ADVERSE EVENTS OF TREATMENT OF CHRONICAL HEPATITIS C WITH PEGYLATED INTERFERON AND RIBAVIRINE

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The efficacy and therapeutic value of hepatitis C treatment is dependent on the degree of tolerability and adherence to the drugs, which in turn are related to the management of the side effects. The aim of this study was the evaluation of the prevalence of adverse events during the treatment of chronical hepatitis C with pegylated interferon and ribavirine.

Over a period of two years (2009-2011), in the service of Hepatology and Gastroenterology UHC "Mother Tereza" were treated 47 patients (26 F, 55.3%; 21 M, 44.7%, with average age 46,14 ± 7,77 years old), diagnosed with chronical hepatitis C (5 patients with compensated form of liver cirrhosis) Most with genotype 1 (22 patients, 46.9%, 1b 20 patients); 20 patients with genotype 2, 42.5% (16 with genotype 2a/2c), 4 patients with genotype 3a (8.5%) and only one with genotype 4h (2.1%). All the patients were treated with pegylated INF (180 ìg s.c/week) and Ribavirine 800-1200 mg/day (according to body weight and genotype). The duration of treatment varied from 24-48 weeks according to the virological response. Adverse events were assessed throughout the treatment period, dividing it into quarters.

In the first 12 weeks the most frequent complications were: Body weakness and fatigue in 33 patients (70.2%), fever (38-39° C) in 27 patients (57.44%), muscular-articular pain in 22 cases (46.8%), headache 14 patients, etc. Allergic dermatitis was diagnosed in 4 patients and 6 patients experienced sleep disorders.

In the second 12 weeks most frequent adverse events, except fatigue, body weakness, and muscular-articular pain (whose intensity gradually decreased) were found: skin problems in 9 patients (allergic dermatitis, seborrhoic dermatitis, acute eczema, hair loss), mood change (3 patients), worsens of diabetes (1 patient), various infections 4 cases (external otitis, BPOC with pneumonia, acute cholecistitis, urinary infection). In patient with genotype 1 and 4 the treatment duration was 48 weeks and the side effects during 24 to 48 weeks were: mood disorders (in 4 patients and one of them with depression), pneumonia (2 patients), hyperthyroidism, (1 patient).

Hematological disorders during treatment were: Anemia in 25 patients (53.1%), thrombocytopenia in 16 (34%) and leucopenia in 25 (53.1%) of the patients.

The treatment was interrupted in 4 patients (in 3 cases because of severe thrombocytopenia, and in one of them because of edemo-ascitic decompensation). Because of side effects doses of INF were modified in 8 patients and of ribavirine in 18 patients. 24 weeks after the end of treatment 2 patients wre diagnosed with Hashimoto tyroiditis with hypothyroidism.

As a conclusion we must say that beacause of early recognition and proper management of adverse events 43 patients (89.5%) ended the treatment with pegylated INF/Ribavirine. Most frequent complications in the beginning of treatment were body weakness and fatigue, fever and muscular-articular pain.

The most important implication was thrombocytopenia, which when severe, results in cessation of treatment, particularly in patients with established liver cirrhosis.

Introduction

Hepatitis C is a major public health concern and one of the leading cause of chronic liver diseases. With 170 million people affected worldwide is the single most common indication for liver transplantation (1,2,3). Current standart of treatment is the combination of pegylated INF and Ribavirin (4). According to EASL guideline 2011, SVR rates in HCV treatment are in USA 40% and in Western Europe 50% for genotype 1 and 80% for genotypes 2 and 3.

Both preparations are associated with numerous side effects that are predictable, manageable, and improve with dose modification or discontinuation of treatment (5).

However these side effects directly affect adaptation to treatment and can reduce the chances of achieving sustained virological response (SVR). These complications also reduce the quality of life during antiviral therapy (6).

Therefore, the goal during the treatment, is to maximize the chances of achieving SVR while improving tolerance and quality of life. Clarifieing the mechanisms of their antiviral action, is imperative for understanding better the side effects of INF and ribavirin.

HCV is a hepatotropic, noncytopathic virus of the family Flaviviridae, which induces both acute and chronic necroinflammatory liver disease (10). HCV escapes immune control in 60–85% of cases. When infecting the liver parenchyma, HCV continuously releases viral particles into the blood stream. The first line of defense that HCV will encounter includes natural killer (NK) cells and natural killer T (NKT) cells. (11).

