

Management of Inflammatory Bowel Disease during COVID-19 Pandemic. A Practical Review

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ABSTRACT

From mid-December of 2019 a newly diagnosed Corona virus with a highly human to human transmission rate was discovered in china which rapidly involved many countries and became pandemic. Although most infected cases are mild but this virus can cause severe lung injury which lead to severe mortality and morbidity. The mortality rate of this virus is high in immunosuppressed patient or with previous medical disorder. Many Inflammatory bowel disease patient are using immunosuppressive or immunomodulating agents which has raised the concern of severe disease in these patients.

In this review we are going to discuss about treatment challenges in these patients.

Keywords: Inflammatory Bowel Disease, COVID-19, Pandemic

please cite this paper as:

Aletaha N, Taher M, Ebrahimi Daryani N, Miroliaee A, Alborzi Avanaki F. Management of Inflammatory Bowel Disease during COVID-19 Pandemic. A Practical Review. *Govaresh* 2020;25:44-50.

INTRODUCTION

A 40 year old man have come to our hospital (Imam Khomeini Hospital Complex affiliated to Tehran University of medical sciences) due to recent onset of fever, coughs and chest tightness. His symptoms has develop from five days ago which was progressive during these days. He has been diagnosed as ileal Crohn's disease from two months ago and was treated with 20 mg prednisolone, 3 gram of mesalamin and 100 mg of azathioprine.

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Received: 15 Mar. 2020

Edited: 24 Mar. 2020

Accepted: 25 Mar. 2020

Five days before the initiation of his symptoms 160 mg adalimumab was started for him. He has taken his first dose of adalimumab during the pandemic of COVID -19.

Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus, that was identified at the end of 2019 (named COVID-19), now named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the world health organization (WHO). This RNA virus causes an illness that clinically have ranged from mild to severe disease, and even death (1).

This rapidly spreading infection commonly causes fever, chills, myalgia, cough, dyspnea, sore throat, which eventually can cause acute respiratory failure and even death. Other than respiratory symptoms, some patient experience gastrointestinal symptoms like nausea, vomiting, diarrhea and abdominal pain. Interestingly the patient with gastrointestinal symptoms had more severe course of the disease (2).

Inflammatory bowel diseases (IBD) is comprised of two major disorders: ulcerative colitis (UC) and

Crohn's disease (CD). The prevalence of this disease is increasing in Iranian population. In addition the new IBD patients have more severe disease compare to the past (3).

Patients with IBD are often taking biologics and immunosuppressant medications. Therefore, there is concern about the increasing risk of infection in IBD patients and whether these patients are more susceptible to SARS-CoV-2 (4).

In a preliminary follow up of 132 patients from 1120 patient of our institute which has been done via social network, 19% had mild symptoms of COVID-19, 5 % had been admitted in the hospital and one case was admitted in the ICU and no death was reported up to now.

Many issues such as possibility of IBD flare, continuing IBD medications during this pandemic and management of IBD patient who develop COVID-19 infection are of significant importance for both physicians and patients.

In this practical review we are going to discuss about these issues with regards to recent data and guidelines.

Are patients with inflammatory bowel disease (IBD) more susceptible to coronavirus 2 infection?

As we know, Coronaviruses bind to their target cells through angiotensin-converting enzyme 2 (ACE2). ACE 2 is expressed in many tissues. Epithelial cells of the lung, intestine, kidney, blood vessels, heart, colon and small intestine including terminal ileum and duodenum. Compared with other organs, the concentration of ACE2 is higher in terminal ileum & colon (5).

Some studies showed that up to 50% of fecal samples from patients with SARS-CoV-2 were positive (4,6,7). Therefore fecal-oral route may be a role in infection spreading.

Despite higher intestinal ACE2 concentration, based on previous report in china, there is no evidence to suggest that Covid-19 occurs more frequently in IBD patients than in the general population. Because there are two forms of ACE2 in lung and intestine which had different function. Full-length ACE2 in lung acts as a receptor for SARS-CoV-2 and structural transmembrane domain and soluble form of ACE2 acts as a competitive that prevents binding of the

viral particle to the surface. This form of ACE2 is up-regulated in IBD patients and probably restrict SARS-CoV-2 infection (4).

