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Research Article

Interferon Induced Ulcerative Colitis in Chronic HCV Patients: Management and Review of Literature

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ABSTRACT

Background: Interferon induces ulcerative colitis in chronic HCV patients treated with PegIFN and ribavirin therapy. The aim of the work is to assess the role of interferon in inducing ulcerative colitis in chronic HCV patients treated with PegIFN and ribavirin therapy as well as discussing the management for both ulcerative colitis and HCV. Materials and Methods: The study included four chronic HCV patients, their age ranged from 28-61 years, they were subjected to combination therapy (Peg IFN and ribavirin). All cases developed early gastrointestinal symptoms (4-20 weeks during treatment) comprising loose motions and bloody diarrhea. The diagnosis was established on clinical, laboratory, endoscopy and histology findings. Determination of anti-Saccharomyces cervisae antibodies (ASCA) and perinuclear anti-neutrophil cytoplasmic (p-ANCA) antibodies was performed using indirect immunofluorescence technique and ELISA, respectively. The calprotectin (FC) in stool was estimated. Results: Chronic HCV patients treated with interferon developed ulcerative colitis that was diagnosed by calprotectin in stool and proctosigmoidoscopy or colonoscopy. Colonoscopy showed a picture suggestive of the mild form of ulcerative colitis. The examined biopsies showed the active form of ulcerative colitis. Serologically P-ANCA was positive in two cases and negative in two cases. While ASCA was negative in all patients. Moreover, the calprotectin in stool was positive in all cases. All four cases were treated with mesalazine (5-ASA) 3 g/day in divided doses for the ulcerative colitis for 6 months while they were on Peg IFN and ribavirin for HCV therapy. The bleeding stopped, re-endoscopy and biopsy revealed complete resolution and the patients showed sustained virological response (SVR). Conclusion: Interferon used in treating chronic HCV patients can be considered an initiating factor of ulcerative colitis that can be diagnosed by estimating calprotectin in stool, proctosigmoidoscopy or colonoscopy, ~~and~~ ASCA and P-ANCA. Our study suggests the treatment of ulcerative colitis with 5-ASA in HCV patients treated with combination therapy (IFN and ribavirin) for 6 months after completing HCV treatment.

Keywords: Chronic HCV patients, ulcerative colitis, ASCA, P-ANCA, fecal calprotectin.

INTRODUCTION

The HCV infection is highly prevalent in Africa and the Eastern Mediterranean region[1]. Above 170 million people globally are infected with HCV[2-4]. The primary goal of HCV therapy is to cure the infection[5]. The combination of pegylated interferon (PegIFN)-α and ribavirin for 24 or 48 weeks was the approved treatment for chronic hepatitis C until 2011. Accordingly, IFN and ribavirin is still the recommended choice in HCV treatment[6,7]. Gastrointestinal disorders especially diarrhea was observed in a proportion of patients treated with the currently approved combination treatment of chronic hepatitis C (CHC), pegylated-interferon alpha (PEG-IFNa) plus ribavirin (RIB)[8]. At the same time, several case reports of one to two cases revealed that treatment of chronic viral hepatitis with IFNa or PEG-IFNa with or without RIB was related with the onset of clinically and histologically confirmed acute colitis of the inflammatory bowel disease (IBD)[8,9].

Moreover, Interferon (IFN) alpha was described as a trigger of several autoimmune disorders as Ulcerative colitis (UC), a relapsing chronic inflammatory disorder of the colon[10,11]. Several reports suggested that the presence of inflammatory bowel disease (IBD) is not a contraindication for interferon-alpha (IFN α) based treatments. Furthermore, a randomized placebo-controlled trial of PEG-IFN α in patients with active ulcerative colitis concluded that PEG-IFN α is safe if given in small doses but not effective treatment for these patients[12]. Currently biomarkers applied in diagnosing ulcerative colitis include perinuclear anti-neutrophil cytoplasmic (pANCA), anti-Saccharomyces cerevisiae antibodies (ASCA), and fecal calprotectin[13]. Among these biomarkers, calprotectin showed the best correlation with endoscopic activity in both CD and UC[14].

