Neutropenia in chronic hepatitis C during Interferon and Ribavirin Therapy.

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Abstract

Background: Neutropenia is a condition characterized by an abnormally low number of a type of white blood cells called Neutrophils, up to 25% of people who take pegylated interferon, ribavirin and an HCV protease inhibitor experience Neutropenia.

Aim of the work: The study will be intended to analyze neutrophil counts and associated conditions of the liver and spleen, platelet count, liver enzymes and infections, during Interferon and Ribavirin therapy.

Patients and methods: One hundred forty two patients with chronic hepatitis C virus infection, their age between (18-59) years, selected from the National Hepatology and Tropical Medicine Research Institute were included in this study, during Interferon and Ribavirin therapy.

All the patients were subjected to the following history, through clinical examination, abdominal ultrasonography and collection of blood samples for routine investigations, CBCs and serological assay for ALT, Bilirubin.

Results: Our results revealed presence of 32.4% anaemia, 18.3% Thrombocytopenia, 16.9% elevated ALT, 2.8% elevated bilirubine, 16.9% coarse liver, 25.4% hepatomegaly, 16.2% splenomegaly, and 16.9% of cases complained different shapes of infection, associated with Neutropenia in patients of chronic hepatitis C during interferon and ribavirin therapy.

Conclusion: Our study concluded that the prevalence of Neutropenia in chronic hepatitis C virus infection patients 23.8% during interferon and ribavirin therapy but it is not usually associated with infection.

Recommendations: Neutropenia is a complicated process that requires expert guidance from a medical provider.

Key Words: Neutropenia, chronic hepatitis C, side effect of interferon and ribavirin therapy.

Introduction

Many patients with chronic hepatitis C (HCV) infection undergoing treatment with pegylated interferon-alpha (PEG-IFN-alpha) and ribavirin develop neutropenia requiring dose reduction or granulocyte colony-stimulating factor (G-CSF) supp (Koirala, et al 2007). Hematologic side effects are common during treatment with pegylated interferon and ribavirin (Nachnani et al, 2009). To meet normal physiologic needs, a healthy adult produces roughly 60 billion neutrophils each day. While neutrophils are produced by the bone marrow at a prodigious rate, their blood halflife is short, 8 hours in a normal individual-Hence, lifespan vastly outnumber neutrophils by a ratio of about one thousand to one in the peripheral blood (Bolyard, et al., 2010). Under normal physiologic conditions, as stable equilibrium exists between marrow neutrophil production and peripheral utilization. When the production of neutrophils by the bone marrow is outpaced by utilization in periphery, the number of circulating neutrophils in the peripheral blood decreases and Neutropenia results (Bolyard, et al., 2010).

A common side effect of interferon alpha therapy is bone marrow suppression and particulary a reduction in white blood cell counts. Absolute neutrophil and lymphocyte counts typically decrease by 30% to 50% of baseline during therapy with the doses of interferon required to treat hepatitis C (Wongs, et al., 1996). Neutrophil counts can fall to levels that are
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associated with an increase in risk of bacterial infections and sepsis, in the large randomized controlled trials of pegylated or standard interferon combined with ribavirin neutropenia was listed as the most common reason for dose reduction (18 % of patients) and was a reason for early drug discontinuation in 1 % of patients (Manns, et al., 2010).

Neutropenia was defined as a peripheral absolute neutrophil count below 1,500 cells /ul, during therapy (Soza, et al., 2002). Patients with severe neutropenia, and particularly those with neutrophils levels less than 0.2 x 109 / L, have a significantly increased risk of infection due to invasion of asurface bacteria in the mouth, intestinal tract or skin. Such patients frequently demonstrate mucosal inflammation, particularly of the gingival and perirectal areas and often manifest cellulites, abcess, furunculosis, pneumonia or septicemia (Bolyard, et al.,2010)

Patients and Methods

One hundred forty two patients with chronic hepatitis C virus infection, their age between (18-59) years, selected from the National Hepatology and Tropical Medicine Research Institute were included in this study, during Interferon and Ribavirin therapy.