The available data proposes that IBD patients are not more susceptible to Covid-19 (4,8).

Is there increasing risk of COVID-19 in IBD patients on immunomodulation/immunosuppressive medications?

IBD patient taking immunosuppressive or immunomodulator medicines may be at a higher risk of a more severe infection or complications from the virus if they are infected (9).

The impact of immunosuppression on the severity of COVID-19 disease remains unclear. Although data from immunosuppressed patients and risk and severity of infection by SARS- COV2 in this situation is negligible, based on the rare published data, immunosuppressed patients do not appear to be at higher risk of complications. On the other hand, some experts considered the role of cytokine storm in severity of COVID-19 and immunosuppressive drugs may prevent Covid19-driven pneumonia. In addition, those patients over 60 years and/or with comorbidities such as coronary heart disease, hypertension, diabetes mellitus, lung disease, cerebrovascular diseases, who have been reported to have a greater risk for Covid-19 and severe complication (4,10). However, there is evidence that high susceptibility of smoker people to COVID-19 (11).

Tobacco increases the gene expression of the angiotensin converting enzyme, the binding receptor for this virus.

Does COVID-19 cause IBD flare up?

Although some patients infected by SARS_COV2 presented with gastrointestinal symptoms including diarrhea, nausea and some symptoms mimic IBD flares symptoms (12,13).

At the moment, no data have been published that SARS-CoV-2 stimulate IBD flare up (4,8,10). One expert from European Crohn's and Colitis Organization (ECCO) said: "However, this situation would not be unexpected, as even without causing gastrointestinal infection, H1N1v was associated with mild flares during the first week of viral infection, mostly in ulcerative colitis patients" (10,14).

IBD MEDICATIONS

Should IBD patients stop taking 5-ASAs during COVID-19 pandemic?

5-ASAs are not in the same group of medicines as the non-steroidal anti-inflammatory drugs (NSAIDs), like ibuprofen. Drugs like mesalamine and sulfasalazine work to inhibit inflammation in the gut. They may be given orally or topically (via enemas or suppositories), but either way is not believed to raise the risk of infections.

Should IBD patients stop taking their immunomodulation medicine, without COVID-19 infection?

According to the current evidence, IBD patients on immunomodulatory drugs including thiopurines (azathioprine, 6-mercaptopurine), cyclosporine, and methotrexate and the JAK-2 inhibitor tofacitinib, should not stop taking their drugs (10,15). If IBD patients stop taking their medicine, they may have a flare-up and increase their visits to the doctor's office and more hospitalization which will increase their risk of exposure to virus. (cases up to three months) to leave the body (16).

Do patients with COVID-19 who are on steroid therapy have a worse prognosis?

3. Steroids consumption during COVID-19 is controversial. Some experts propose to avoid steroids during COVID-19, because they believe corticosteroids therapy, has increased mortality and secondary infection rates in influenza infections and impaired clearance of SARS CoV and MERS-CoV, and causes complications in survivors (12,17). But other experts advise low-dose, short-term steroids (≤ 0.5 -1 mg/kg for 7 days) in acute respiratory distress syndrome (ARDS), and reported low dose short term steroid are not associated with worse prognosis even in patients with critical COVID-19 pneumonia (17,18).

IBD and steroid medications:

- Steroid without systemic effect (budesonide, budesonide MMX) and locally acting steroids (steroid enemas) can be continued.
- If patients are taking steroids for IBD treatment,

never stop them suddenly but if patients are in remission phase and are taking prednisolone ≥ 20 mg daily, tapering (10 mg/week) should be considered where possible.

- Similarly, IBD patients should not start steroids on their own if they have flare symptoms and should consult with their doctor (15,16).
- Corticosteroids can be used with caution if needed to treat IBD flares (4).

Should IBD patients stop their ant TNF drugs?

Although it is recommended to all IBD patients to be vaccinated against seasonal flu, the efficacy of vaccine is not complete and most of them are non-immune (19). Considering this low threshold of immunity, there have been low mortality reported even with seasonal flu (20).