These cells are activated by type 1 IFN (alpha and beta). NK and NKT cells constitute a relevant source of IFN-gamma and TNF-alpha (12). NK cells are activated by IL-12 released from dendritic cells (DCs) and thus become empowered to eliminate infected cells (13). NK cells may also induce partial or total DCs maturation (14).

DCs can process viral antigens and present them to specific immune system cells via class I and class II major histocompatibility complex (MHC) molecules. DCs capture viral particles through Toll-like receptors (TLRs). Upon activation, DCs secrete several types of cytokines (IL-12, TNF alpha, IFN-alpha, IL-10) that will regulate and polarize the response of adjacent cells (15). Mature DCs leave the liver after viral epitope collection and head for lymph nodes, where they will activate T cells in the specific immune system (16). In the lymph node, T cells expressing T-cell receptors (TCRs) appropriate for the recognition of epitopes presented by DCs in their MHC molecules are activated. The interaction between the TCR and MHC-viral epitope complex results in specific T-cell activation. Certain specific CD8 T cells, cytotoxic T lymphocytes (CTLs), become cytolytic, secrete type 1 cytokines, and travel to the infected liver (17) and destruct the cells.

Specific CD4+ T cells play an important rol in adaptive imunity by secreting Th1 cytokines (IL-2, IFN-gamma, TNF-alpha) to facilitate a cell-mediated immune response and Th2 cytokines (IL-4, IL-10, IL-13) to regulate the humoral immunity (Anti HCV) So, cytokines produced by T cells play a role in the regulation of humoral responses; nevertheless, these responses cannot control chronic viral hepatitis, even though they play a role in the pathogenesis of extrahepatic manifestations

IFN-alpha is actually the only cytokine widely used for treatment of chronic hepatitis C. INF-alfa has a direct antiviral effect, but it has also immunomodulator effects which enhance TH1/TCL response (18), very important in viral eradication.

The second preparat used in HCV treatment is Ribavirin, which has also immunomodulator effects with production of TH1 cytokines.(19). Ribavirin is a synthetic nucleoside which is structurally similar to guanosine (20, 21). Ribavirin enters into the eukaryotic cells rapidly and, after it undergoes intracellular phosphorylation, shows virustatic activity against a broad spectrum of DNA and RNA viruses. The exact mechanism of the antiviral action of ribavirin has not yet been totally elucidated (22).

However, some studies suggest the following possible mechanisms:

a) direct inhibition of HCV replication;

b) inhibition of the enzyme inosine monophosphate dehydrogenase of the host;

c) induction of mutagenesis in the viral RNA;

d) immunomodulation by the induction of a T helper 1 (Th1)-type immune response

Pra shohim se Interferon alfa dhe Ribavirina mund të induktojnë, frenojnë apo përndryshojnë shumë rrugë që përfshijnë citokinat pro-inflamatore (IFN-g, IL-1, IL-2, IL-6, IL-8, dhe TNF).

Just most of these side effects come from these imunomodulatore interactions, and their intracellular mechanisms of action, not only on hepatic cells infected from hepatitis C virus, but also in other cells of the body.

Aim of the study

Evaluation of the prevalence of adverse events during the treatment of chronical hepatitis C with pegylated interferon and ribavirine

Patients and methods

Over a period of two years (september 2009 – september 2011), in the service of Hepatology and Gastroenterology UHC "Mother Tereza" were treated 47 patients (26 F, 55.3%; 21 M, 44.7%, with average age 46,14 ± 7,77 years old), diagnosed with chronical hepatitis C (5 patients with compensated form of liver cirrhosis) Most with genotype 1 (22 patients, 46.9%, 1b 20 patients); 20 patients with genotype 2, 42.5% (16 with genotype 2a/2c), 4 patients with genotype 3a (8.5%) and only one with genotype 4h (2.1%). All the patients were treated with pegylated INF (180 ìg s.c/week) and Ribavirine 800-1200 mg/day (according to body weight and genotype). The duration of treatment varied from 24-48 weeks according to the virological response. Adverse events were assessed throughout the treatment period, dividing it into quarters

Results

In the first 12 weeks the most frequent complications were: Body weakness and fatigue in 33 patients (70.2%), fever (38-39° C) in 27 patients (57.44%), muscular-articular pain in 22 cases (46.8%), headache 14 patients, etc. Allergic dermatitis was diagnosed in 4 patients and 6 of them experienced sleep disorders.

