

Chronic viral hepatitis “B” and “C” in patients with ulcerative colitis

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Abstract

Ulcerative colitis (UC) is a chronic inflammatory disorder of the large intestine which represents with constant exacerbations and remissions. Few of these patients also have a chronic Hepatitis ‘B’ (HBV) or chronic Hepatitis ‘C’ (HCV) infection. Treatment of moderate and severe forms of UC requires immunosuppression, whilst interferon therapy for HBV- and HCV-infections stimulates the immune system. Case Description: Four patients with UC were included. One with HBV-infection (male) and three had HCV-infection (2 males and 1 female). Patients were treated with specific antiviral therapy, as well as, with immunosuppressant medications (Corticosteroids and Azathioprine) for UC. Patient with chronic HBV-infection: had severe UC with frequent exacerbation. Despite that Pegylated Interferon alfa was initiated and UC exacerbation followed. Lamivudine was conducted and when viral replication was undetectable immunosuppression was restarted. Remission of UC was achieved. Patients with chronic HCV-infection: one of them was with mild UC, the other two were with a severe form of the disease. In all of the patients, first of all stable remission of the UC was achieved, afterwards they were all treated for HCV-infection with Pegylated Interferon and Ribavirin. During the antiviral treatment the UC did not exacerbate in any of the patients. Conclusions: 1. Before starting interferon treatment in patients with UC who have HBV and HCV-infection, remission of the UC must be achieved; 2. Nucleotide/side analogues in chronic HBV-infection allow rigorous immunosuppressive treatment of UC; 3. All HBsAg(+) positive patients with UC, regardless of their replication rate, who will undergo immunosuppressive therapy must be treated with Nucleotide/side analogues.

Key words

ulcerative colitis, chronic hepatitis B, chronic hepatitis C, Pegylated interferon alpha, NUC

Background

Ulcerative colitis (UC) is a chronic immune mediated inflammatory disorder of the large intestine (1) which represents with constant exacerbations and remissions. The rectum is always affected spreading from the distal to the proximal colonic segments. The etiology is currently unknown. Chronic, uncontrolled mucosal inflammation is observed (2).

Traditional immunosuppressors, mainly azathioprine, methotrexate and cyclosporin, represent an important therapeutic option for patients with moderate and severe UC (3, 4).

However, few of these patients also have a chronic hepatitis "B" (HBV) or "C" (HCV) infection (5). Immunosuppressive therapy can be associated with a number of severe adverse events, including reactivation of viral hepatitis infection (6, 7) or worsening of active chronic HBV or HCV infection.

As part of the multifactorial etiology of UC, immune disturbances and imbalance are discussed, while chronic HBV and HCV are infections that have immune pathogenesis (8). Thus, immunosuppressive therapy can worsen the course of chronic HBV and HCV infections, whilst immunomodulatory drugs used to cure HBV and HCV can deteriorate UC.

Patients who have both active UC and chronic viral hepatitis are a therapeutic problem. Pegylated interferon alpha (peg-IFN) therapy for HBV- and HCV-infections stimulates the immune system and may exacerbate UC.

Case Description

We present 4 clinical cases of patients with ulcerative colitis and chronic HCV and HBV infections.

Case number 1: 30 years old male with mild ulcerative colitis, diagnosed in 2005. The disease affected rectum and sigmoid colon. He had less than one exacerbation per year. He received maintenance therapy with Mesalazine 3 grams/daily. During the active phase of the disease he received corticosteroids with maximum dose of 40 mg/daily, which were then tapered and stopped, Methronidazole 500mg/twice daily and Ciprofloxacin 400mg/ twice daily.

In the year 2007 HCV-infection - genotype 1 was found. Liver biopsy was performed showing chronic active hepatitis. The patient underwent one year treatment with peg-IFN and Ribavirin. When this therapy was started the UC was in remission. The patient had sustained virological response and no deterioration of UC was observed during peg-IFN treatment.

Case number 2: a 61 years old female with long-standing (more than 15 years), severe UC. She had a chronic active course of the disease. She was treated with high doses of Corticosteroids during the severe flares and kept on low doses in order to sustain remission. She received Mesalazine 3 grams/daily constantly. The patient underwent colectomy which resulted in long lasting remission.

The patient also had long-standing HCV-infection, genotype 1. The liver biopsy revealed chronic hepatitis progressing to liver cirrhosis.

After the colectomy, when the UC was under control, the patient received one year therapy with peg-IFN and Ribavirin. No exacerbation of the bowel disease occurred during the anti-viral treatment.

