been from the United States (2207 patients as of 27 May 2021). Spain (which had previously been the country with the second highest number of registrations) dropped to third place with 437 patients, and Russia moved to second place with 461 registered patients. The number of newly registered patients in the United States has finally decreased, but this number is still increasing in Russia and the Netherlands. As of 27 May 2021, the number of patients with IBD who developed COVID-19 worldwide was 6176, including 53 Japanese patients.

3. Activities of the Japan IBD COVID-19 taskforce

The Japan IBD COVID-19 Taskforce is supported by the Japan Sciences Research Grant for Research on Intractable Diseases (Japanese Inflammatory Bowel Disease Research Group) affiliated with the Japan Ministry of Health, Labour and Welfare. The taskforce was formed in April 2020. The purpose of the Japan IBD COVID-19 Taskforce is to correctly and promptly convey information collected from experts to help clinical practitioners understand the vast volume of information that has become available since the start of the COVID-19 pandemic. The Japan IBD COVID-19 Taskforce analyzes SECURE-IBD data on a regular basis and communicates these data to Japanese practitioners. This activity is ongoing and the 18th taskforce report was released on May 30, 2021. Additionally, the Japan IBD COVID-19 Taskforce has published an expert consensus on IBD management [5], in addition to a wide range of other activities such as creating leaflets for practitioners and patients and disseminating information on vaccination. The Japan IBD COVID-19 Taskforce also leads three important clinical studies: 1) Japan COVID-19 Surveillance in Inflammatory Bowel Disease (J-COSMOS) registry for Japanese IBD patients with COVID-19, 2) the Japan COVID-19 Survey and Questionnaire in Inflammatory Bowel Disease (J-DESIRE) to investigate the changes in patient behavior under the COVID-19 pandemic, and 3) the Japan Prospective Multicenter Study for the Optimization of COVID-19 Vaccination According to the Immune Response and Safety Profile in Patients with IBD (J-COMBAT) to identify the influence of IBD treatment on the response to vaccination (Table 1).

4. General management of IBD during the COVID-19 pandemic

To date, there is no evidence that IBD itself increases the risk of SARS-CoV-2 infection. There is also no evidence that IBD is involved in the aggravation of COVID-19 symptoms [6,7]. The COVID-19 European Crohn’s and Colitis Organization (ECCO) Taskforce recommends that physicians treat patients with IBD as they did before the pandemic, and the taskforce states that controlling disease activity is important in terms of reducing patient visits. The importance of providing guidance regarding social distancing and introducing telemedicine (ECCO INFORMATIVE EXPERT INTERVIEWS, https://ecco-ibd.eu/publications/covid-19.html) is also highlighted by the ECCO Taskforce. The JAPAN IBD Taskforce emphasizes that having IBD is not a risk factor for COVID-19 and that the importance of controlling disease activity remains the same during the COVID-19 pandemic [5]. Notably, on the basis of SECURE-IBD data or data from Italy and China among patients with IBD as well as the general population, older patients are considered to be at increased risk of severe COVID-19 infection and death [8].

| Table 1. Ongoing projects by the JAPAN IBD COVID-19 Taskforce supported by the Japan Sciences Research Grant for Research on Intractable Diseases (Japanese Inflammatory Bowel Disease Research Group) affiliated with the Japan Ministry of Health, Labour and Welfare. |
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| J-COSMOS (Japan COVID-19 surveillance in inflammatory bowel disease) Registry construction for patients with patients and new SARS-Cov-2 infection in Japan. |
| J-DESIRE (Japan COVID-19 survey and questionnaire in inflammatory bowel disease) Multicenter prospective observational and questionnaire survey study on anxiety and behavioral changes among patients with inflammatory bowel disease in Japan caused by the coronavirus disease 2019 (COVID-19) pandemic. |
| J-COMBAT (Japan Prospective Multicenter Study for the Optimization of COVID-19 vaccination according to the immune response and safety profile in IBD patients) To investigate the impact of treatment for inflammatory bowel disease (IBD) on the efficacy and safety of vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) in patients with IBD. |
Endoscopy is indispensable in the management of IBD. Preventing infection involves the use of personal protective equipment (PPE) in upper gastrointestinal endoscopy, which is an aerosol-generating procedure. Furthermore, treatment of feces and intestinal juice is necessary in lower gastrointestinal endoscopy, even though the procedure does not generate aerosols. In IBD practice, endoscopy is performed for the purpose of diagnosis, evaluation of disease activity, and cancer monitoring. However, during the COVID-19 pandemic, routine endoscopy may be delayed for patients in stable condition, to reduce the infection risk to patients and practitioners. It is appropriate to suspend regular endoscopy and surveillance endoscopy. However, endoscopy that is necessary for diagnosis and treatment should be performed, with proper infection prevention measures [9].