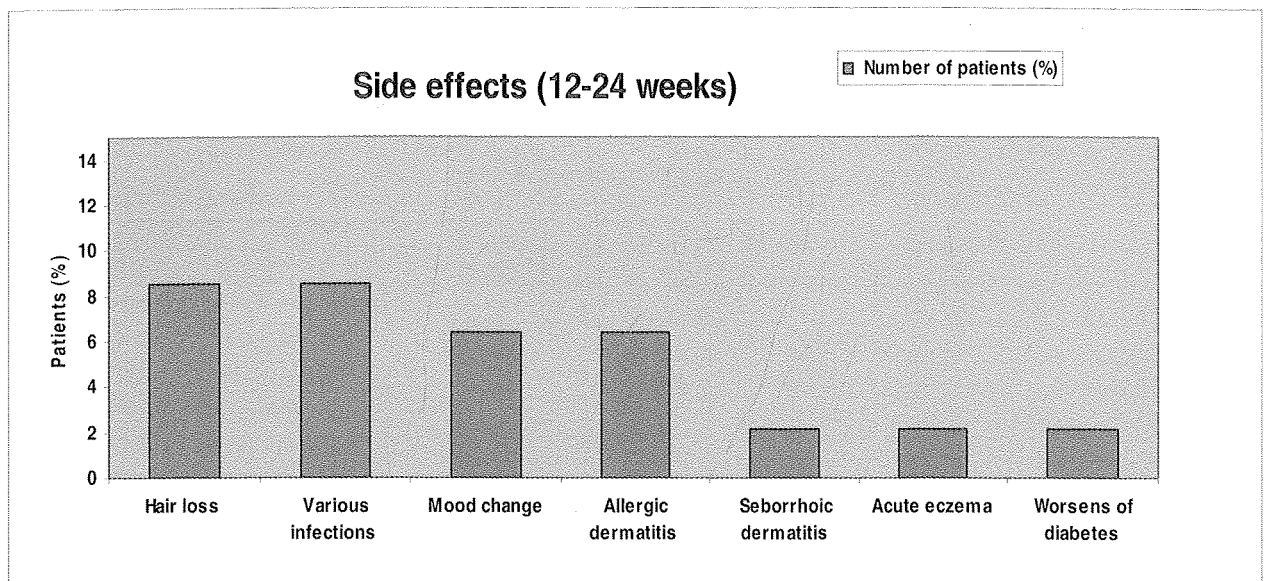Side effects during first 12 weeks — Number of patients (%)
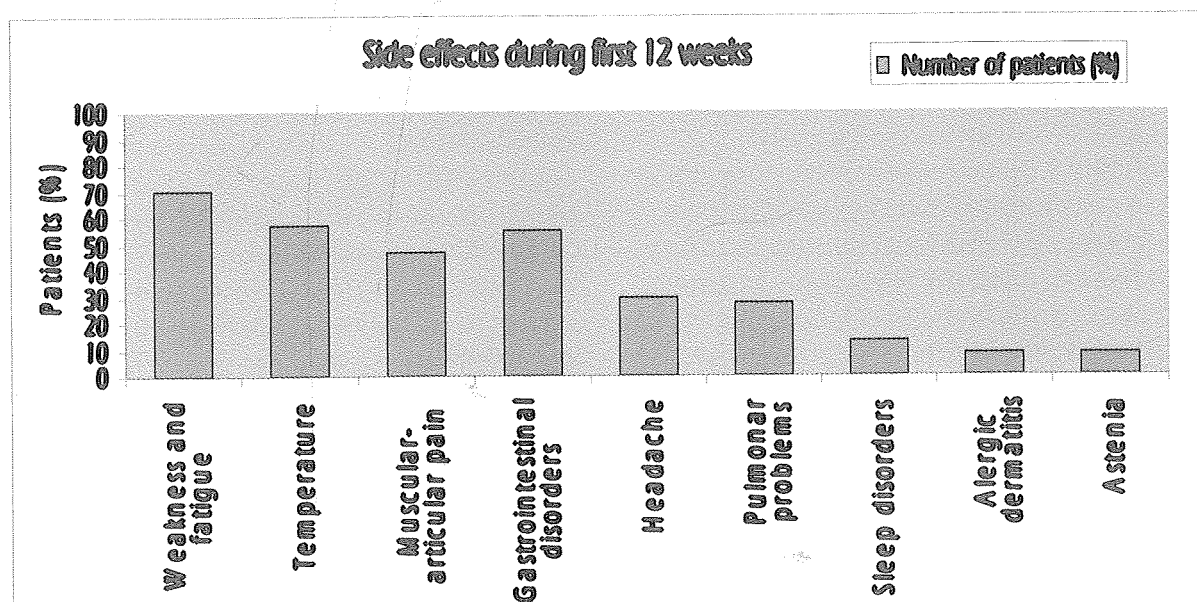
In the period 12 week-24 weeks most frequent adverse events, except fatigue, body weakness, and muscular-articular pain (whose intensity gradually decreased) were found: skin problems in 9 patients (allergic dermatitis, seborrhoic dermatitis, acute