A recent study by Norsa et al. showed that there was no case of documented COVID-19 in 539 IBD patients (21). Based on these limited studies there is no increased risk of COVID-19 infection in IBD patients even those who are using immunosuppressive drugs (4,8).

- There is no strong recommendation for patient using anti TNF α medications to stop or reduce their drugs (22).
- It is recommended to take the infusion in hospitals with low disease rate of COVID-19 patients
- If the patient had been in complete remission for more than one year, increasing the Anti TNF infusion interval may be considered (23).
- There is no recommendation to change the Intravenous drugs to drugs which can be administered at home due to increased risk of flare up in some studies.

Can we initiate Anti TNF drugs and other immune suppressive drugs in this pandemic?

In case of severe colitis, it is appropriate to investigate for other causes of disease flare. Evaluation for *Clostridium difficile*, ova, cysts, parasite and *CMV* colitis is recommended. If all causes of IBD flare were negative, then it is logical to evaluate for COVID-19 disease as a cause of flare-up.

Due to high transmission rate of this virus and risk of severe disease among involved patients, it is reasonable not to initiate Anti TNF drugs at this pandemic. If the patient symptoms do not resolve

after optimizing medications and the symptoms are severe and unresponsive, new administration of these drugs could be considered with caution.

Is it necessary to test the patient for COVID-19 before initiation of anti-TNF?

Anti-TNF drugs can lead to reactivation of opportunistic infection and also activation of some viral infection which may lead to severe viral infections. Therefore it is necessary to evaluate tuberculosis, hepatitis B and C and other active infections before initiating these drugs (24).

As COVID-19 is pandemic now it can easily transmit from human to human even in asymptomatic patients. It is recommended to evaluate this infection before initiation of Anti-TNF drugs or high dose of steroids (24). There is no clinical or paraclinical method for diagnosis of this infection so far. We can use CT scan for its good sensitivity, but we're still awaiting for serologic markers when they become commercially available.

How to manage IBD patients who have infected with this virus?

Asymptomatic SARS-Cov-2 positive patient:

This is the situation which we will be highly encountered with more availability of diagnostic tests in near future.

- There is no need to discontinue 5-ASAs and topical drugs.
- It would be better to reduce the corticosteroid dose.
- Considering two weeks for the average common period of infection, it would be appropriate to stop immunomodulators for at least two weeks.
- It's better to postpone the next infusion of biologic drugs for at least two weeks. At that time the infection usually will show its severity (23).
- It is also recommended to stop tofacitinib, vedolizumab and ustekinumab for the next two weeks.

IBD patients with symptomatic COVID-19 disease

As it has shown in many studies, several proinflammatory cytokines have been involved in producing inflammatory cascade and pathogenesis of severe lung injury of these infection. The major cytokines are IL1 and IL6 and TNF- α (4).

This increase in serum TNF α had led to the hypothesis that TNF α blockers may downregulate the cytokine storm and even may have therapeutic effect for COVID-19 disease (25). These hypothesis may also be the cause of less severe infection in IBD patients who are taking these drugs (26). Until proven data will be available, it is not logical to continue these drugs during such severe viral infection.

These conditions would be occurred:

1. When Colitis is in remission:

- It is recommended to continue 5-ASAs. These drugs are not immunosuppressive agent and based on evidence don't have adverse effect in patients that infected by SARS-CoV2 and patient must be continue these drugs in COVID-19 pandemic.
- Topical steroids are also allowed to be used.
- Although, there was no data that show the effect of immunomodulator drugs on COVID-19 course, stopping thiopurines in case of suspected infection may be reasonable.
- Methotrexate does not appear to affect the course or severity of the disease, but postponing the injection may be advisable.
- JAK inhibitors such as tofacitinib can decrease the number of lymphocytes, therefore stopping them until the resolution of infection may be reasonable.
- Biologic drugs should be held.
- Steroid dose should be reduced.

2. When the colitis is severe:

This would be a challenging issue. Treatment of viremia and viral infection has the priority because it will determine the survival of the patient (23).