Case number 3: a 43 years old male diagnosed with severe UC in 2003, spreading to the splenic flexure of the bowel. The patient had 2-3 flares per year in the first years after he was diagnosed. He was constantly treated with Mesalazine 3 grams/daily. During the exacerbations he received Corticosteroids and antibiotics.

The patient also had chronic active hepatitis C. Initially, he received only supportive therapy because of the active UC. After 8 months of remission of the bowel disease, the patient started peg-IFN and Ribavirin and continued it for 1 year (genotype 1). No exacerbation of UC was registered for this period. Sustained virological response was achieved.

Azathioprine was added as a maintenance therapy for the UC.

Case number 4: a 44 years old male with severe UC, diagnosed in 2007. The patient had frequent exacerbations. The disease affected the left colon. The patient had been diagnosed with chronic HBV-infection in 1988, with liver histology showing high grade activity. Because of the viral infection, the UC was treated with antibiotics during the exacerbations, Mesalazine constantly and Azathioprine for a short term. Peg-IFN treatment of HBV-infection was tried for 10 months but no response was achieved and deterioration of UC occurred. Lamivudine therapy was started for the HBV-infection, when HBV-DNA was undetectable, Azathioprine was added as a maintenance therapy for UC and a long-lasting remission was observed.

Discussion

These cases demonstrate that when UC is in remission peg-IFN can be given in order to treat HBV or HCV infection. Several reports suggest that the presence of inflammatory bowel disease is not a contraindication for interferon-alpha-based treatments (9, 10). One randomised placebo-controlled trial of peg-IFN in patients with active ulcerative colitis concluded that peg-IFN is a safe but not effective treatment for these patients (11).

However, several reports revealed that treatment of chronic viral hepatitis with peg-IFN with or without Ribavirin was related with the onset of clinically and histologically confirmed acute colitis (12, 13, 14, 15). The result of another study (16) conducted in Crohn's disease (CD) patients with HCV-infection indicate that peg-IFN and Ribavirin for chronic hepatitis C is effective in patients with CD. Despite an increase in the number of loose stools in some patients, therapy was well tolerated and severe exacerbations were not registered. Patients with an increasing number of stools responded to short-term glucocorticoid therapy.

Interferon-based antiviral therapy affects UC activity. IFN-alpha is an immunoregulatory cytokine and has proinflammatory effects by stimulating a Th-1 response, which leads to IFN- and interleukin-2 production (17). As a result antiviral HCV treatment with peg-IFN may induce CD and UC activity. As mentioned before, inflammatory bowel disease flares are described in patients under peg-IFN treatment (12, 13, 14, 15). Anyhow, other investigators observed no increase in CD activity during treatment with peg-IFN with or without Ribavirin (18).

For HCV treatment oral, interferon-free regimens are expected in the near future. These novel drugs do not influence the immune system, act directly on viral replication and treatment duration is relatively short.

Chronic HBV-infection in UC patients is best treated with nucleotide/side analogues because the mechanism of action does not involve immune stimulation, thus there is no exacerbation of UC. They inhibit directly the viral replication. Several nucleotide/side analogues for HBV exist. The best are Tenofovir and Entecavir. A major drawback is that this class of drugs has to be taken constantly. If therapy is interrupted, viral reactivation occurs, in some cases resulting in severe hepatic failure and death (8).

To prevent HBV reactivation nucleotide/side analogues must be used in patients who are HBsAg+ inactive carriers but have to undergo immunosuppression with anti-tumor necrosis factor antibodies. HBV reactivation has ranged from self-limiting anicteric relapse to severe hepatitis, up to liver failure and death (19). On the other hand, the effect of conventional immunosuppressive drugs does not appear to be associated with high risk of HBV reactivation. Only three cases of reactivation, which resulted in hepatic failure, with two of them during conventional immunosuppressive therapy, such as prednisolone and/or azathioprine, are reported in the literature (20, 21). Patients undergoing double immunosuppression are at a higher risk of reactivation which usually occurs after more than one year of treatment (22). As preventive measures, all IBD patients should be screened for HBV markers at diagnosis and those who are positive for the hepatitis B surface antigen should receive antiviral prophylaxis before undergoing immunosuppression. Those who are negative should be vaccinated.

Conclusion

1. Before starting interferon treatment in patients with UC who have HBV and HCV-infection, remission of the UC must be achieved;
2. Nucleotide/side analogues in chronic HBV-infection allow rigorous immunosuppressive treatment of UC;
3. All HBsAg-positive patients with UC, regardless of their replication rate, who will undergo immunosuppressive therapy, must be treated with Nucleotide/side analogues.

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