During the pandemic, hospitalization and surgery should be limited to life-threatening situations as much as possible [7]. However, delays in hospitalization and surgery lead to increased disease activity and worse prognosis among patients with IBD. Appropriate hospitalization and surgery should continue under strict infection control guidelines, while aiming to minimize the length of hospital stay as much as possible [10].

5. Immunoregulatory treatment for IBD during the COVID-19 pandemic

Patients with IBD often receive immunoregulatory treatment such as with steroids, immunomodulators, and biologics. To date, drugs used to treat IBD are thought to have no effect on SARS-CoV-2 infectivity or aggravation of COVID-19, except for systemic high-dose steroids. According to analysis using the SECURE-IBD database, systemic corticosteroid administration has been associated with severe COVID-19 symptoms among patients with IBD; however, tumor necrosis factor (TNF) antagonists do not appear to be associated with severe COVID-19 (8). A retrospective study at two New York hospitals showed that in a comparison between patients with and without COVID-19, patients who had IBD and COVID-19 infection tended to have greater disease activity, and a higher proportion of these patients were receiving steroid treatment. There was no difference between the two groups for overall biologics [11]. Although vedolizumab (VED), an anti-α4β7 integrin antibody, is thought to have less impact on COVID-19, Khan et al. reported that VED-treated patients had a higher risk of SARS-CoV-2 infection than those treated with mesalazine monotherapy in a retrospective analysis using data from the Veterans Affairs Healthcare System [12].
Analysis using the SECURE-IBD database showed that in a small number of patients treated with tofacitinib, there was no apparent risk of SARS-CoV-2 infection or aggravation of COVID-19. Moreover, none of the patients treated with tofacitinib developed thrombosis [13]. According to these results, the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) has published recommendations for IBD treatment during the COVID-19 pandemic. According to the guidelines, only systemic corticosteroids are considered to increase the risks of SARS-CoV-2 infection and COVID-19 aggravation. For all biologics, immunomodulators, and tofacitinib, reducing or withdrawing these owing to COVID-19 risk is not recommended for patients who are stable under these treatments [14].

On the basis of the limited evidence and expert opinion to date, this author suggests the following. Systemic steroid treatment is not necessarily contraindicated and should be started with a sufficient initial dose among patients in need of treatment. Since before the pandemic, in principle, it has been recommended that the effect of steroids should be judged within 1 week after administration and drugs should be tapered until the patient is steroid-free. It is of utmost importance to adhere to this principle and not continue to use steroids indiscriminately. Older people are generally at high risk of steroid-induced infections and thrombosis, and also have a high risk of COVID-19 aggravation and death owing to this disease. Therefore, as the initial treatment in older patients with IBD who have moderate to severe disease activity, the strategy of avoiding systemic steroids and considering the use of biologics seems reasonable. This author also believes that there is no need to change the use of biologics and tofacitinib, even under the COVID-19 pandemic (Table 2). If a patient treated with these drugs becomes infected with SARS-CoV-2, there is no urgent need to discontinue treatment of IBD. It is possible to balance the treatment of both COVID-19 and IBD, always in consultation with infectious disease experts.

6. Influence of the COVID-19 pandemic on patient behaviors

The COVID-19 pandemic may cause various behavioral changes in patients such as self-interruption of treatment, avoiding hospital visits, and decreased medication adherence. Furthermore, mental stress owing to the COVID-19 pandemic may cause insomnia and depression.

A cross-sectional anonymous survey of patients with IBD (N=415) and control participants (N=116) in Germany showed that patients with IBD were more fearful of contracting SARS-CoV-2 infection than controls, especially those receiving immunoregulatory therapy. Patients with IBD tended to refrain from going outside the home and were more rigorous about hand washing. Media, such as television and the Internet, were the main sources of information about COVID-19 among patients. However, 17.3% of patients cited doctors as an important source of information [15]. In a survey of 228 patients with IBD in the United Kingdom (UK), 89% said they were concerned about the impact of COVID-19 on their health. In that study, access to a specialized source of information on IBD was associated with alleviating patients’ concerns whereas Internet searches and social media had limited effectiveness. Patients tended to think that their risk of infection was higher than the estimated risk, especially patients receiving immunosuppressive treatment [16]. The results of an online survey in Australia found that 98% of patients were concerned about the impact of COVID-19 and 43% felt that their risk of COVID-19 infection was above average. Sixty-two percent of patients reported concerns about their risk of COVID-19 because they were taking medication for IBD, and 11% discontinued their medications because of COVID-19. In this survey, patients believed that all drugs increased the risk of COVID-19 susceptibility and severity. In terms of clinical management, 45% preferred telemedicine and 16% preferred face-to-face clinical visits [17]. Although the spread of SARS-CoV-2 infection was slower in Australia than in the UK and Germany, the fears and concerns felt by patients may be independent of the actual infection situation. A study conducted in Portugal found that COVID-19 did not affect medication adherence but increased psychological anxiety in patients with IBD [18].

