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EFFICACY AND SAFETY OF TREATMENT OF HEPATITIS C IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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Abstract

Background & Aims—There is uncertainty about the efficacy and safety of treatment for hepatitis C virus (HCV) infection in patients with inflammatory bowel disease (IBD). IBD can become exacerbated during treatment with interferon (IFN) and serious adverse events, such as pancytopenia or hepatotoxicity, can be compounded by drug interactions. We investigated the risk of exacerbation of IBD during HCV therapy and the rate of adverse effects of concomitant therapy for HCV and IBD. We also evaluated the efficacy of HCV treatment in the IBD population.

Methods—We conducted a retrospective review of all patients who underwent IFN-based treatment for HCV at the Mayo Clinic in Rochester, Minnesota from 2001 through 2012. Exacerbation of IBD was evaluated by clinical, endoscopic, and histologic parameters during antiviral therapy and the ensuing 12 months. Hematologic toxicity was assessed by levels of all 3 cell lineages at baseline and during therapy. Efficacy of antiviral treatment was assessed by serum levels of HCV RNA until 24 weeks after completion of therapy. We also conducted a detailed Medline database search and reviewed the literature on this topic.

Results—We identified 15 subjects with concomitant IBD (8 with ulcerative colitis and 7 with Crohn's disease). Only 1 patient experienced an exacerbation of the disease during therapy; symptoms were controlled with mesalamine enemas. Another patient developed a flare shortly after completing antiviral therapy; symptoms returned spontaneously to baseline 2 weeks later. All subjects experienced an anticipated degree of pancytopenia while on IFN-based therapy. The rate of sustained virologic response was 67 %. A concise review of available literature regarding the safety and efficacy of HCV treatment in IBD patients is also presented; although limited, the published data appears to support the safety of treatment with IFN in patients whose IBD is under control.

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Conclusions—In conjunction with data from the literature, our findings indicate that the efficacy and safety of HCV therapy with IFN and ribavirin for patients with IBD are comparable to those of subjects without IBD.

Keywords

UC; CD; SVR; inflammation

INTRODUCTION

Patients with concomitant inflammatory bowel disease (IBD) and hepatitis C virus (HCV) infection represent a complex subset of patients. HCV is a common infection worldwide, with a high and increasing rate of progression to cirrhosis and hepatocellular carcinoma (HCC).

The concern with IFN therapy is its immune-modulatory action, which may possibly worsen the clinical course of IBD. On the other hand, the immunosuppressive therapy for IBD can potentially lead to a more rapid progression of fibrosis in HCV-infected patients¹. Another aspect underlying the reluctance to treat HCV is the potential for serious adverse events, such as pancytopenia or hepatotoxicity, resulting from the interaction between HCV- and IBD- specific agents².

Thus, the management of patients with concomitant IBD and HCV infection remains a clinical challenge. Evidence based recommendation about the efficacy and safety of HCV treatment in patients with IBD is difficult to make, in part because of the paucity of data.

The aims of this study are: (i) to determine the risk of IBD exacerbation during HCV therapy and the rate of adverse effects of concomitant therapy for HCV and IBD; and (ii) to evaluate the efficacy of HCV treatment in the IBD population. In addition, we review the available literature on this topic.

PATIENTS AND METHODS

We conducted a retrospective review of all patients who underwent IFN-based treatment for HCV at Mayo Clinic, Rochester, Minnesota, between 2001 and 2012. The study was approved by the Institutional Review Board of Mayo Clinic.

Exacerbation of inflammatory bowel disease was evaluated by clinical, endoscopic and histologic parameters during antiviral therapy and the ensuing 12 months. Clinical assessment was extracted from medical records documented during the aforementioned period by any medical provider. Management of viral hepatitis in our practice involved frequent blood testing and scheduled telephone conversations with viral hepatitis nurses, as well as clinic visits with the hepatologist at baseline, weeks 4, 12, 24 and 48 of therapy, and week 24 from completion. This close follow-up ensured that no IBD flares were missed. All available endoscopic evaluations and histology reports were reviewed. IBD flares were defined as an increase in baseline stool frequency, presence of blood in stool, abdominal discomfort, correlated with increased disease activity per endoscopic and histologic assessment.

For the secondary end-point of **safety profile** of concomitant antiviral and IBD treatment, hematologic toxicity was assessed by levels of all 3 cell lineages at baseline and during therapy. Results were reported in median values and median of changes in values.

