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ORIGINAL PAPERS

BACTERIAL INFECTIONS IN PATIENTS WITH CHRONIC HEPATITIS C TREATED WITH PEG-INTERFERON AND RIBAVIRIN

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Abstract. Introduction. Treatment with peg-interferon (Peg-IFN) and ribavirin in patients with chronic hepatitis C (CHC) represents current standard therapy, although it is accompanied by multiple side effects. **Objectives.** The present study aims at analysing the prevalence and etiology of acute bacterial infections in patients with CHC who are following peg-interferon and ribavirin combination therapy. **Patients and methods.** We have retrospectively investigated the medical records of 62 patients with CHC who were managed at the Hospital of Infectious Diseases in Timișoara, Romania. We have included in the study the patients who presented detectable HCV RNA, normal or increased alanine aminotransferase levels, histological rate ≥ 1, fibrosis and were aged ≤ 65 years. All patients were treated with Peg-IFN α-2a (Pegasys, Roche), 180 μg/week and ribavirin (Copegus, Roche, 1 tablet = 200 mg), 1000-1200 mg/day (1000 mg/day for patients under 75 kilos and 1200 mg/day for patients over 75 kilos) for 48 weeks. The patients have been evaluated monthly clinically and biologically and different explorations were carried out in selected cases in accordance to the disease management protocol. **Results.** In the study group, 22 (35.5%, male=10, female=12) patients with acute bacterial infections were diagnosed as follows: 5 patients with staphylococcal infections, 3 with urinary infections, 3 with acute bronchitis, 2 with bacterial pneumonia, 3 with acute sinusitis, 4 with acute tonsillitis and 2 with acute angiocholitis. The development of acute bacterial infections in our study group was associated with an advanced stage of liver fibrosis (F3-F4 – 16 patients), neutropenia (N-II – 11 patients), anemia (AII – 16 patients) and advanced thrombocytopenia (TII – 18 patients). **Conclusions.** The high prevalence (35.5%) of acute bacterial infections in patients with chronic hepatitis C treated with Peg-IFN and ribavirin requires a rigorous clinical, laboratory and therapeutic monitoring of the patients during this period.
Keywords: hematological disorders, leukopenia, neutropenia, thrombocytopenia

Introduction

Chronic hepatitis C (CHC) is one of the most common chronic viral infections in our country and frequently evolves to cirrhosis and hepatocellular carcinoma [1].

Treatment with peginterferon (Peg-IFN) alpha and ribavirin for a period of 24-48 weeks in patients with CHC is the current standard therapy leading to sustained eradication of the virus associated with improved long-term changes in liver histology and reduced risk of cirrhosis and hepatocellular carcinoma [1,2].

This complex and long-term treatment is accompanied by multiple side effects, and consequently requires a careful clinical and laboratory monitoring in accordance to the therapeutic protocol established at national level by a committee of specialists.

The most common side effects are the hematological ones. Thus, the most common side effect of IFN therapy is bone marrow suppression, resulting in a decrease of the leukocyte count [3]. The absolute number of neutrophils and lymphocytes may decrease by 30-50% during therapy with IFN [4].

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Neutropenia induced by IFN therapy and associated with the risk of developing bacterial infections is being considered the most frequent reason for reduction or sometimes cessation of Peg-IFN dosage [1,2].

Objectives

The aim of this study was to determine the prevalence and etiology of acute bacterial infections in a group of patients with CHC who were treated with Peg-IFN and ribavirin.

Patients and Methods

We have retrospectively investigated the medical records of 62 patients with CHC who were managed at the Hospital of Infectious Diseases in Timişoara, Romania.

Diagnosis was based on epidemiological assessment (risk factors for CHC), clinical data (asthenia, loss of appetite, hepatalgia, hepatomegaly, jaundice), laboratory results (blood counts, erythrocyte sedimentation rate, alanine aminotransferase, aspartate aminotransferase, unconjugated bilirubin, conjugated bilirubin, total bilirubin, gamma-glutamyl transpeptidase, serum alpha-fetoprotein, alkaline phosphatase, C-reactive protein, glycemia, uremia, serum creatinine, uric acid, protein electrophoresis, serum amylase, amylasuria, cholesterol, triglycerides, urinalysis, immunoglobulin M antibody to hepatitis A virus, IgM antibody against hepatitis B core antigen, hepatitis B surface antigen, antibodies against the hepatitis C virus (anti-HCV), HCV RNA PCR and other tests and explorations (liver biopsy, thoracic radiography, abdominal echography, abdominal computed tomography). An automatic biochemical analyzer (Konelab 301) with wide access for both routine and specific tests has been used for biochemical determinations. Bacterial identification and antibiotic susceptibility testing were performed using an automated system, VITEK 2 Compact. Detection of the DNA or RNA of the hepatic viruses was performed using COBAS TaqMan 48 that allows automatic real-time amplification. The diagnosis of the bacterial infections in patients with unspecified etiology (n=7) was performed based on clinical findings, laboratory tests and other specific investigations.

