Management of Inflammatory Bowel Disease during Coronavirus Disease 2019 Pandemic

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Abstract

Inflammatory bowel disease (IBD) is a chronic inflammation consisted of ulcerative colitis and Crohn's disease. IBD is a global disease with heavy economic burden. Coronavirus disease-2019 (COVID-19) is a novel disease which spread rapidly and becomes a pandemic. This pandemic situation affects the management of IBD. Severe acute respiratory syndrome coronavirus-2 as the etiology of COVID-19 requires angiotensin-converting enzyme (ACE2) as its receptor. ACE2 is found to be abundant in the gastrointestinal tract, particularly the small intestine and colon. This causes the presence of gastrointestinal symptoms in COVID-19 and interacts with gastrointestinal diseases including IBD. The diagnosis of IBD in patients with COVID-19 is similar with general population with precautions regarding endoscopic procedure. IBD does not increase the risk for contracting COVID-19 nor worsen the outcome of COVID-19. The first step in managing patients with IBD during pandemic is by implicating strict health protocol. There is still a controversy regarding surgery for IBD during pandemic. Medications for IBD are safe during pandemic except systemic corticosteroids. IBD patients without COVID-19 should continue their medications until the goal of disease remission is achieved. If asymptomatic COVID-19 is present, corticosteroid dose should be lowered, tapered, and stopped if available. Anti-tumor necrosis factor (TNF) administration should be postponed for 2 weeks. If COVID-19 manifestations exist, systemic corticosteroid, thiopurine, methotrexate, and anti-TNF should be discontinued. Supporting treatment for COVID-19 can be administered safely. In case of relapsing, the treatment of IBD must be started with the limitation of systemic corticosteroid.

Introduction

Inflammatory bowel disease (IBD) is a condition characterized by uncontrolled immune-mediated inflammatory response to environmental and internal triggers in the alimentary tract [1]. IBD is a chronic disease consisted of two subtypes: ulcerative colitis (UC) and Crohn's disease (CD) [1], [2], [3]. UC was firstly identified in 1875 by Wilks and Moxon, whereas CD was introduced in 1932 by Burrill Crohn, Leon Ginzburg, and Gordon Oppenheimer [1], [2], [4]. In the 1950s, the concept of immune response in IBD was proposed since the symptoms ameliorates with the administration of steroid [1]. IBD is usually labeled as a disease of white people or the Western world [1], [2], [4]. Europe has the highest prevalence of IBD in the world [2], [5], [6]. Even though IBD does not cause significant mortality, it carries heavy economic burden and disrupt patient's quality of life. This is the result of hospitalization, surgery, ambulatory care, and medications. Annual direct healthcare cost of IBD in Europe ranges from €4.6 to 5.6 billion annually [2]. Economic burden from IBD in the USA exceeds 6 billion USD in 2004 [2], [3]. Recently, IBD has spread to all regions in the world and become a global disease [2].

Coronavirus disease-2019 (COVID-19) is a new emerging disease caused by a virus known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [5], [6], [7], [8], [9], [10], [11], [12]. The etiology of the disease is a positive-sense single-stranded ribonucleic acid (RNA) betacoronavirus. The virus is a member of *Coronaviridae* family [13], [14]. It is originally descended from bat and infecting human through intermediate reservoirs such as civet [15]. The SARS-CoV-2 is round in shape with approximate diameter of 60–140 nm. In the past, coronaviruses have caused two disease outbreaks, which were SARS and the Middle East respiratory syndrome [7]. COVID-19 itself was firstly reported as an atypical pneumonia in Wuhan, China in December 2019. The disease spread rapidly throughout the world and was declared as a pandemic on March 11, 2020, by the World Health Organization (WHO) [16], [17]. As per May 20, 2021, total cases of confirmed COVID-19 are 163,869,893 with 3,398,302 deaths. Americas and Europe are regions with the highest confirmed case number [18].

As a pandemic, COVID-19 affects every aspect of life particularly subjects with chronic diseases such as IBD. In this review, we will discuss about management of IBD in the COVID-19 pandemic from risk of infection, prevention of disease, and management of coexisting IBD and COVID-19. Literatures in this review were gathered from Pubmed

database using keywords COVID-19, "COVID-19", "IBD", "UC", "CD", "management", and "treatment". Literatures in English and published between 2020 and 2021 were included.