MATERIALS AND METHODS

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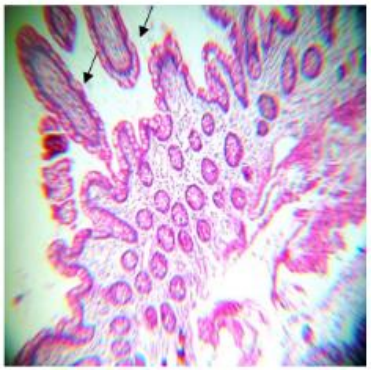

Figure 1: Hematoxylin and Eosin (H&E) stained endoscopic biopsy showing case (1) with mild ulcerative colitis and evidence of crypt abscess on the left of the micrograph (thin arrows) as the lumen of the gland is filled with acute inflammatory infiltrate (X100).

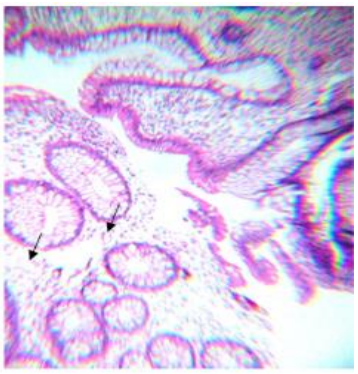

Figure 2: H&E stained endoscopic biopsy showing case (1) with healing ulcerative colitis and minimal to mild inflammation of the crypts and lamina propria (X100).

The study included four chronic HCV patients, their age ranged from 28-61 years that were subjected to combination therapy (Peg IFN and ribavirin). The four patients were subjected to full colonoscopy with ileal visualization and assessed using endoscopic component of the Mayo score[15]. Colonic biopsies were accomplished and a sample was taken from the suspected lesions for histo-pathological studies. Moreover, blood and stool samples were performed for both serological antibody markers (ASCA and P-ANCA) and calprotectin respectively. The study was carried out in compliance with the Declaration of Helsinki and approved by the Ethical Committee of the National Hepatology and Tropical Medicine Research Institute Research.

Histopathology

The biopsy specimens were fixed in 10% buffered formalin in room temperature and then embedded in paraffin blocks. Histopathological sections were stained using hematoxylin and eosin routine examination and were assessed for detection of mucosal ulceration and its extent, degree and type of inflammation, presence of crypt abscesses, granulomas, fibrosis, glandular distortion, goblet cells preservation and dysplasia and its degree[16].

Assays of fecal calprotectin and lactoferrin

Patients provided a stool sample for the measurements of calprotectin. The collection of stool was performed before the start of bowel cleansing for ileo-colonoscopy. All samples were stored at -20C, thawed, and analyzed by an ELISA test (Calprotectin Bühlmann ELISA; Bühlmann, Schonenbuch, Switzerland).

RESULTS

Four chronic HCV patients developed early (4-20 weeks during treatment) gastrointestinal symptoms comprising loose motions and bloody diarrhea. All cases denied any past history of ulcerative colitis (UC). Stool examination of all patients were negative for ovae, parasites and closridium difficle toxins. Colonoscopy showed a picture suggestive of the mild form of ulcerative colitis (abnormal vascular pattern, multiple superficial ulcerations and sub-mucosal hemorrhagic spots at the recto-sigmoid colon in three cases and pan-colitis in one case only) (Table1). The examined biopsies showed the active form of ulcerative colitis (marked congestion of the mucosa with superficial ulcerations and heavily infiltrated by chronic inflammatory cells with crypt abscess formation) (Fig.1). Serologically P-ANCA was positive in two cases (case 1 and 2) and negative in the other two cases. While ASCA was negative in all patients. Moreover, the calprotectin in stool was positive in all cases. All four cases were treated with mesalazine (5-ASA) for 6 months by 3 g/day on divided doses in addition to Peg IFN and ribavirin for HCV therapy. Consequently, the bleeding stopped, re-endoscopy and biopsy revealed complete resolution of the previous findings (Fig. 2) and a sustained virological response (SVR).

DISCUSSION

In this review, we listed cases of IFN induced UC and discussed their findings aiming to exploring the relation between IFN and ulcerative colitis in HCV patients as well as highlighting the best management regimen for both HCV and UC in those cases. The colonoscopy and histopathology revealed mild symptoms that need only modest doses of 5-ASA without the use of steroids. Moreover, on follow up the symptoms as well as colonoscopic and histopathological findings of UC disappeared after 6 months of treatment in all cases (Table 1). This coincides with the observations of previous investigators who explained that peginterferon's immune modulatory properties, may cause an emergence or exacerbation of immune-mediated disorders, such as thyroiditis, inflammatory bowel disease, atopic dermatitis, or psoriasis[17-19].