eczema, hair loss), mood change (3 patients), worsens of diabetes (1 patient), various infections 4 cases (external otitis, BPOC with pneumonia, acute cholecistitis, urinary infection).

Side effects (12-24 weeks)

☐ Number of patients (%)

In patient with genotype 1 and 4 the treatment duration was 48 weeks and the side effects during 24 to 48 weeks were: mood disorders (in 4 patients and one of them with depression), pneumonia (2 patients), hyperthyroidism (1 patient).

Hematological disorders during treatment were: Anemia in 25 patients (53.1%), thrombocytopenia in 16 (34%) and leucopenia in 25 (53.1%) of the patients.

The treatment was interrupted in 4 patients (in 3 cases because of severe thrombocytopenia, and in one of them because of edemo-ascitic decompensation).

Because of side effects doses of INF were modified in 8 patients and of ribavirine in 18 patients.

24 weeks after the end of treatment 2 patients were diagnosed with Hashimoto tyroiditis with hypothyroidism.

Discussion

Constitutional symptoms or also called flu-like syndrome are the most common adverse effects from interferon during treatment of chronic hepatitis C. Generally the severity of these side effects is inversely related to the amount of time after the interferon injection. Fatigue, musculoarticular pain and fever are reported in about 50% to 60% of treated patients, which in our study resulted respectively (70.2%), (46.8%), and (57.44%). These effects can manifest early during therapy, even after the first dose of interferon (25). However, several constitutional effects (e.g., fever) resolve or wane after the first several injections. As resulted in our study their intesity was lower after first 12 weeks of treatment. It is important in these situations maintaining adequate hydration and light to moderate exercise. The prophylactic use of acetaminophen or ibuprofen before the injection can also ameliorate many of the constitutional adverse effects. Ibuprofen should be avoided in patients with liver cirrhosis. Fever has come to be viewed as an adaptive mechanism that facilitates body defenses. Many of the cytokines, including the interferons, interleukins, and TNF-?, are endogenous mediators of fever (endogenous pyrogens), although TNF may also be an endogenous antipyretic (30).

Interferon alfa modulates fever by changing the body's release of hypothalamic prostaglandin E2, which may stimulate a neurotransmitterlike substance to raise the temperature set point (26).

Fatigue is a multidimensional condition with several theoretic foundations: physiologic,

pathologic, and psychological (31). Two different types of fatigue are associated with

interferon: (1) physical fatigue or weakness that occurs from activation of the interferon cascade and subsequent flulike syndrome (31) neuroendocrine system fatigue that is associated with neuropsychological fatigue (mental or depressive) that may be accompanied by cognitive (CNS) slowing or decreased performance status (32). Fatigue accompanying interferon administration is frequently a dose-limiting or treatment-limiting toxicity and may lead to dose reduction in 10% to 49% of all patients (32).

Ribavirin may cause an acute decrease in Hgb during the first 1 to 2 weeks of administration (a mean Hgb drop of 2.7 g/dL) that can quickly cause a patient to experience acute fatigue (33).

