

Concomitant Therapy of Crohn's Disease and Hepatitis C With Budesonide and Antivirals

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A high prevalence of hepatitis B and C infections, primarily related to multiple surgical procedures and blood transfusions, has been reported in patients with Crohn's disease. For example, a large trial from Italy found a positive serology for hepatitis C virus in 7.4% of 332 patients with Crohn's disease.¹ Many drugs that affect immune function and could promote viral replication (such as glucocorticoids, azathioprine, 6-mercaptopurine, and anti-tumor necrosis factor [TNF] antibodies) are used in the treatment of Crohn's disease. In addition, there have been scattered reports of exacerbation of Crohn's disease during interferon-based antiviral treatment of chronic hepatitis C.^{2,3} Interferon treatment of chronic hepatitis C has been shown to induce celiac disease by the stimulation of a T-helper-cell type 1 immune response⁴ and could theoretically exacerbate Crohn's disease by the same mechanism.

There have been only a few reports in the literature on the treatment of Crohn's disease in a patient also receiving antiviral therapy with interferon and ribavirin for chronic hepatitis C. We report a patient who developed an exacerbation of Crohn's disease after initiating therapy for chronic hepatitis C. The patient was given 9 mg daily of budesonide for a period of 1 year to treat his Crohn's disease while continuing antivirals, and achieved a sustained virologic response.

Case Report

A 58-year-old white man with Crohn's disease for 25 years presented with a 3–4-week history of 10–12

watery stools daily. He was in his 13th week of therapy with peginterferon alfa-2a 180 mcg weekly and ribavirin 600 mg BID for chronic hepatitis C genotype 1A. He had apparently acquired hepatitis C following a blood transfusion during a thyroidectomy. A liver biopsy 5 years prior to presentation showed changes consistent with chronic hepatitis C of moderate activity, with mild-to-moderate portal fibrosis and fatty metamorphosis. The patient experienced a rapid response after 4 weeks of antiviral treatment, as his hepatitis C virus load dropped from 1,018,360 IU/mL to an undetectable level (reportable range, 615–7,692,310 IU/mL).

The patient had received corticosteroids at the onset of his Crohn's disease and had been maintained in remission on mesalamine 500 mg 4 times daily for the past 15 years. His last colonoscopy, performed 2 years prior to presentation, showed terminal ileitis with erythema, ulceration, and edema. There was also a loss of vascular pattern in the cecum. A terminal ileal biopsy showed ulceration and acute and chronic exudative inflammation.

To treat his Crohn's disease flare, the patient was started on budesonide 9 mg daily and continued on mesalamine 2 g daily. Therapy for his chronic hepatitis C was continued, though the dose of ribavirin was decreased to 1,000 mg daily because of a mild drop in serum hemoglobin level to 10.2 g/dL. Four weeks after the commencement of budesonide, his Crohn's disease improved. He was followed in a gastrointestinal clinic and remained stable, with occasional mid-abdominal cramping and mild diarrhea. He had a chronic facial rash, but no erythema nodosum or pyoderma was noted. No eye inflammation or perianal disease occurred. His hepatitis C virus-polymerase chain reaction test remained negative while on interferon and ribavirin therapy. During concomitant treatment of his Crohn's disease and chronic hepatitis C, he experienced a transient elevation of his

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aspartate aminotransferase and alanine aminotransferase levels from 31 IU and 35 IU to 104 IU and 129 IU, respectively, which subsequently normalized without treatment modification.

After 8 months of uneventful therapy for Crohn's disease and chronic hepatitis C, the patient complained of abdominal pain, 15–20 stools daily, fecal incontinence, bright red blood per rectum, and rectal burning. The possibility of his Crohn's disease worsening was considered; however, his C-reactive protein was 0.23 mg/dL (normal range, 0–0.8 mg/dL). A computed tomography scan of the abdomen/pelvis that was obtained to further evaluate the abdominal pain revealed diffuse thickening of the wall of the distal small bowel (which is consistent with Crohn's disease) and sigmoid diverticula. Consideration was given to using 6-mercaptopurine or anti-TNF α therapy, but, as the patient was close to completing his 48 weeks of antiviral therapy, no changes were made to his medications. His diarrhea lessened over the next 3–4 weeks with the addition of occasional doses of loperamide. He successfully achieved an end-of-treatment response to the antivirals.

No further flare-up of his Crohn's disease occurred after the completion of antiviral therapy while continuing on budesonide. At a follow-up visit approximately 4 months after completing his antiviral treatment and 14 months after starting the budesonide, the patient reported that his appetite was fair and his weight stable. He had 3–6 loose-to-formed stools per day with some incontinence, but no bleeding per rectum and no extraintestinal manifestations of inflammatory bowel disease. Six months after completion of antiviral therapy, the patient had undetectable levels of hepatitis C virus and had achieved a sustained virologic response.

