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Case Report

Spontaneous Lower Gastrointestinal Bleeding Following Casirivimab/Imdevimab Treatment for COVID-19 Infection: A Case Presentation and Short Literature Review

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Abstract

Coronavirus disease 2019 (Covid-19), which is caused by the novel severe acute respiratory syndrome coronavirus (SARS-CoV)-2, has been a global pandemic since January 2020. The scale and rate of efforts to develop vaccines and therapies for Covid-19 are unprecedented. For mild to moderate disease, two recombinant neutralizing monoclonal antibodies (mAb) therapies, bamlanivimab (LY-CoV555) and casirivimab/imdevimab (REGN-COV2), have been approved by the United States Food and Drug Administration to be administered within 10 days of symptom onset. The efficacy and safety of mAbs are well documented. In this report, we present the first case of life-threatening lower gastrointestinal bleeding potentially related to REGN-COV2 treatment.

Keywords: COVID-19; Monoclonal antibodies; Polyclonal antibodies; CASIRIVIMAB/IMDEVIMAB (REGN-COV2); Gastro-Intestinal (GI) bleeding

1. Introduction

Since the coronavirus disease 2019 (Covid-19) outbreak was declared as a pandemic by the World Health Organization (WHO) on March 11th, 2020 [1], a variety of therapeutic options have become available

[2]. As fatalities from Covid-19 have continued to increase, the development of preventative and therapeutic treatment modalities has proceeded on an unprecedented scale. Currently, available treatment options [2, 3] for moderate-to-severe hospitalized cases in the United States (US) include vaccines (primary prevention) or passive immunotherapy with monoclonal antibodies (mAbs) or polyclonal antibodies (pAbs; secondary prevention), dexamethasone/remdesivir, and interleukin (IL)-6 inhibitors such as tocilizumab. For laboratory-proven, high-risk, mild-to-moderate, non-hospitalized Covid-19 cases, the US Food and Drug Administration (FDA) has granted emergency use authorization for the mAb cocktails casirivimab/imdevimab (REGN-COV2; approved on November 2020) and bamlanivimab/etesevimab (approved on February 2021) [4, 5]. Here we present the first case of a patient who developed spontaneous gastrointestinal (GI) bleeding after receiving REGN-COV2 treatment.

2. Methods

A systematic review of medical literature with the keywords "covid-19," "covid-19 pathophysiology", "covid-19 treatment", "monoclonal antibody", "polyclonal antibody", "REGN-COV2", was performed on publicly available three databases-PubMed, Google Scholar, and Science Direct. Articles that involved definition, pathophysiology, and mechanism of action, treatment, and side effects were identified. All types of articles, including reviews (narrative and systematic), meta-analysis, literature review, randomized controlled trials (RCTs), case-control cohorts, case series, and case reports were screened for relevant content. Nineteen (19) relevant articles were used in this paper in addition to data obtained from CDC/FDA web page. Pertinent information was summarized and organized for ease of understanding.

3. Case Presentation

A 70-year-old male with past medical history (PMH) of hypertension, benign prostatic hyperplasia, chronic kidney disease (CKD 3b), asthma, no history of bleeding or clotting disorder, and who was vaccinated for COVID-19 presented to the Emergency Room (ER) secondary to bright red blood per rectum. The patient reported that his symptoms started about 7 days prior to the arrival after his granddaughter visited him who was later diagnosed with COVID-19. His symptoms mainly included dry cough, loss of appetite, and sore throat. He denied having any shortness of breath, chest pain, fever, chills, loss of taste or smell sensation, abdominal pain, nausea, vomiting, or diarrhea. He was treating his symptoms with over-the-counter (OTC) NyQuil and denied any recent use of OTC NSAIDs. He was tested for COVID-19 the same day his symptoms started and the result came back positive the next day. He was referred by his PCP to get monoclonal antibody treatment.

The patient, given his risk factors, qualified for receiving casirivimab/imdevimab (600mg/600mg) monoclonal antibody IV treatment. The patient tolerated the treatment well without any immediate adverse effects or hypersensitivity reaction and was discharged home in stable condition.

3.1 Past surgical history

History of unremarkable colonoscopy within last 10 years, history of cystoscopy, and transurethral

resection of the prostate (TURP).

3.2 Family history

Positive for hypertension. Negative for bleeding/clotting disorder or cancer.

3.3 Home medications

Amlodipine, as needed (PRN) albuterol inhaler, fluticasone propionate inhaler.