In our study, colonoscopy and histopathology as well as serological markers and faecal calprotectin were used to diagnose UC cases. Calprotectin showed significant correlation with endoscopic findings in both CD and UC. Similarly, several meta-analyses confirmed the value of calprotectin in discriminating IBD from non-IBD[20]. Furthermore, we continued the combination therapy (PegIFN and ribavirin) while treating the UC with (mesalazine) simultaneously, and for another 6 months after completing the HCV treatment, although other

Table 1: Demographic data of patients and comparing to previous studies.

Author's name	age / sex	P/H of IBD	HCV treatment	Onset of symptoms (W)	Diagnostic tools	Action taken	Treatment given	F/U (prognosis)
El-Atrebi,2015								
Case 1:	53 yrs (M)	-ve	PegIFN ∝ 2a and ribavirin	W 20	Pos. FC in stool and P-ANCA Colonoscopy and histopathology	Continue HCV treatment till 48W	mesalazine 3 g/day	Clinical and endoscopic improvement
Case 2:	44 yrs (F)	-ve	Peg IFN ∝ 2b and ribavirin	W 4	Pos. FC in stool and P-ANCA Colonoscopy and histopathology	Continue HCV treatment till 48W	mesalazine 3 g/day	Clinical and endoscopic improvement
Case 3:	61 yrs (M)	+ve	Peg IFN ∝ 2b and ribavirin	W 16	Pos. FC but neg P-ANCA Colonoscopy and histopathology	Continue HCV treatment till 48W	mesalazine 3 g/day	Clinical and endoscopic improvement
Case 4:	28 yrs (F)	-ve	PegIFN ∝ 2a and ribavirin	W 20	Pos. FC but neg P-ANCA Colonoscopy and histopathology	Continue HCV treatment till 48W	mesalazine 3 g/day	Clinical and endoscopic improvement
Akif, et al.,[10]	34 yrs (F)	-ve	PegIFN and Ribavirin	W 4	Colonoscopy (Lt sided colon) and histopathology	Stop HCV treatment	Mesalazine 2g/d	Healing mucosa by third month of therapy
Tursi, [23]	63 yrs (M)	-ve	PegIFN 2b and Ribavirin	W12	Colonoscop (pan-colitis) and histopathology	Stop HCV treatment	Mesalazine 2.5g/d and steroid	Clinical improvement after one month
Watanabe et al., [24]	55 yrs (M)	+ve	PegIFN 2b and Ribavirin	W 10	Colonoscopy and histopathology	Stop HCV treatment	Mesalazine and steroid	improved
Sprenger et al., [25]	54 yrs (M)	-ve	PegIFN 2a and Ribavirin	W 14	Colonoscopy (pan-colitis) and histopathology	Stop HCV treatment	Mesalazine and steroid	improved

Pos.=positive FC= Fecal Calprotectin Neg.=negative

studies stopped the HCV treatment. This was safe for our patients and carried no risks, as steroid unfortunately often increase the hepatitis C viral load and cautious use of systemic corticosteroids is warranted given their adverse effects on hepatitis C viral load[21]. The safety in using IFN in ulcerative colitis cases was supported by Konstantinos et al., in his randomized placebo-controlled trial as well as it was not contraindicated in those cases in previous reports[10,12,22]. Moreover, it was important to determine whether systemic corticosteroids are required to treat IFN associated UC. Our study suggested that IFN induced mild form of UC that does not need systemic steroid as treatment.

CONCLUSION

Interferon used in treating chronic HCV patients can be considered an initiating factor for ulcerative colitis that can be diagnosed by calprotectin in stools, procto-sigmoidoscopy or colonoscopy, ASCA and P-ANCA. Our study suggests the treatment of ulcerative colitis with 5-ASA in HCV patients who are treated by combination therapy (IFN and ribavirin) for 6 months after completing the HCV treatment.

The Authors declared no conflicts of interest.

INFORMED CONSENT STATEMENT

All studied participants, or their legal guardian, provided informed written consent prior to study enrollment

CONFLICT-OF-INTEREST STATEMENT

Authors declared no conflict of interest

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