Discussion

Limited data are available on the safety and efficacy of the treatment of hepatitis C in patients with Crohn's disease. Small series and case reports have reported exacerbations of Crohn's disease with interferon-based treatment.^{2,3} In a retrospective study, 11 patients with Crohn's disease and chronic hepatitis C infection received antiviral therapy.⁵ Eight patients were on Crohn's disease therapy during antiviral treatment (4 on mesalamine, 3 on azathioprine, and 1 on mycophenolate mofetil). In 6 patients, Crohn's disease activity worsened during antiviral treatment, with the number of loose stools rising from 5 daily to 14.5 daily. Additional Crohn's disease treatment (eg, a course of glucocorticoids, mesalamine, or antibiotics) was required during antiviral therapy, but the authors felt that, overall, antivirals for chronic hepatitis C in Crohn's disease patients were well tolerated. Abdelmalek and associates recently reported a patient whose Crohn's disease flared

5 weeks after starting treatment for chronic hepatitis C with interferon and ribavirin.⁶ In this patient, antiviral therapy was discontinued and the Crohn's disease was treated with prednisone and infliximab. After resolution of the patient's Crohn's disease flare, the prednisone was discontinued, and infliximab infusions were given every 6 weeks concomitant with treatment for his hepatitis C. The authors reported that this patient remained negative for hepatitis C nearly 4 years after completion of his antiviral therapy.

There is also limited information on the impact that Crohn's disease medications have on the efficacy of antiviral treatment for hepatitis C. In a series by Scherzer and colleagues, 11 patients with Crohn's disease and chronic hepatitis C infection received antiviral therapy.⁵ Of these patients, 3 (27%) were nonresponders (all genotype 1B). Eight (73%) patients experienced an end-of-treatment response, and 5 (46%) patients achieved a sustained virologic response.

There have also been several reported cases of successfully using biologic therapy for Crohn's disease in patients with evidence of hepatitis C infection, despite theoretical concerns for TNF α inhibition causing immunosuppression and activation of hepatitis C.⁷ Aslanidis and coworkers treated 2 patients, 1 with ankylosing spondylitis and 1 with psoriatic arthritis, with long-term anti-TNF agents without reactivation of their hepatitis C infection or deterioration of their liver function.⁸ Chronic viral hepatitis has been reported to alter TNF and TNF receptor levels and biologic activity.⁹ Further studies are needed on the effect of anti-TNF antibodies on the clinical course of chronic viral hepatitis and the response to antiviral therapy.

Our patient experienced a flare of his Crohn's disease after 13 weeks of antiviral treatment for hepatitis C. He had achieved a rapid virologic response at 4 weeks of treatment, making it highly likely that he would achieve a sustained virologic response following a full course of therapy. We elected to continue his peginterferon and ribavirin and treat his Crohn's disease with budesonide. We chose budesonide because its rapid first-pass metabolism by cytochrome P450 isoenzyme CYP3A4 limits systemic corticosteroid exposure, and we reasoned that budesonide would be less likely than conventional steroids to affect viral replication. Prednisone has been reported to cause an increase in hepatitis C virus RNA titer, and steroid withdrawal causes an elevation in serum transaminases.¹⁰ Multiple studies have reported that the efficacy of budesonide is comparable to that of conventional corticosteroids in the treatment of acute Crohn's disease and that it has fewer systemic side effects.^{11,12} A recent meta-analysis (Cochrane review) of the use of oral budesonide for maintenance of Crohn's disease remission, however, suggested only mod-

est benefit compared to placebo. At 6 and 12 months, treatment with 6 mg daily of budesonide resulted in only a weighted mean difference of approximately -25 in the Crohn's Disease Activity Index score.¹³ Our patient experienced an exacerbation of his Crohn's disease after 8 months of budesonide treatment that subsided after discontinuation of his antiviral treatment.

In summary, after initiation of antiviral therapy with peginterferon and ribavirin, the patient reported here experienced a flare of his Crohn's disease that was successfully managed with budesonide along with the continuation of antivirals. The patient also achieved a sustained virologic response. We believe that this is the first report of this approach for concomitant management of these disorders and recommend that it be considered for treatment of other patients with active Crohn's disease and chronic hepatitis C.