3.4 Social history

No history of tobacco, alcohol, or substance abuse. However, the very next morning he started to feel weak with periumbilical abdominal discomfort and had four watery bowel movements mixed with bright red blood in large quantities. Hence he decided to return to the ER. The patient continued to get bloody bowel movements throughout the day and even while in the ER. The patient was ordered two units of packed red blood cells (PRBC) and was admitted to the Intensive Care Unit (ICU) for close monitoring.

3.5 Vital signs (VS)

On arrival, the temperature 97.5, heart rate 82-105, respiratory rate 19-26, blood pressure was 101/58, and 0xgen saturation of 100% on room air.

3.6 Blood work

Day 0 blood work significant for hemoglobin of 13.0 followed by 11.9 on recheck post two units PRBC transfusion. He was again tested positive for COVID-19.

3.7 Imaging

CT scan of the abdomen/pelvis without contrast showed patchy bilateral airspace opacities in lung bases, no free air or fluid in the abdomen.

3.8 Treatment

Mass transfusion protocol (MTP) was initiated along with IV Protonix, and aggressive IV hydration. As the night progressed, the patient became more confused, hypotensive, and started to complain of shortness of breath. He was urgently intubated and was placed on ventilator support. Arterial blood gas (ABG) post-intubation showed, pH of 6.9, PCo2 36, pO2 202, HCO3 8.3. IV norepinephrine and vasopressin drip were also started secondary to hypotension with goal MAP>65, along with propofol drip for sedation. Repeat blood work showed lactic acid of 16.6. IV bicarbonate bolus followed by bicarbonate drip was started to correct metabolic acidosis. The on-call gastroenterologist performed urgent bedside esophagogastroduodenoscopy (EGD) which revealed coffee ground liquid in the stomach without any fresh bright blood. A 5 mm linear antral ulcer was also seen without any active bleeding. Day 1 blood work in the morning showed, hemoglobin dropping to 7.6 g/dL from 13.0 g/dL despite receiving 4 units PRBC transfusion overnight, platelet count dropping from 211 (10x3/uL) to 47 (10x3/uL), worsening kidney function with serum creatinine from 2.4 mg/dL to 4.3 mg/dL and GFR 31 mL/min to 15 mL/min. A nuclear medicine bleeding scan showed acute GI bleed emanating from the right colon. The patient had so far received 16 units of packed RBC, 10 units of FFP, and 2 units of platelets under MTP. Hemoglobin trended from 11.9 g/dL on arrival to a nadir of 7.6 g/dL. Figure 1 explains the hemoglobin/hematocrit trend throughout the hospitalization.

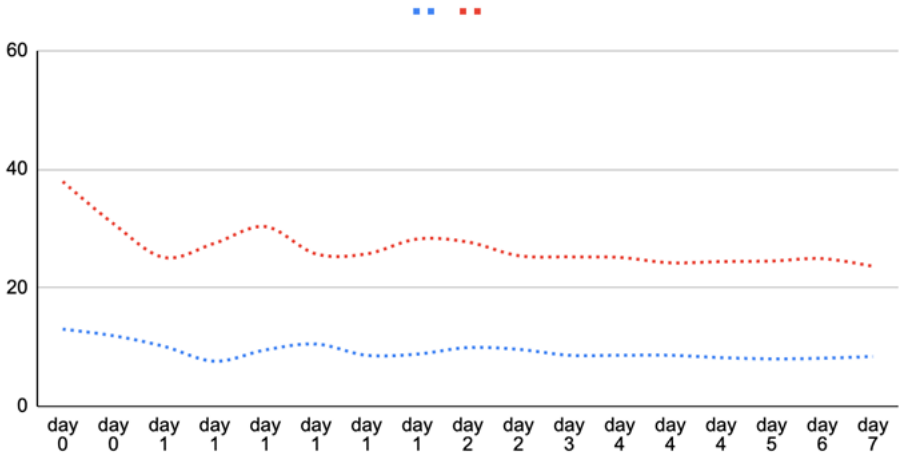

Figure 1: Trend in hemoglobin (in blue) and hematocrit (in red) values.

An attempt was made to transfer the patient to the tertiary care facility for further management including interventional radiology (IR) guided embolization secondary to active bleeding. However, due to rapidly declining status, he underwent urgent exploratory laparotomy with extended right hemicolectomy and anastomosis. The pathology report of the specimen showed a viable colon and terminal ileum with diverticulosis. Vermiform appendix. No distinct bleeding site was identified. The patient started to do well post-surgery, H&H had stabilized without active bleeding and he was extubated. The patient was subsequently transferred out of the ICU to the regular floor and started on a soft renal diet that he tolerated well. The patient was discharged home in stable condition with instructions to get a follow-up colonoscopy in 6 weeks.