Epidemiology of IBD

The epidemiology of IBD is changing recently. In the 21st century, the incidence of IBD is increasing all over the world [1], [3], [4]. This is the result of industrialization and westernization. Europe holds the highest prevalence of IBD with 505 per 100,000 UC cases in Norway and 322 per 100,000 CD cases in Germany [4]. However, the incidence of IBD in western countries is stable and even decreasing. The incidence of IBD is rising in newly industrialized countries in Africa, Asia, and South America particularly Brazil, India, China, and Taiwan [1], [3], [4]. The prevalence of IBD is expected to be 660 per 100,000 population in 2025 [2]. The peak onset of the disease is in adolescence and early adulthood [3]. For CD, the peak onset is between 20 and 30 years, whereas for UC is between 30 and 40 years. Gender predilection is comparable with slight male predominance [1].

Risk Factors and Pathogenesis of IBD

Some unhealthy lifestyles have been associated with IBD such as smoking, reduced fiber intake, less or absent breastfeeding, sedentary occupation, and pollution exposure. Improvement in sanitation and socioeconomic status also increases the risk of IBD [1], [2]. Oral contraceptives, hormonal replacement therapy, non-steroidal anti-inflammatory drug, and antibiotic utilization may alter intestinal microorganism balance and increase the risk of IBD [1]. Genetic factor also increases the susceptibility of IBD incidence particularly regarding NOD2, IL23R, and ATG16L1 genes [2], [3], [19]. However, genetic factors alone can not trigger the disease without the presence of environmental factors [2], [3]. The antigens enter host's alimentary tract and being processed and presented by antigen-presenting cells to T-helper cells. This process induces inflammatory response and releases pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor (TNF)-α. In subjects with genetic susceptibility to IBD, the inflammation is galvanized and occurs chronically. In addition, anti-inflammatory cytokines such as IL-2, IL-10, TNF-β, and transforming growth factor-β are also downregulated [1].

Pathogenesis of COVID-19 and its Relationship with the Gastrointestinal Tract

In order to enter host's cell, SARS-CoV-2 needs angiotensin-converting enzyme (ACE) 2 as the receptor [5], [6], [7], [17]. The spike glycoprotein (S protein) in the surface of the virus binds with ACE2 and starts membrane fusion. The process is also facilitated by transmembrane serine protease (TMPRSS)2. After the fusion, viral RNA will be released into the host cell and translated into viral proteins by cell's ribosome. The proteins, as the parts of virus, together with viral RNA are assembled to form new viruses. Newly formed viruses will be released from host cell via exocytosis, leaving damage and death to host cell damage. They will invade new cells and create a vicious cycle [7], [20], [21]. Besides damaging and killing host cells, viral invasion also down-regulates the ACE2 and stimulates renin-angiotensin-aldosterone system activation which promotes organ-specific injury [22]. Gastrointestinal symptoms such as anorexia, nausea, vomiting, ageusia, diarrhea, and abdominal pain have been reported in patients with COVID-19. Viable virus is also excreted in stool, suggesting a possible feco-oral transmission other than aerosol. The involvement of the gastrointestinal tract is suspected from the fact that ACE2 and TMPRSS2 are abundant in the small intestine and colon [14], [23], [24], [25]. Diminished ACE2 causes loss of intestinal inflammatory control. Enterocytes damage is also occurred, increasing the permeability of the gastrointestinal tract and permitting translocation of luminal antigens [14], [26], [27].

Management of IBD during COVID-19 Pandemic

The diagnosis of IBD is not different between general population and subjects with COVID-19. The symptoms are similar with diarrhea as the most prominent one [28]. Endoscopic procedures should be done prudently during pandemic since the risk of transmission is high. Thorough screening for COVID-19 should be done before the procedure [29], [30]. Fecal calprotectin and capsule endoscopy may be used as an alternative from endoscopy to detect disease flare [31]. The presence of new-onset gastrointestinal symptom in patient with remission state should raise suspicion for COVID-19 thus need further evaluation [29]. Serological markers such as anti-Saccharomyces cerevisiae antibody and anti-neutrophil cytoplasmic autoantibody can aid in the diagnosis of IBD. The disease is classified based on the Montreal classification [19]. A systematic

review of several studies showed that approximately 800 patients suffer from coexisting COVID-19 and IBD with a case fatality rate ranged from 0% to 20% [31]. Guerra _et al._ reported a prevalence rate of COVID-19 in IBD patients in Madrid as high as 10.2% [28]. Other study reported a total of 525 cases with a 3% case fatality rate [32]. Worse outcome of COVID-19 in IBD patients is associated with older age, UC compared to CD, presence of comorbidity, and male gender [28], [30], [31], [32], [33]. There is no relationship between worse outcome of COVID-19 and IBD directly [29].