All patients were treated with Peg-IFN α-2a (Pegasys, Roche), 180 μg/week and ribavirin (Copegus, Roche, 1 tablet = 200 mg), 1000-1200 mg/day (1000 mg/day for patients under 75 kilos and 1200 mg/day for patients over 75 kilos) for 48 weeks. The patients have been evaluated clinically and biologically and different explorations were carried out in selected cases in accordance to the disease management protocol.

Anemia was classified according to hemoglobin (Hb) values as follows: mild (Hb <12 g/dL), moderate (Hb <10 g/dL) and severe (Hb <8.5 g/dL).

Neutropenia was defined as absolute neutrophil count of less than 1500 cells/μL and classified as follows: mild (1499-750 cells/μL), moderate (749-500 cells/μL) and severe (<500 cells/μL).

Thrombocytopenia was classified as follows: mild (149,000-50,000 platelets/mm^3), moderate (49,000-25,000 platelets/mm^3) and severe (<25,000 platelets/mm^3).

Statistical evaluation was performed using Epi Info statistical software package (Centers for Disease Control, 1994).

Results

Of the study group, 35 patients (56.5%) were male and 27 (43.5%) were female (figure 1). The overall mean age was 48.14 years (range 35-64 years).

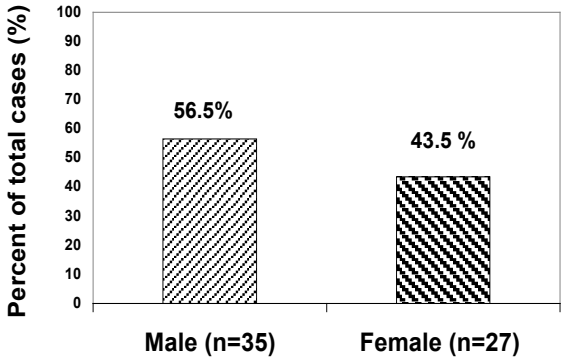

Figure 1. Gender distribution of the study group

According to clinical features, laboratory specific tests and different explorations, 22 patients (35.5%, male=10, female=12, mean age was 46.12 years) had acute bacterial infections that occurred during the combined therapy with Peg-IFN and ribavirin (figure 2). The remaining 40 patients (64.4%, 18 males and 22 females with the mean age of 45.21 years) did not develop bacterial infections during the treatment.

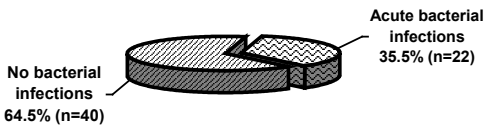

Figure 2. Frequency of patients with acute bacterial infections in the study group

Patients with CHC who were enrolled in the therapy program with Peg-IFN and ribavirin developed acute skin infections (cutaneous staphylococcosis), urinary infections, acute respiratory infections (acute bronchitis, acute pneumonia, acute sinusitis, acute angina) and infections of the biliary tract (acute angiocholitis, table I).

Diagnosis	No. of patients	% of total cases (n=62)
Cutaneous staphylococcosis	5	8.1
Urinary infection	3	4.8
Acute bronchitis	3	4.8
Acute pneumonia	2	3.2
Acute sinusitis	3	4.8
Acute angina	4	6.5
Acute angiocholitis	2	3.2
Total	**22**	**35.5**

Figure I. Bacterial infections in the study group

Liver biopsy was performed in all patients included in the National Program for the Treatment of CHC and allowed to establish the stages of fibrosis and necroinflammatory activity of the liver (METAVIR score). According to the histological exam of the biopsy samples, 16 out of 22 patients with bacterial infections were in the F3-F4 stage (liver fibrosis METAVIR score) and 4 out of 40 patients (p = 0.0004) without bacterial infections were in the F3-F4 stage (figure 3).