All patients have anti-HCV antibodies, HCV RNA in serum, evidence of chronic hepatitis on liver biopsy, elevated levels of aminotransferase above the upper limit, serum albumin, bilirubine, and prothombine time within normal limit with negative history of drug abuse, non reactive HBsAg, with exclusion of other chronic disease and pregnancy no clinical signs of decompensated liver disease. All the patients were subjected to the following history and through clinical examination, abdominal ultrasonography and collection of blood samples. A 5 ml whole blood was obtained by venipuncture plus edeta samples were analysed at Celltac F Automated Haematology analyzer, M E K-8222 J / K Japan Giza Medical.

Ethical consideration:

Informed consent was obtained from each patient at the time of drawing blood . The Research Ethical Committee of the General Organization for Teaching Hospitals and Institutes approved the study protocol.

Statistical analysis : Analysis of data was done by IBM computer using SPSS (Statistical program for social scienceversion 12). Data were expressed as description of qualitative valuable as numbers and percentage.

Results

The study included 142 patients of chronic hepatitis C virus infection with Neutropenia during interferon and ribavirin therapy.

We found that: neutropenia was associated with:

* anaemia in 46 patients ( 32.4 %) during treatment (Graph 1).
*16.9 % (24 patients) with cirrhosis (Graph 2).
*25 % (36 patients) with hepatomegaly (Graph 3).
*16.2 % (23 patients) with splenomegaly (Graph 4).
*18 % (26 patients) with thrombocytopenia (Graph 5).
*17 % (24 patients) with ALT elevation (Graph 6).
*2.8 % (4 patients) with bilirubin elevation (Graph 7).
*16.9 % (24 patients) with infection (Graph 8).
*23.8 % the prevalence of neutropenia in CHVC infection (Graph 9).

CBCs before Interferon and Ribavirin were within normal limit.

<table>
<thead>
<tr>
<th>CBCs during Interferon and Ribavirin Therapy :</th>
<th>Test (CBCs)</th>
<th>Hb</th>
<th>Platelet</th>
<th>WBCs</th>
<th>Neutrophils</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lab. Abnormality</td>
<td>8 – 10.9 g / dl 50.000-100.000/cmm RBCs count: 2.9-5.1 Millions/cmm</td>
<td>1.6000-2.9000 /cmm 500-1000 /cmm</td>
<td>Differential Leucocytic count :</td>
<td>Neutrophils : 500- 1000 /cmm Staff : 0 – 5 % Segmented : 40 – 61 % Lymphocytes :20 – 59.2 % Monocytes : 2-17 % Eosinophils : 1-6 % Basophils : 0-1 %</td>
<td></td>
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</tbody>
</table>
Graph (1): Illustrate the presence of 32.4% anaemia in neutropenic CHCV patients during interferon and ribavirin therapy.

Graph (2): Illustrate the presence of 16.9% liver cirrhosis in neutropenic CHCV patients during interferon and ribavirin therapy.
Graph (3): Illustrate the presence of 25% hepatomegaly in neutropenic CHCV patients during interferon and ribavirin therapy.

Graph (4): Illustrate the presence of 16.2% splenomegaly in neutropenic CHCV patients during interferon and ribavirin therapy.
Graph (5): Illustrate the presence of 18% thrombocytopenia in Neutropenic CHCV patients during interferon and ribavirin therapy.

Graph (6): Illustrate the presence of 17% ALT elevation in neutropenic CHCV patients during interferon and ribavirin therapy.
Graph (7): Illustrate the presence of 2.8% bilirubin elevation in neutropenic CHCV patients during interferon and ribavirin therapy.

Graph (8): Illustrate the presence of 16.9% bacterial infection in neutropenic CHCV patients during interferon and ribavirin therapy.
Graph (9): Illustrate the percentage ratio of neutropenia in CHCV patients during interferon and ribavirin therapy.

**Discussion**

In the large randomized trials of pegylated interferon combined with ribavirin neutropenia was listed as the common reason for dose reduction (18%) of patients, and was a reason for early drug discontinuation in 1% of patients (Manns, et al., 2001). Neutropenia was defined as a peripheral absolute neutrophil count below 1,500 cells/UL. During therapy, neutropenia was assessed at levels of 1,000, 750, and 500 cells/UL. The usual thresholds for dose reduction of interferon or discontinuation in therapy of hepatitis C (Soza, et al., 2002).