4. Discussion

According to the WHO, as of August 30th, 2021 more than 21 million people worldwide have been infected with severe acute respiratory syndrome coronavirus (SARS-CoV)-2 and more than 4 million people have died from Covid-19 [6]. Because of the continuous mutation of the virus and the emergence of new strains, the pandemic has been ongoing for almost 2 years, with devastating effects on the global economy. The clinical manifestation of Covid-19 can be divided into two stages: the early stage of SARS-CoV-2 viral replication, followed by a late hyperinflammatory stage induced by the release of cytokines (tumor necrosis factor [TNF]-α, granulocyte-macrophage colony-stimulating factor [GM-CSF], IL-1, IL-6, and interferon [IFN]-γ) and a prothrombotic state [7, 8]. Optimal therapy is based on disease status: antiviral therapy and antibody-based treatments mainly target the early phase of the illness, while immunomodulating/anti-inflammatory therapies (e.g., tocilizumab) along with respiratory support, intubation, and prone positioning are more effective in the later cytokine-mediated hyperinflammatory state [7-9].

The mAb drugs used to combat Covid-19 are human

proteins that mimic the immune system to provide a defense against SARS-CoV-2. They are derived from a single cell lineage and block virus entry into host cells by binding to virus surface glycoproteins (spike protein/epitope) [10], thereby preventing viral replication and reducing viral load, which in turn reduces the risk of disease progression to the cytokine-mediated hyperinflammatory phase [11-14]. mAbs can also act as immunosuppressants that prevent cytokine-induced damage in the late phase of infection [14]. A combination of two noncompeting antibodies, also known as an antibody cocktail, is typically used to prevent the development of viral resistance against single mAbs (known as viral escape) [8]. This type of cocktail is most useful in patients in whom a native immune response has not yet been induced. In general, mAbs are preferred over pAbs (convalescent plasma therapy) because they have fewer side effects [15], higher specificity, a better safety profile and achieve >1000 times higher neutralizing antibody titers [16].

Unlike bamlanivimab, which was derived from the plasma of a patient with Covid-19 [16], REGN-COV2 is a fully human IgG1 antibody cocktail containing two anti–SARS-CoV-2 neutralizing antibodies—namely, casirivimab and imdevimab [17]. REGN-COV2 is recommended for patients aged >12 years with mild-to-moderate Covid-19 who are at high risk of progressing to severe disease [18]. Common side effects of REGN-COV2 listed by the FDA include allergic reactions such as fever, chills, nausea, headache, dyspnea, hives, and itching as well as pain, bruising, and soreness at the injection site [19]. Interim results from an ongoing multicenter, randomized, double-blind, placebo-controlled clinical trial funded by Regeneron Pharmaceuticals of 275 patients with Covid-19 showed that REGN-COV2 had the same hypersensitivity reaction profile as the placebo [10].

GI bleeding [20, 21] and lower GI bleeding [22] have been reported in patients with Covid-19 treated with tocilizumab [22, 23], an anti–IL-6 receptor mAb often used in hospitalized patients (aged ≥2 years) with severe Covid-19 receiving supplemental oxygen, systemic steroids, and non-invasive or invasive mechanical ventilation [24]. The GI bleeding observed with tocilizumab is thought to be secondary to its anti–IL-6 activity, as IL-6 normally protects against bowel injury by stimulating enterocyte proliferation [25].

This is the first documented case of lower GI bleeding following REGN-COV2 treatment. Rojo et al. [22] also described a case of bleeding in the right colon, as was observed in our patient. This phenomenon warrants further investigation in a larger clinical trial. It is possible that GI bleeding in our patient was caused by Covid-19; however, the timing of the bleeding immediately after REGN-COV2 treatment in the absence of any other risk factors suggests that it was a treatment-related adverse event.

5. Conclusion

mAb drugs for Covid-19 can reduce viral load, severe symptoms, and hospitalization, leading to better recovery. However, as more data emerge from their use in a larger real-world population, their safety profile is becoming increasingly apparent. Covid-19 patients treated with mAbs should be advised to

watch for GI bleeding and seek prompt medical attention if it occurs to avoid life-threatening complications.

Disclosure

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