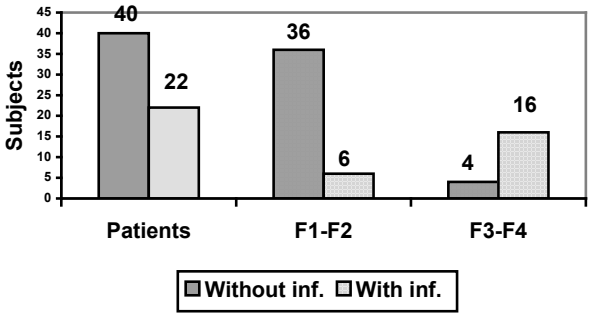

Figure 3. Distribution of hepatic fibrosis in patients of the study group

Of the 22 patients found to have acute bacterial infections, 5 presented normal levels of neutrophils and 17 had neutropenia (mild neutropenia n=6, and moderate neutropenia n=11) versus only 5 patients with neutropenia out of 40 patients (p = 0.0007) without bacterial infections (figure 4).

Noteworthy was that 77.3% of infections occurred as a result of leukopenia and neutropenia produced by Peg-IFN during months 4 to 8 of treatment. Of the 22 cases with acute bacterial infections, 6 had mild anemia, whereas 16 had moderate anemia versus only 8 patients with anemia out of 40 patients (p = 0.0006) without bacterial infections (figure 5).

Thrombocytopenia represents one of the first side effects of the treatment with Peg-IFN, and this may produce numerous difficulties to physicians towards the management of such patients. Of the 22 patients with acute bacterial infections, mild thrombocytopenia was detected in 4 cases and

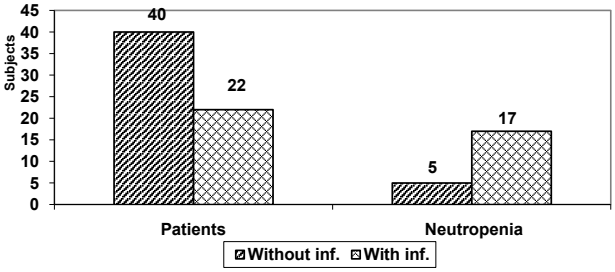

Figure 4. Frequency of neutropenia in patients of the study group

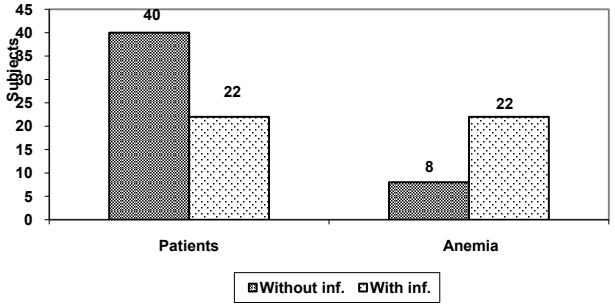

Figure 5. Distribution of anemia in patients of the study group

moderate thrombocytopenia in 18 cases versus 8 patients with anemia out of 40 patients (p = 0.005) without bacterial infections (figure 6).

Bacterial identification and antibiotic sensitivity testing were performed using bacteriology techniques in 13 (59.1%) out of 22 cases of acute bacterial infections. Thus, *Staphylococcus aureus* was isolated in 7 cases, *Escherichia coli* in 2 cases

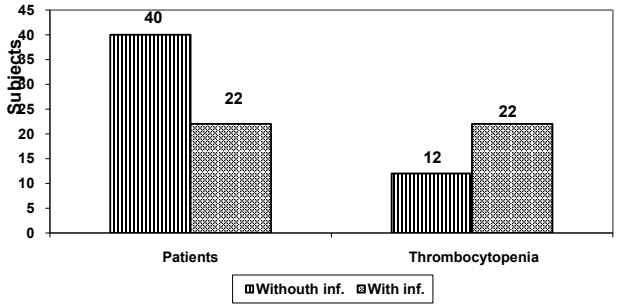

Figure 6. Distribution of thrombocytopenia in patients of study group

and Beta-hemolytic *Streptococcus* in 4 cases.

Discussions

CHC is a major cause of morbidity and mortality from liver disease worldwide. Treatment of CHC remains a topical issue that continues to raise the interests of researchers in the fields of hepatology and molecular biology. In the past decade, Peg-IFN/ribavirin combination therapy has reached a rate of sustained virologic response of 50-60% in patients with HCV genotype 1. Favorable therapeutic response in patients with genotype 1 requires adequate treatment in the dosage prescribed, avoiding interruptions, and eventually lowering the doses when needed [1].

Patient's adherence and compliance are important factors for obtaining therapeutic success [5]. Appropriate follow-up and treatment of adverse effects by the physician may have favorable influences on these factors.