This work estimates neutrophil count by CBCs differential count examinations, and the associated factors, eg: anaemia (CBCs), liver cirrhosis, hepatomegaly and splenomegaly illustrated by ultrasound examination, thrombocytopenia (CBCs), ALT elevation, elevated bilirubin levels (serum), infections illustrated by culture and sensitivity or radiograph and clinical examination in chronic hepatitis C virus infection patients during pegylated interferon and ribavirin therapy.

In the present study, we found that the decrease in Hb % levels (anaemia) appear by frequent levels, associated with neutropenia during interferon therapy. (Kelleher, et al., 2010) found that anaemia is extremely among patients taking PEG / RBV combination therapy for chronic hepatitis C and this finding is in agreement with our results.

In our work, we observed by ultrasound examinations that liver cirrhosis was present by 16.9% of the patients. (Poynard, et al., 1997 & Poynard, et al., 2000) & Poynard, et al., (2001) postulated that chronic hepatitis C disease is generally slowly progressive: cirrhosis develops within 20 years in about 10-20% of patients with chronic disease. (Shepard, et al., 2005) found that 2.3% of the world population are persistently infected with HCV, worldwide up to 170 million individuals may be chronically infected, and are at risk of developing cirrhosis. Reherman and Nascimbeni, (2005) explained that fibrosis in chronic hepatitis C infection occurs as a result of the activation of hepatic stellate cells by cytokine and signaling.
molecules induced by the inflammatory process. These produce and deposit extracellular matrix proteins then fibrosis begins around the portal tracts and gradually extends out into the lobules towards the central veins, factors shown to accelerate the progression to cirrhosis, include older age at HCV acquisition, male gender, and steatosis may lead to advancing fibrosis. Thein, et al., (2008) explained that a recent meta analysis examining stage specific transition probabilities suggested that the probability of transition to a higher stage of fibrosis is greatest between f 2 and f 3 (4 stage system);Metavir. This results correlated with our study, that the group included for interferon therapy (f 2 and f 3) after liver biopsy, and liver cirrhosis was present by 16.9 %.

European Pediatric hepatitis C virus Networks, (2005) demonstrate that in HCV infection 30 % develop chronic active infection with persistent viremia, frequent abnormal and in some cases, hepatomegaly likely indicating liver inflammation and an early stage HCV related liver damage. Deutsch,(2010) observed that the physical examination of HCV patients may be normal or may demonstrate mild hepatomegaly or tenderness in advanced disease or cirrhosis the symptomatology and physical finding include hepatomegaly , splenomegaly, jaundice are more prominent and laboratory finding by significant for leucopenia. In the present study hepatomegaly associated with neutropenia in CHCV infection 25 % and this finding in agreement with our results.

Mistry and Jain(2011) postulated that chronic liver disease is usually accompanied “hypersplenism” diminished erythrocyte survival is frequent. In the present work splenomegaly in neutropenia in CHCV patients 16.2 % and this results correlated with our study.

Koirala, et al., (2007) found that hematological abnormalities including anaemia, thrombocytopenia and neutropenia are common adverse effects antiviral agents that are used to treat chronic HCV infection. In the present study we found that thrombocytopenia in neutropenia with CHCV infection 18 % and this results correlated with our results.

Cox, et al., (2005) discovered that serum aminotransferase decline from the peak values encountered in the acute phase of the hepatitis C disease, but typically remain abnormal by two fold to eight fold, serum ALT concentrations may fluctuate over time, and may even be intermittently or consistently normal. Serum aminotransferase levels remain abnormal after 12 months in 60 to 85 % of patients with C sporadic hepatitis. In the present work ALT elevation in neutropenia with CHCV infection patients during interferon and ribavirin therapy 17 % and this results in agreement with our results.

Fornari, et al., (1994) explained that all patients with hepatocellular disease show a variable degree of haemolysis. Chang, et al., (2005) observed that hepatitis C is associated with a higher incidence of gall bladder stones than patients with hepatitis B. Mistry and Jain, (2011) found that hepatocellular failure, and jaundice may affect the blood picture. Chronic liver disease is usually accompanied by "hypersplenism", diminished erythrocyte survival is frequent. In our work we found that 2.8 % of neutropenic CHCV patients have elevated bilirubin level during interferon and ribavirin therapy and this finding coincide with our results.