The impact of COVID-19 on the management of pediatric patients with IBD also varies among countries. An anonymous cross-sectional survey of pediatric patients with IBD in Germany showed that these patients and their parents appeared to be coping appropriately, even during the COVID-19 pandemic. Medication adherence and hand washing were appropriate, even among pediatric patients, and social distancing was respected, such as by refraining from going outside the home. Interestingly, parents considered school attendance to increase the risk of infection more than their children. In that survey, pediatric patients preferred face-to-face care via telemedicine [19]. In a telephone survey conducted by a tertiary medical institution in Israel, many pediatric patients were afraid of infection because of having IBD or feared...
aggravation of COVID-19 because of taking medication for IBD. Most patients followed public health guidance and nearly half took additional precautions, such as avoiding school or staying at home. There were also concerns about visiting a regular clinic; however, the rate of visiting an emergency room was high with IBD relapse. In this study, treatment for IBD was changed or discontinued in seven patients with IBD [20].

According to the results of surveys conducted in the above countries, the effects of COVID-19 on changes in patient behavior vary. The magnitude of the impact does not necessarily correlate with the spread of infection but rather may be influenced by social media coverage and sources of information. In particular, patients and their families do not always obtain information from reputable public health sources, and it is conceivable that the influence of television and the Internet is strong.

Thus, there is strong concern about COVID-19 among patients with IBD, especially patients undergoing immunoregulatory therapy. However, the manner of obtaining information and usefulness of IBD-specific information tools may vary by country or region. In Japan, a large-scale multi-center patient survey (J-DESIRE; UMIN000041191) has been conducted by the JAPAN IBD COVID-19 Taskforce since June 2020. J-DESIRE is a nationwide survey of more than 1000 patients, and it is expected to clarify the behavioral changes brought about owing to the COVID-19 pandemic among Japanese patients with IBD and to identify differences by region, age group, and according to the second and third waves.

7. Vaccination against SARS-CoV-2 infection among patients with IBD

The Government of Japan has agreed to purchase vaccines from Pfizer, Moderna, and AstraZeneca. Pfizer and Moderna manufacture mRNA vaccines, and AstraZeneca manufactures a viral vector vaccine. SARS-CoV-2 invades human cells via the spike protein expressed on the surface of the virus. All of the above vaccines induce the synthesis of spike protein in human cells. The mRNA vaccines transport SARS-CoV-2 spike protein mRNA into human cells encased in a lipid nanoparticle. Adenovirus vector vaccines incorporate DNA encoding the SARS-CoV-2 spike protein. Adenovirus vectors infect human cells and synthesize spike protein within the cells. Because the adenovirus vector theoretically lacks the ability to replicate, it is thought not to multiply in the human body. These vaccine development methods have the advantage that vaccines can be produced rapidly once the genetic information of the virus is known and they are also suitable for rapid vaccine development against variants of SARS-CoV-2. Additionally, it is thought that the effectiveness of these vaccines is enhanced because they can induce strong T-cell immunity. Nevertheless, it is the first time that an mRNA vaccine has been administered to humans. Adenovirus vectors are also used in Ebola virus vaccines and cancer vaccines, but their use to date has been limited. It should therefore be noted that there are few data on the safety of these vaccines, especially regarding long-term safety.

Data on both the safety and immunogenicity of two types of mRNA vaccine have been reported: BNT162b1, which encodes a secreted trimerized SARS-CoV-2 receptor-binding domain, and BNT162b2, which encodes a membrane-anchored SARS-CoV-2 full-length spike protein. Both types of vaccine elicit dose-dependent SARS-CoV-2 neutralizing antibody geometric mean titers. BNT162b2 shows a lower incidence and severity of post-inoculation systemic reactions than BNT162b1 [21]. The efficacy and safety of BNT162b2 have been demonstrated in a multi-national, placebo-controlled, observer-blinded, pivotal efficacy trial. A two-dose regimen of BNT162b2 (BioNTech and Pfizer) conferred 95% protection against COVID-19 among individuals 16 years of age or older. Safety over a median of 2 months was similar to that of other viral vaccines [22].