However, treatment with Peg-IFN and ribavirin has numerous and multiple side effects which represent a challenge for the practitioner. A common side effect of combination therapy is bone marrow suppression, including reduction in the leukocyte count. Neutropenia is the most common cause of Peg-IFN dose reduction or drug discontinuation [2,4].

Treatment with Peg-IFN causes direct inhibition of the bone marrow and subsequent peripheral leukopenia and neutropenia, which are often associated with acute bacterial infections [8]. Decreased neutrophil counts may increase the susceptibility to infections [2,6].

In our study group, acute bacterial infections that occurred during therapy with Peg-IFN and ribavirin were associated with neutropenia (5/40 patients versus 17/22, figure 4). The prevalence of bacterial infections was similar to that reported by Curtis, 34% versus 35% [2].

Peg-IFN α-2a dosage was reduced to 135 μg/week in patients with moderate neutropenia. There were no cases with severe neutropenia, therefore Peg-IFN α-2a was not discontinued in any patient. Filgrastim (granulocyte colony-stimulating factor, G-CSF) has not been used for treating neutropenia secondary to antiviral therapy in the Clinic of Infectious Diseases yet.

J.F. Yang and his colleagues reported that 86% of patients with HCV treated with Peg-IFN and ribavirin developed severe neutropenia within the first 4 weeks of combined therapy, but afterwards the neutrophil count stabilized at >1000 cells/μL [7].

Infectious complications were more prevalent in the study of Curtis and his colleagues (67 of 192 patients with combined antiviral treatment; 40% had infections of the respiratory tract) [2].

In our study, the immunocompromised status may have represented another favorable factor for bacterial infections in 17 patients who had at-risk co-morbidities (diabetes mellitus, obesity, vitiligo, psoriasis, sequelary pulmonary tuberculosis, chronic duodenal ulcer, chronic bronchitis, chronic gastritis). By comparison, 5 patients (out of 22 with acute bacterial infections) with normal neutrophil counts did not present any comorbidities which could promote the infections. Of the 40 patients without bacterial infections, 24 did not present any comorbidities and 16 had associated diseases which could not facilitate the development of the infections (spasmophilia, gastroenteritis, acute hypertension, irritable bowel syndrome, cervical spondylosis, biliary dyskinesia, lumbar discopathy, giardiasis).

Iacobellis and his colleagues reported a 28.8% rate of infection (16.6% with severe infections) in a group of 66 patients with CHC and decompensated cirrhosis treated with Peg-IFN and ribavirin. Predictive factors of infection were Child-Turcotte-Pugh score class C and neutrophil count less than 900 cells/μL during therapy. Their results suggest the importance of neutropenia in increasing susceptibility to infection in patients with hepatic decompensation [9]. In our study group, the advanced stage of liver fibrosis was associated with the development of bacterial infections (4/20 patients versus 16/22, figure 3).

Acute bacterial infections were significantly associated with anemia (8/40 patients versus 22/22, p=0.0006, figure 5). Ribavirin doses were not reduced in cases with mild anemia associated with acute bacterial infections (n=6), but in patients with moderate anemia (n=16) the ribavirin dose was reduced to 600 mg/day. Discontinuation of therapy was not necessary because none of the patients had severe anemia.

Our results show a significant association (p=0.005) between acute bacterial infections (n=22) and thrombocytopenia (12/40 patients versus 22/22, figure 6). Peg-IFN doses were not changed in patients with mild thrombocytopenia (n=4), but in cases with moderate thrombocytopenia (n=18)

Peg-IFN doses were reduced to 135 μg/week. Discontinuation of therapy was not necessary because none of the patients had severe thrombocytopenia.

Conclusions

Patients with CHC undergoing treatment with Peg-IFN and ribavirin have an increased risk of bacterial infection as a result of IFN-induced reversible bone marrow suppression with myelopoiesis inhibition.

Temporary dose reduction of Peg-IFN as well as antibiotic and symptomatic treatment for a limited period of time allow for control of bacterial infections without stopping antiviral therapy.

In our study group, acute bacterial infections occurred in 35.5% of patients under therapy, but most of them were mild infections and required short-term antibiotic therapy; none of the patients developed complications. Our results show a significant association between acute bacterial infections and thrombocytopenia, neutropenia, anemia and F3-F4 stage of liver fibrosis (METAVIR score).

Clinical monitoring and therapy should be individualized in each patient with CHC treated with Peg-IFN and ribavirin.

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