Franciscus, (2011) explained that the primary function of white blood cells is to fight off a variety of infections. There are many different types of white blood cells such as neutrophils. It is important to note that the vast majority of patients who develop interferon-induced neutropenia do not develop any serious infections that would be expected when compared to patients who develop neutropenia while on chemotherapy. In the present study, infection in neutropenic patients during interferon and ribavirin therapy affected 16.9 % in the form of pharyngitis, gingivitis, otitis media, urinary tract infection, and cellulitis and results correlated with our results.

Soza, et al., (2002) observed that neutropenia is frequent during treatment of hepatitis C with interferon and ribavirin but it is not usually associated with infection. Koirala, et al., (2007) found that after starting treatment with PEG-IFN-alpha, the absolute neutrophil counts (ANC) of 30 patients dropped below 1000 cells / ul after an average of 13 weeks, SD 10 weeks. Fraciscus (2011) postulated that clinical studies have shown that most people on HCV treatment experience some reduction in neutrophil count below the normal range, up to 20 % of people who take pegylated interferon and ribavirin experience neutropenia, up to 25 % of people who take pegylated interferon, ribavirin and an HCV protease inhibitor experience neutropenia. Wong, et al., (1996) who proved that a common side effect of interferon alfa therapy is bone marrow suppression and particularly a reduction in white blood cell counts. Absolute neutrophil and lymphocyte counts typically decrease by 30 % to 50 % baseline during therapy with the doses of interferon required to treat hepatitis C. In the present study neutropenia affected 23.8 % of CHCV
patients during interferon and ribavirin therapy and this finding in agreement with our results.

References


http://www.clinicaladvisor.com/hepatitis-c-the-silent-epidemic/artic...


إنخفاض في عدد كريات الدم البيضاء المتعادلة في مرضى الالتهاب الكبدى الوبائي سى المعالجين بعقار الانترفيرون و الريبافيرين

الخلفية:
إنخفاض في عدد كريات الدم البيضاء المتعادلة (النيتروفيل) يصل إلى 25% في المرضى المعالجين بالانترفيرون + الريبافيرين والمعالجين بعقار البروتياز الرادع (إنهبيتور) في مرضى الالتهاب الكبدى الوبائي سي.

الهدف من البحث:
دراسه تحليلية لنسبة الإنخفاض في عدد كريات الدم البيضاء المتعادلة (النيتروفيل) و يصاحبها من تأثير بالنسبه ( للكبد , الطحال , الصفائح الدموية , الإنزيمات الكبدية "الأدين ، صفراء " )

الطريقة البحث:
شملت الدراسة عدد 142 من مرضى الالتهاب الكبدى الوبائي سي المزمن متوسط أعمارهم ما بين (59-18) عاماً و العينات من مرضى المعهد القومي للكبد والأمراض المتعطشة و يجري جمع العينات خلال فترة تناول عقار الانترفيرون + الريبافيرين و جميع الحالات خضعتحللفحص الطبي بالسيرة الذاتية للمرضى و عمل الموجات الصوتية على البطن لجميع المرضى الذين لديهم ( أقسام مضادة للفيروس سي بالدم ، بي سي أر رقمى ، عينه كبدية تفيد الإصابة المزمنة بالفيروس ) مع وجود ارتفاع في نسبة الأمينوترايسيراز فوق المستوى العادى بالدم . قد تم أخذ عينات الدم للمريض لعمل الفحوصات الروتينيه السيرولوجى و صورة الدم الكامل .

النتائج:
أسفرت نتائج هذه الدراسة عن وجود انخفاض في عدد كريات الدم البيضاء المتعادلة (النيتروفيل) بنسبة 23.8% و يصاحبها انخفاض في عدد كريات الدم البيضاء المتعادلة (النيتروفيل) ب 32.4% . مع وجود تلف في الكبد بنسبة 19.6% و تضخم في الكبد بنسبة 25.4% و انخفاض في الصفائح الدمية بنسبة 16.2% و انخفاض في إنزيم الالانين ترانسفراز بنسبة 16.9% و وجود ارتفاع في نسبة الصفراء بنسبة 2.8% و نسبة العدوى المصاحبة للنيتروفيليا تصل إلى نسبة 16.9% .

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