Efficacy of antiviral treatment was assessed by measurement of serum HCV RNA level at baseline and up to 24 weeks after discontinuation of therapy. Testing was performed by COBAS Ampli/Prep HCV test (Roche Molecular Systems Inc., quantification range 43 IU/mL to 69,000,000 IU/mL). Sustained virologic response (SVR) was defined as undetectable HCV RNA levels at 24 weeks after completion of antiviral therapy.

RESULTS

Exacerbation of inflammatory bowel disease during HCV therapy

Of 1017 patients treated for HCV during the study period, 15 had concomitant IBD [8 with ulcerative colitis (UC) and 7 with Crohn's disease (CD)]. The median age at initiation of antiviral therapy was 53 years (range, 30–68). Two patients received antiviral therapy twice; therefore, 17 treatment courses were observed. The bowel disease characteristics of the study population are summarized in Table 1, whereas the liver disease characteristics are summarized in Table 2.

All subjects had inactive bowel disease prior to IFN initiation, except 1 patient with CD who had not been on maintenance treatment. He was started on budesonide at the time of HCV therapy and maintained clinical remission throughout the study period. Eight patients were on IBD-specific therapy prior to HCV treatment (5 on mesalamine, 2 on mesalamine plus azathioprine, and one on budesonide).

Only 1 patient experienced increased stool frequency (from 4–6 to 6–8 stools/day) and abdominal cramping within 1 month of IFN initiation (patient 7, Table 3). The patient had a diagnosis of left-sided UC and was on maintenance therapy with oral mesalamine and intermittent mesalamine enemas. She carried a concomitant diagnosis of irritable bowel syndrome (IBS), based on similar prior intermittent complaints of increased stool frequency and abdominal cramping, in the context of endoscopic and histologic evidence of inactive or mildly active colitis. Her symptoms were controlled with the addition of mesalamine enemas, but persisted after antiviral therapy was discontinued at 12 weeks, given her nonresponder status. Colonoscopy performed 9 months later showed features of chronic inactive left-sided colitis, similar to the endoscopic features noted immediately prior to antiviral therapy. Random colon biopsies revealed moderately active UC (previously with minimal activity).

Another patient (no. 15) with mildly active CD, on budesonide treatment, tolerated 6 months of pegylated IFN (PegIFN) and ribavirin, but developed worse non-bloody diarrhea and abdominal pain within 2 weeks from ending antiviral treatment. Budesonide was continued and symptoms returned to baseline spontaneously 2–3 weeks later.

Safety profile of concomitant therapy for IBD and HCV

All patients experienced an anticipated degree of pancytopenia while on IFN-based therapy. The mean decline in all three cell lines is summarized in Table 4. No treatment was stopped due to pancytopenia. Five patients required adjustment of therapy (lower azathioprine dose in 1 patient for leukopenia, lower ribavirin dose in 2 patients for anemia, and lower PegIFN dose in 2 patients for leukopenia and anemia, respectively). Erythropoietin was used in 2 patients.

Hepatotoxicity was not observed in subjects under concomitant treatment with azathioprine.

Efficacy of HCV treatment in IBD population

Antiviral treatment consisted mainly of the combination of PegIFN- α and ribavirin in 12 patients. One patient was treated with PegIFN- α monotherapy due to baseline anemia, and two patients received telaprevir-containing triple therapy. Treatment was completed and well tolerated in all but 1 subject (6.6%), who discontinued therapy at week 20 due to abdominal pain, without diarrhea.

Individual treatment responses are summarized in Table 3. Overall SVR rate was 67% (50% for genotype 1, 100% for genotype 2 and 100% for genotype 3).

LITERATURE REVIEW

Risk of IBD exacerbation with interferon

The effects of IFN on IBD activity, perhaps the major concern underlying the reluctance to treat HCV in these patients, have been mixed. Currently still the mainstay of HCV therapy, IFN- α is a pro-inflammatory cytokine which stimulates a Th1-type immune response, similar to the immunologic milieu of CD³. On the other hand, IFN- α has anti-inflammatory properties via regulation and down-modulation of Th2 cytokines, which are upregulated in UC⁴. Therefore, both theoretical assumptions of IBD exacerbation or remission are plausible, but none have been confirmed in the literature. These studies, however, are limited by a small number of patients.