Inflammation in IBD is suspected to increase the expression of ACE2 in patients' intestine [25], [28], [29], [31]. However, this hypothesis is proven wrong. The expression of ACE2 in patient with UC is lower compared to healthy control and is not significantly higher in patient with CD. Patients with IBD do not have higher risk for contracting COVID-19 [25], [31]. Verstockt _et al._ reported different findings. In their study, the expression of ACE2 was elevated in the colon of patients with IBD compared to healthy controls. Chronic inflammation contributed to the elevation of ACE2 expression, but this study also proved that patients with IBD have similar odds for COVID-19 and its related complication [33].

The first step to manage patients with IBD during this pandemic is by implicating strict health protocol, similar with other healthy patients [29], [30], [34], [35]. Application of health protocol must be applied in all IBD patients despite their COVID-19 status [29]. The strictest health protocol must be applied in patients with comorbidity, advanced age, and active disease even with a high dose of medications [30]. Routine follow-up may be minimized or done virtually. Direct visits can be done with strict screening and health protocol implementation. The safety of healthcare staffs should also be put in concern. A set of level 2 personal protective device should be used in managing these patients [29], [30], [34]. Regarding surgical approach in managing IBD, postponing scheduled surgery is potential to increase emergency presentation and complications. Therefore, surgery should still be performed by following advised protocol for COVID-19 [34]. In contrast, other literature suggested postponing elective surgeries as possible [30].

In general, all IBD patients who is not suffering from COVID-19 should continue his or her medication until the goal of disease remission is achieved [29], [30], [35]. All medication regimens must be administered completely to prevent relapse since relapsing IBD requires more aggressive management such as hospitalization and possesses worse outcomes [29], [30], [34]. Several drugs for IBD can interference immune system activation [28], [31] such as corticosteroid, thiopurine, infliximab, and methotrexate [28], [33]. The impact of anti-TNF is reported to be insignificant in increasing the risk for contracting COVID-19. However, patients in the study have had been vaccinated against influenza [34]. This is supported by a systematic review by Macaluso and Orlando. They concluded that systemic corticosteroid, but not immunomodulators and biologic agents, is associated with worse prognosis [31]. Another study confirmed this result. The study concluded that systemic corticosteroid increases the risk for COVID-19 in patients with IBD as high as 6.9 times [32]. The utilization of anti-inflammatory such as sulfasalazine is still unclear and needs further investigation [29], [30], [31], [33]. Only a study reported sulfasalazine as a risk factor for COVID-19 with an odds ratio of 3.1 [32]. Anti-TNF even may provide protective effect in the state of COVID-19 cytokine storm [29], [31], [32]. The protective effect may be elicited from its restoring effect for dysregulated ACE2 expression in the colon [33]. A study from Madrid failed to prove that immunosuppression from IBD medications can aggravate the COVID-19 course of disease [28]. Therefore, administration of medications via intravenous route can be continued by separating patients with COVID-19 from negative ones and by still implementing strict health protocol. However, switching from oral to intravenous drug is not recommended for stable IBD patients during pandemic [29], [30].

Patients with coexisting IBD and COVID-19 should be managed according to the disease severity of COVID-19. For IBD patients with asymptomatic COVID-19, several steps should be taken. Isolation is mandatory by applying virtual visits or direct visits with implementation of health protocol [29], [30], [34]. Lower dose of corticosteroid and switching between corticosteroids should be done. Lower dose of prednisone and switching to budesonide is advised. Rapid tapering of corticosteroids should be considered if available. Sudden cessation may lead to recurrent flare [30]. Thiopurine and methotrexate should be discontinued temporarily [29], [30]. Anti-TNF agent administration is better postponed for 2 weeks after the diagnosis of COVID-19 and absence of any symptoms [29]. Antibody anti-SARS-CoV-2 testing needs to be done before initiating anti-TNF [29], [35]. The presence of immunoglobulin G anti-SARS-CoV-2 is the recommended time to start anti-TNF [33], [34].