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Review

Treatment of Chronic Hepatitis C in Patients With Crohn's Disease

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Patients with Crohn's disease (CD) have an increased prevalence of hepatitis C (HCV) infection as compared to the general population because of the need for blood transfusions and multiple surgical and/or endoscopic procedures.¹ The dilemma facing clinicians is the possibility that HCV therapy could flare a patient with stable CD. However, it is difficult to withhold potentially curative HCV treatment and risk progression to advanced liver disease. The medical literature provides little guidance for the challenge of how to approach this situation or what is the long-term outcome of untreated HCV in an immunosuppressed patient with CD.

Interferon- α has immunomodulatory properties that may impact immune pathways that control and may even induce inflammatory bowel disease (IBD) or other immune-mediated diseases. Patients with autoimmune diseases have been excluded from HCV clinical trials, and in clinical practice, these patients are not usually treated for HCV due to the high likelihood of inducing a flare of the immune-mediated condition.² It is well recognized that in chronic hepatitis B viral infection, corticosteroids, anti-tumor necrosis factor (TNF)- α agents, and other immunosuppressant medications can cause a hepatitis flare, whereas in chronic HCV, there is little information regarding the effect of immunomodulatory drugs on the clinical course of liver disease in CD patients.^{1,3}

To date, the available information suggests that HCV should not influence treatment strategies for CD. However, immunosuppressive therapies for IBD such as corticosteroids, azathioprine, and 6-mercaptopurine may decrease the therapeutic effects of antiviral therapy. Corticosteroid immunosuppression has been shown to accelerate the progression of fibrosis and the develop-

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ment of cirrhosis in HCV.⁴ Although antiviral therapy for HCV may be utilized in combination with immunosuppression, sustained viral response (SVR) rates in the transplant population are significantly decreased when compared to SVR rates in nonimmunosuppressed individuals.⁵ Scherzer and colleagues⁶ recently reported a series of 11 patients with CD and HCV who were treated for HCV. Four (3 on azathioprine and 1 on mycophenolate mofetil) of the 11 patients were on immunosuppressive therapy, and 2 of these patients achieved sustained virologic response—a rate that was comparable to the patients without immunosuppressive therapy. An increase in CD activity occurred in 6 of the 11 patients (55%) while on HCV therapy, resulting in a short course of corticosteroids in 4 patients. In these patients, corticosteroid treatment did not increase HCV RNA levels while continuing antiviral therapy.

There is a single case report of the use of an anti-TNF- α agent to control a flare of CD while undergoing treatment for HCV.⁷ Anti-TNF- α agents do not generally increase HCV RNA levels in CD patients or rheumatoid arthritis patients^{8,9} and do not appear to interfere with treatment of HCV.^{7,10} Gupta and Sitrin¹¹ have taken another approach to avoid possible immunosuppressive interference with HCV treatment by taking advantage of the high first-pass hepatic metabolism of budesonide. In their case study, the CD patient experienced a flare of his condition after 13 weeks of treatment for HCV and was treated with 9 mg daily of delayed-release budesonide. He was able to remain on HCV treatment and achieved SVR. The authors reported that the patient had been in remission for 15 years on oral mesalamine; however, he had terminal ileal inflammation and ulceration on colonoscopy 2 years before starting HCV therapy, suggesting persistent active disease. Documentation that a patient is in clinical remission (including C-reactive protein and fecal lactoferrin or calprotectin) and/or endoscopic remission is advisable prior to starting treatment of HCV. After 8 months on budesonide, while continuing treatment for HCV, the patient flared, resulting in 15–20 stools per day and fecal incontinence. Despite these symptoms, he was able to complete his HCV therapy. As the authors noted, budesonide, as with all corticosteroids, has not been shown to maintain remission in CD, though it may delay relapse for several months compared to placebo.¹² One can speculate on the outcome if the patient had been treated intermittently with budesonide as needed through the course of his HCV treatment or if an anti-TNF- α agent had been started, but the literature is too sparse to recommend any standard approach. Not all CD patients

experience a CD flare on HCV therapy, as demonstrated in the series by Scherzer and coworkers, in which 45% of the CD patients did not flare, including those who were only on mesalamine.⁶ Thus, for the CD patient in remission, a recommendation to start any particular medication before initiation of HCV therapy to try to keep the CD in remission during HCV therapy does not appear to be justified.

The 2002 National Institutes of Health Consensus Statement on Management of Hepatitis C states that “all patients with chronic hepatitis C are potential candidates for antiviral therapy” and that “treatment is recommended for patients with an increased risk of developing cirrhosis.”¹³ The consensus statement does have a caveat that in some populations, such as those with autoimmune diseases, the risks and benefits of therapy should be determined on an individual basis. Given the potential outcome of severe CD versus developing cirrhosis from untreated HCV, a thorough assessment of the risks and outcomes is required, as well as a planned treatment approach, should treatment of HCV result in a CD flare.

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