- Evaluate the patient for other cause of severity of disease. (stool exam, fecal calprotectin, *Clostridium difficile*, CMV colitis)
- Discontinue all immunosuppressive drugs. Although there are some theories for the benefit of anti-inflammatory drugs, but until strong data will be available, it is appropriate to hold all immunosuppressive drugs (27).
- Using steroids and IL6 suppressors can be used depend on pulmonary and bowel situation and will be advised based on special situations (28).
- Depend on the availability of colonoscopy in

each center colonoscopy and biopsy for CMV or blood PCR would be chosen.

- Restart Anti TNF drugs and immunomodulators at least two weeks after patient recovery.

Endoscopy during COVID-19 pandemic

It has shown that upper GI endoscopy is an aerosol generating model for transmission of SARS Cov-2. It is recommended to cancel all elective procedures. Endoscopies will be limited to emergent procedures.

Viral shedding of virus have been reported in some studies and therefore there is possibility of viral transmission from feces.

According to these findings and with regards to BSG, IOPA and AGA guidelines (9,29,30), all physicians and endoscopic personnels should be aware of adequate personal protection equipment. Using N95 or N99 masks, wearing two gloves, waterproofs' covers is recommended for every colonoscopy (30).

Another important issue is selecting emergent patients for doing colonoscopy. Ulcerative colitis patient with severe active disease who do not respond to initial treatment are the main candidate. Other procedures such as polypectomy and EMR for polypoid lesions could be delayed after suppression of pandemic. Surveillance colonoscopies, colonoscopies for crohn's disease patient after surgery would also be deferred until proper time.

Surgical Implications of IBD Patients during COVID-19 Pandemic

Approximately 20% of patients with ulcerative colitis and 80% of CD patients need an operation during their course of the disease (31).

But, according to the data extracted from a Chinese experience in Wuhan, the mortality rate of patients undergoing elective surgeries during COVID-19 pandemic was about 21% (32).

This is very important, because therapeutic surgeries can expose patients to contamination with SARS Cov-2 and severe cases may develop.

In order to triage for surgical indications in IBD patients, we should consider the following points:

- All elective surgeries should be deferred at this time.(e.g. closure of ileostomy)
- Discuss in virtual meetings about surgical

indications.

- Urgent conditions should be done with special attention to PPE in operating rooms.

- Common urgent conditions include: perianal abscess in perianal CD, toxic megacolon, bowel perforation and bowel obstruction.

- In emergency surgeries, all patients should be tested for COVID-19 and thoracic CT scan should be done in the last 24 hours.

- Surgical resection in IBD patients with LGD/HGD colonic lesions already detected in a previous colonoscopy should be performed as a highest priority after COVID-19 pandemic.

- Abdominal abscesses should be drained percutaneously by interventional radiologists (9,23).

How can patients with inflammatory bowel disease protect themselves?

Because the major route of SARS-CoV2 infection is upper respiratory tract, patients with IBD should follow the same recommendations given by the WHO to the general population (33).

- Stay home if possible.
- Avoid contact with infected people.
- Avoid touching eyes, nose, or mouth with unwashed hands.

- Clean hands often by washing them with soap and water, for at least 20 seconds, and/or using an alcohol-based hand sanitizer that contains 60% – 95% alcohol.

- Clean surfaces with an alcohol-based sanitizer where infected droplets may lie

- Maintain at least 1 m (3 feet) distance from anyone who is coughing or sneezing.

- Stay at home if one feels unwell and wear a mask to avoid infecting other people

- Wear gloves when going shopping

- Use surgical mask in crowded area

- Don't travel.

- Work remotely when possible.

- Continuing medications including infusions and injections unless exposed to COVID-19.

- Obtain a 3-month supply of your medications.

- Don't take non-steroidal anti-inflammatory drugs (NSAIDs)

CONCLUSION

Our patient was admitted in the hospital. Steroid was decreased, Anti TNF and Azathioprine was stopped. Hydroxychloroquine was started for him. One week later oxygen saturation was dropped below 80%, he was transferred to ICU. Hydroxychloroquine was discontinued. Azatanavir was started. Respiratory insufficiency was treated with the assist of continuous positive air was pressure (CPAP). After 10 days his saturation improved and he was discharged after 20 days from hospital. The colonic symptoms did not change and he was advised to reinitiate the next dose of Anti TNF after two weeks.

CONFLICT OF INTEREST

The authors declare no conflict of interests related to this work.

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