If the patient has mild COVID-19 severity, the dose of corticosteroid should be tapered off or switched to budesonide [29], [30]. Topical medications can be continued but not with thioputine, methotrexate, and tofacitinib. Similar with IBD patients with asymptomatic COVID-19, biologic agents should be postponed up to 2 weeks after COVID-19 diagnosis and absence of symptoms. Similar with patients with mild COVID-19 severity, those with moderate to severe COVID-19 severity should have systemic corticosteroid, thiopurine, methotrexate, and anti-TNF be discontinued. Supportive treatments for symptoms are safe to be administered. Management is focused in overcoming COVID-19 such as life support, anti-inflammatory, anti-cytokine, and anti-viral. Management for IBD can be administered after

COVID-19 has been resolved [29]. Furthermore, maintaining IBD remission with steroid-sparing agents could be beneficial in the present time [31], [32]. Summary of recommendation for management of IBD patients during pandemic can be seen in Table 1.

Table 1: Recommendations for management of IBD patients during COVID-19 pandemic

Citation number	Authors	Publication year	Main findings
29	Rubin *et al*.	2020	IBD patients without COVID-19 should continue their medications
			IBD patients with asymptomatic, mild, moderate, and severe COVID-19 should have lower dose of corticosteroid and postponed thiopurine, methotrexate, and tofacitinib for 2 weeks
			Focus on COVID-19 management should be applied for IBD patients with moderate and severe COVID-19 severity
30	Kennedy *et al*.	2020	Health protocol should be strictly followed by all IBD patients
			Medications should be continued during a pandemic if COVID-19 is absent
			The dose of corticosteroid should be lowered or switched to budesonide
			Biologic agents have no negative effect toward COVID-19
31	Macaluso and Orlando	2020	Systemic steroid is associated with worse prognosis of COVID-19
			Immunomodulators or biologic agents is not associated with poor COVID-19 outcome
32	Brenner *et al*.	2020	Systemic corticosteroid is a risk factor for severe COVID-19 among patients with IBD
34	Danese *et al*	2020	Continue all treatment including immunologic and biologic agents for patients with IBD without COVID-19 during pandemic
			Steroid withdrawing is advised if possible
35	Zingone and Savarino	2020	Viral screening including for SAS-CoV-2 is advised before starting administration of biologic agents

COVID-19: Coronavirus disease-2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; IBD: Inflammatory bowel disease.

Patients with IBD relapse without COVID-19 should undergo reassessment to determine the extent of relapse. Treat mild disease activity with topical therapies, oral budesonide, and symptomatic therapy [30]. If the disease activity is moderate to severe, systemic therapies must be started with avoiding thiopurines, methotrexate, and tofacitinib if available. However, in case of relapsing IBD and COVID-19, the treatment of IBD must be administered without hesitation but still with the limitation of systemic corticosteroid and in accordance with the severity of COVID-19 as described before [29]. To date, there is insufficient data supporting the cessation of immunomodulator and biologic agents in IBD patients during pandemic [33], [34]. Continuing IBD treatment is advised since the risk of active disease is more dangerous compared to the risk for COVID-19 due to immunosuppression [28], [29], [32]. Minimizing corticosteroid utilization, avoiding initial immunomodulator usage, and administering biologic therapy via subcutaneous route can be applied to decrease the risk for COVID-19 [28], [29], [30], [35]. Further studies are mandatory to discover new therapies which benefit both IBD and COVID-19 management [29].

Conclusion

Standard heath protocol for COVID-19 prevention is mandatory for all patients with IBD during pandemic. Patients with IBD do not have higher risk for COVID-19 compared to healthy population. All patients with IBD should continue their medications since maintaining disease remission is very important. Patients with coexisting IBD and asymptomatic COVID-19 should lower corticosteroid dose and postpone anti-TNF administration for 2 weeks. For those with IBD and symptomatic COVID-19, systemic corticosteroid, thiopurine, methotrexate, and anti-TNF should be avoided until active disease remission. Careful assessment of each disease's severity is important to prioritize the management.

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