Randomized controlled trials—Tilg et al. conducted a randomized placebo-controlled trial to evaluate the efficacy of PegIFN- α as treatment agent for UC⁵. The treatment did not appear to be effective, but, more importantly, there were no cases of UC exacerbation in the treatment groups. Although the PegIFN- α doses used in this trial are lower than the ones used to treat HCV, this study supports the safety of IFN even in active UC. Favorable treatment outcomes were also noted in a randomized trial of IFN α -2a versus prednisolone enemas in 32 patients with left sided colitis⁶.

Prospective studies—A case-control study followed 21 patients with IBD and 65 controls during 12 months of IFN monotherapy for HCV. There was no worsening in IBD activity or difference in frequency or severity of side effects between cases and controls⁷. A prospective, open-label study of 28 patients with ulcerative colitis treated with IFN α -2a for 6 months led to complete remission in 82% of cases⁸.

Retrospective studies—Cottone et al evaluated 14 patients with IBD who underwent IFN- α monotherapy for HCV for at least 6 months. Only one patient, with initially inactive disease, had a mild flare during treatment⁹. Scherzer and colleagues¹⁰ assessed 11 patients with CD who were treated for hepatitis C. Therapy was overall well tolerated, with a mild increase in stool frequency in 6 patients. They temporarily required escalation of CD-specific therapy with corticosteroids and/or mesalamine. Favorable outcomes of two patients are also described in another study¹¹.

Case reports—Most of the controversy regarding the negative outcomes of IFN- α on IBD comes from case reports. A review of the literature revealed 24 unfavorable case reports. Of these, 21 were new-onset IBD (15 UC^{12–24}, 5 CD^{21, 25, 26} and 1 “IBD-like”²⁷) and 3 were exacerbations (2 UC^{28, 29} and 1 CD³⁰), either during or after discontinuation of IFN. It is important to note that most of the IBD cases were mild and responded to discontinuation of IFN or administration of mesalamine. Furthermore, most patients who had negative outcome were not on maintenance therapy for IBD prior to HCV treatment, suggesting that perhaps assuring remission of IBD prior to consideration of antiviral therapy may avoid flares.

On the other hand, 6 case reports with a favorable IBD outcome while on treatment with IFN- α with or without ribavirin were found on literature review^{22, 31–35}. All cases were on IBD maintenance therapy during antiviral treatment and no flares were documented.

Safety profile of concomitant therapy for IBD and HCV

Azathioprine (AZA) and 6-mercaptopurine (6-MP) have known dose-related toxicities, such as pancytopenia (related to 6-thioguanine nucleotide (6-TGN) levels) and hepatotoxicity (due to methylated derivatives)³⁶. Ribavirin efficiently blocks inosine monophosphate dehydrogenase (IMPDH)³⁷, therefore shifting the metabolism towards methylated products, and away from 6-TGN (Figure 1)². Two concerns arise from this interaction: hepatotoxicity due to an accumulation of 6-MMPN, and potential IBD flares, due to lower 6-TGN levels.

Efficacy of HCV treatment in IBD population

There is consensus that the efficacy of HCV treatment in IBD patients is comparable to that in the non-IBD population. In a case-control study⁷ assessing the efficacy of non-PegIFN monotherapy for HCV in patients with IBD versus controls, similar SVR rates were reported. The efficacy of HCV therapy with a combination of PegIFN- α and ribavirin was assessed in a prospective study¹⁰ of 11 CD patients, of whom 46% achieved SVR, 27% relapsed and 27% were non-responders.

Effects of IBD therapy on HCV infection

Corticosteroids—There are no studies directed at the effects of corticosteroids used for IBD flares on the course of HCV, except for case reports^{38, 39}. The liver transplantation literature suggests a significant increase of HCV viremia in patients receiving corticosteroid boluses (much higher doses than typically used for IBD exacerbations) for acute allograft rejection after liver transplantation for HCV⁴⁰. The effects of corticosteroid use on progression of HCV-related liver fibrosis are controversial^{1, 41}. Based on this scarce data, we believe it is reasonable to conclude that steroids may temporarily allow uninhibited HCV replication, either related to high doses or to rapid dose alterations. If steroid use is inevitable for control of IBD exacerbations, the lowest beneficial dose and slow tapering is advisable.