Regarding SARS-CoV-2 vaccination in patients with IBD, only limited evidence has been reported. The IOIBD has published a consensus statement, using a modified Delphi method. The consensus statement recommends, with a high degree of agreement, that (1) vaccination does not affect the disease activity of IBD itself; (2) even patients undergoing immune-modifying therapies can safely receive all non-live vaccines; (3) because patients with IBD have the same risk of infection with SARS-CoV-2 as the general population, these patients should be vaccinated against SARS-CoV-2 [23]. Of course, pros and cons can be considered for SARS-CoV-2 vaccination in patients with IBD [24]. A high protection rate can be expected, with a high safety profile, although this evidence is based on short-term data; currently, long-term safety data are insufficient. The effect of vaccination on the clinical course of IBD is unknown. The influence of immunoregulatory drugs on the efficacy of these vaccines is unknown. Furthermore, the rapid expansion of mutant SARS-CoV-2 strains that has occurred during 2021 must be recognized, and there is concern regarding whether the vaccines have the same efficacy against mutant strains as against conventional strains. On 15 February 2021, the Japan IBD COVID-19
Taskforce issued a statement regarding SARS-CoV-2 vaccination for patients with IBD recommending vaccination in consideration of individual risks and benefits (http://www.ibdjapan.org/task/pdf/qa01.pdf).

The British Society of Gastroenterology and the Inflammatory Bowel Disease Clinical Research Group support SARS-CoV-2 vaccination for patients with IBD, considering that the risks of vaccination in these patients are anticipated to be very low. Instead, there is a theoretical concern about reduced vaccine responsiveness in patients receiving immunomodulatory therapy [25]. It has been reported that immunosuppressive drugs, including biologics and immunomodulators, could reduce the effectiveness of vaccines against other infectious diseases. Infliximab (IFX), an anti-TNF-α monoclonal antibody, reduced the immune response of vaccination against hepatitis B virus [26], pneumococcus [27], and influenza [28,29]. Insufficient data have been collected for new biologics and Janus kinase inhibitors (JAK). Furthermore, the effect of immunomodulatory drugs on vaccines may differ depending on the underlying immune disease (e.g., psoriasis, rheumatoid arthritis, IBD), the presence or absence of concomitant use of immunomodulators, and the type of vaccine. For example, tofacitinib, a JAK inhibitor, diminishes the effect of pneumococcal vaccination but does not affect influenza vaccination [30]. There are insufficient data on how immunomodulatory therapy for IBD influences the effectiveness of SARS-CoV-2 vaccines. In patients with SARS-CoV-2 infection confirmed by PCR, the obtained antibody titers are lower in patients treated with IFX than in those treated with VED [31]. In a UK-wide, multi-center, prospective observational cohort study, the impact of IFX and VED on anti-SARS-CoV-2 antibodies 3–10 weeks after primary vaccination was investigated. Two kinds of vaccines were analyzed: BNT162b2 and ChAdOx1 nCoV-19. In that study, antibody titers were lower in the IFX-treated group than in the VED-treated group for both BNT162b2 and ChAdOx1 nCoV-19 vaccines. Seroconversion rates after a single dose of either vaccine were higher in patients with prior SARS-CoV-2 infection. Importantly, for BNT162b2 vaccines and in the IFX group, the antibody titer was sufficiently elevated after the second inoculation. These results suggest the importance of two doses of vaccine administered at appropriate intervals, especially in patients with IBD receiving IFX treatment [32]. Responses to the vaccine may vary by ethnicity, and additional data from Japanese patients with IBD are needed. The J-COMBAT trial has begun, with support from the Japan Research Grant for Research on Intractable Diseases (Japanese Inflammatory Bowel Disease Research Group) affiliated with the Japan Ministry of Health, Labour and Welfare and the Japanese Society for Inflammatory Bowel Disease.

8. Conclusions

Although sufficient evidence has not yet been accumulated, many retrospective studies have shown that IBD itself does not increase the risk of SARS-CoV-2 infection or aggravation of COVID-19. With the exception of systemic steroids, no treatment has been identified that clearly increases the risk of COVID-19 infection or aggravation. However, it is important to control disease activity, provide guidance on social distancing, use proper hand hygiene, and to thoroughly prevent general infections such as by wearing a face mask. The effects of immunomodulatory therapy on vaccine efficacy are not yet fully understood, but vaccination against SARS-CoV-2 infection should be recommended in patients with IBD, even if antibody titers may be slightly decreased. However, the views expressed here are according to the currently available evidence, which may change with future data collection.

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