Thiopurines—To date, no studies have evaluated the safety of immunomodulators in HCV among IBD patients. AZA has shown antiviral activity on HCV *in vitro*⁴². In the post-transplant setting, some have suggested that AZA may be beneficial in HCV recurrence⁴³. There is no evidence that the immunosuppressive effects of AZA adversely affect the course of HCV. All in all, we believe that thiopurines in IBD patients with HCV are probably safe and possibly beneficial.

Biologics—Studies have shown that TNF levels correlate with hepatitis activity⁴⁴, suggesting that anti-TNF agents may play a beneficial role on HCV course. In a randomized placebo-controlled trial in HCV patients⁴⁵, adding etanercept to IFN and ribavirin for 24 weeks resulted in a greater rate of viral clearance when compared to a standard regimen. At present, biologic agents appear safe^{11, 46–47} in HCV-infected patients; however, long-term studies are needed.

DISCUSSION

In this study we present our experience with the treatment of hepatitis C in IBD patients, with emphasis on the risk of exacerbation of IBD during therapy with IFN, the safety profile of medications, and the efficacy of HCV therapy in this patient population. In addition, we review all available literature on this controversial topic.

In this retrospective cohort, therapy was overall well tolerated, with only one patient experiencing a mild increase in baseline stool frequency, without gross endoscopic changes, but with slightly increased inflammation per biopsies. It is unclear if the subtle histologic changes were due to IFN or natural progression of her disease, or if her symptoms were related to IBD or IBS. The fact that the patient continued to complain of similar intermittent, self-remitting flares during the following 5 years, with unchanged endoscopic features and stable minimal-moderate activity, points away from IFN as a causal factor. The second patient experienced a temporary flare after completion of HCV treatment, which resolved spontaneously.

Overall our study supports the evidence that IFN-based therapy for HCV is safe and well tolerated in IBD patients, as long as the disease is under control (remission or minimal activity) prior to initiation of antivirals. Although rare, flares are minimal and easily handled with standard therapy. The presence of IBD, while taken into careful consideration, should not lead to automatic deferral of HCV therapy when indicated.

In regards to medication toxicity, antiviral therapy with IFN and ribavirin is safe and should not be withheld only on the premises of concomitant use of immunomodulators. Cytopenias were noted at rates comparable or slightly lower than the ones published in the literature⁴⁸ (Supplementary Table 1). In our study, concomitant treatment with IFN, ribavirin and AZA occurred in 2 patients, and neither experienced IBD flares, hepatotoxicity, or required transfusion or cell stimulating factors. Frequent monitoring for possible myelotoxicity and hepatotoxicity remains imperative, especially in subjects with high TPMT activity, in whom methylated products are expected to increase.

Our single center experience confirms that treatment of hepatitis C in IBD patients is as effective as in general population. The overall SVR rate was 67%. There were 2 patients who completed telaprevir-based triple therapy, both of whom achieved SVR.

The available literature, including our study, has limitations. Most of the reports include patients with, at most, moderately active IBD, as reflected by the IBD-specific agents used. Approximately half of the patients in our study were on maintenance therapy, which included mesalamine and AZA. The risk of IBD exacerbation in harder-to-treat patients, such as those on combination therapy with biologics and immunomodulators, remains unknown. In those situations, HCV treatment should be individualized, and the risks of liver disease progression if left untreated should be carefully weighed against the potential risks of IBD flares. In light of emerging direct-acting anti-HCV agents that may obviate the need for IFN, these patients without advanced fibrosis or other indication for immediate treatment may be best counseled to wait. The number of patients included in these studies and reports, including ours, is relatively small. Although we present only 15 patients, our study provides an additional center experience to the scarce available literature. We report the first 2 cases of telaprevir-containing therapy, which appears safe in IBD patients.

In conclusion, based on our experience, in patients whose IBD activity is under control with or without therapy, HCV treatment with IFN and ribavirin is safe and effective. Thorough evaluation and management of IBD activity prior to initiation of antivirals and continuation of maintenance therapy is recommended. Flares of IBD are mild and easily handled with first-line therapy. Corticosteroids can be cautiously used during exacerbations, but at a minimum effective dose and tapered slowly. Based on the available literature, IBD treatment with immunomodulators and biologics do not seem to alter the course of HCV. AZA and 6-MP can be used concomitantly with IFN and ribavirin, although medication interactions can, in theory, lead to worse hepatotoxicity, myelotoxicity and IBD exacerbation due to relative

resistance to thiopurines. Although TPMT phenotype may help predict toxicities, frequent screening for myelosuppression and hepatotoxicity remains the safest practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Metabolism of azathioprine (AZA). Ribavirin blocks inosine monophosphate dehydrogenase (IMPDH), resulting in increased methylated derivatives and decreased 6- thioguanine nucleotide (6-TGN) levels

Table 1

Baseline bowel disease characteristics of 15 patients with inflammatory bowel disease and hepatitis C infection at the time at treatment initiation.

Characteristics	Data
Median age, years (range)	53 (30–68)
Sex (M/F)	9/6
IBD type	
UC	8
Extensive colitis	5
Left-sided colitis	2
Proctitis	-
Unknown	1
CD	7
Ileitis	3
Colitis	-
Ileocolitis	3
Unknown	1
Median IBD duration, years (range)	15 (0–44)
Baseline IBD activity	
Remission	13
Active	2
Treatment agents	
5-ASA	7
Budesonide	2
Azathioprine	2
Anti-TNF	-

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; 5-ASA, 5-aminosalicylate; TNF, tumor necrosis factor.

Table 2

Baseline liver disease characteristics of 15 patients with inflammatory bowel disease and hepatitis C infection, prior to antiviral therapy initiation.

Characteristics	Subjects (n=15)
Time since HCV diagnosis (median, range)	3.5 (0–17)
Fibrosis stage	
F0	3
F1	-
F2	2
F3	6
F4	4
HCV genotype	
1	10
2	2
3	3
HCV RNA (IU/mL, median, range)	3,800,000 (18,325– 16,000,000)
ALT (U/I, median)	78 (16–232)

HCV, hepatitis C virus; RNA, ribonucleic acid; ALT, alanine transaminase

Table 3

Individual characteristics of treatment response in all 15 patients

Patient no.	Sex	Age (years)	IBD Type	IBD therapy	HCV type	Fibrosis stage	HCV therapy	Length therapy (mo)	HCV treatment outcome	IBD flare
1	M	55	UC	-	1b	2	IFN/Riba	34	NR	N
1'	M	61	UC	5-ASA	1b	3	IFN/Riba	10	NR	N
2	M	37	UC	-	1	0	IFN/Riba	12	SVR	N
3	M	47	CD	-	1a	0	IFN/Riba	12	REL	N
3'	M	56	CD	-	1a	2	IFN/Riba/Tel	12	SVR	N
4	F	54	CD	budesonide	2b	4	IFN/Riba	6	SVR	N
5	M	61	UC	-	1b	4	IFN/Riba	12	SVR	N
6	F	30	CD	-	1a	0	IFN/Riba	3	NR	N
7	F	67	UC	5-ASA	1b	3	IFN/Riba	3	NR	Y
8	M	52	UC	5-ASA	3	4	IFN	6	SVR	N
9	F	33	CD	-	1a	3	IFN/Riba	5	INT	N
10	M	57	UC	AZA+5-ASA	2b	2	IFN/Riba	6	SVR	N
11	F	56	CD	5-ASA	1b	3	IFN/Riba	8	REL	N
12	M	41	UC	5-ASA	1a	3	IFN/Riba	12	SVR	N
13	M	46	UC	-	1	3	IFN/Riba/Tel	12	SVR	N
14	M	57	CD	AZA+5-ASA	3	4	IFN/Riba	6	SVR	N
15	F	35	CD	budesonide	3	0	IFN/Riba	6	SVR	Y

IBD, inflammatory bowel disease; HCV, hepatitis C virus; UC, ulcerative colitis; CD, Crohn's disease; IFN, interferon; Riba, ribavirin; Tel, telaprevir; 5-ASA, 5-aminosalicylate; NR- no response, SVR- sustained virologic response, REL- relapse, INT- intolerance to therapy

Table 4

Hematological parameters before and during HCV treatment.

Parameter	Before (median)	After (median)	Change (median)
WBC ($\times 10^9/L$)	6.4	2.3	4
ANC ($\times 10^9/L$)	3.6	1	2.7
Hemoglobin (g/dL)	14.4	10.9	3.7
Platelets ($\times 10^9/L$)	201	126	75

WBC- white blood cells, ANC- absolute neutrophil count