Adverse effect	Reported Inc	Inc. in study	Management
Constitutional			
Fever	33%–56%	57.44%	Acetaminophen ose NSAIDs
Fatigue/myalgias	48%–64%	70.2%	Acetaminophen ose NSAIDs
Headache	52%–62%	30%	Acetaminophen ose NSAIDs
Nausea	33%–43%	40.4%	Antiemetics, hydration
Arthralgia	25%–34%	46.8%	Acetaminophen ose NSAIDs
Neuropsychiatric		27.6%	
Depression	29%–37%	2.1%	SSRIs
Dermatological		27.6%	
Skin rash	22%–28%	17%	Topical corticosteroids, local moisturizer use
Hematological			
Neutropenia	8%–20%	53.1%	Dose reduction or GCSF
Anemia	9%–25%	53.1%	Dose reduction or discontinuation Epogen analogues, blood transfusion
Thrombocytopenia	<10%	34%	Dose reduction or discontinuation or Trombopoetin

Adverse effect, incidence, incidence in our study, treatment (26,27,28,29)

Endocrinologic Effects

Thyroid abnormalities are the most commonly associated interferon-induced endocrinologic adverse effect, occurring in 1% to 6% of interferon-treated patients (40). In our study resulted 6.3%. Both hypo- and hyperthyroidism can develop but hypothyroidism is more frequent with a ratio 2:1 (as resulted in our study) or 3:1.4.

Patients with hepatitis C may be predisposed to developing thyroid abnormalities because of an increased rate of thyroid autoantibodies prior to starting antiviral therapy (41).

One study described the development of thyroid disorder in 60% of patients with antithyroid microsome antibodies present prior to the initiation of interferon therapy, compared to only 3.3% of patients without these antibodies (42). In a similar study, 38.5% of females with antithyroid peroxidase antibodies developed hypothyroidism versus only 7.8% of females lacking these antibodies (43).

Thyroid function tests should be obtained at baseline and every 12 weeks during antiviral treatment, and after treatment completion. If hypothyroidism is diagnosed, hormone replacement should be initiated while continuing antiviral therapy. Similar to the autoantibody destruction seen in the thyroid, antibodies to the adrenal cortex, pancreatic islet cells, and antiphospholipid antibodies have been reported with the use of interferon (44, 45).

New-onset insulin-dependent diabetes mellitus with the presence of antibodies directed toward islet cells and insulin has been reported in some rare cases (46).

More frequent during interferon treatment is an increase in counter-regulatory hormones as well as a hypermetabolic response, leading to insulin resistance. These effects are dose dependent and decrease over time (59).

Neuropsychiatric Effects

In patients with hepatitis C the prevalence of depression is higher than the general population, and the antiviral therapy increases the likelihood of a variety of neuropsychiatric complications, including worsening depression, anxiety, and suicidal ideation (34). Thus, it is imperative to assess for underlying depression and other preexisting psychiatric illness before considering antiviral therapy.

Patients treated with interferons report depression during therapy or the exacerbation of a preexisting depressive state in about 20% to 30% of cases (23, 35).

In our study neuropsychiatric effects resulted in 13 (27.6%) patients and 1 of them was diagnosed with depression. Patients may be monitored or may be treated with more frequent clinic visits or telephone calls, antidepressant medications, psychiatric referral, or dose modification or even discontinuation. (36).

The greatest experience with antidepressant medications is with selective serotonin reuptake inhibitors (SSRIs) (37, 38). In patients at increased risk of interferon-associated depression, preemptive treatment with SSRIs was associated with a significant reduction in the incidence of major depression (39).

Dermatologic Effects

Dermatologic adverse effects are common in therapy with interferons, with an incidence ranging from 13% to 87% (55, 47) for example: reactions at the site of interferon injection, eritema, pruritus. (23, 48). In our study in the first 12 weeks of treatment these dermatological events resulted in 8.5% of patients and from 12 to 24 weeks in 19.1% of them. Dermatological effects in combinated therapy are characterized from general pruritus, skin dryness and ekzematiform lesiones localized mostly in extremities.

Skin dryness occurs approximately in two of three treated patients and can be exacerbated in cold weather and may be accompanied by intense pruritus. Topical steroids, emollients, and soothing baths may help to alleviate these symptoms (49).

Another typical adverse effect seen with interferons is alopecia, occurring in about one third of patients, with a higher prevalence in females and which is totally recupered after the end of treatment (50).

Pulmonary, neurologic, ophthalmologic adverse events

During treatment with interferon have been reported frequent neurologic, pulmonary, and ophthalmologic adverse effects.

Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis, and sarcoidosis, some resulting in respiratory failure and/or patient deaths, may be induced or aggravated by interferon alfa therapy.

Pulmonary effects are related to autoimmune disorders which cause intersticial pneumonitis or to proinflamatory fibrogenic cytokines (PDGF ose TGF beta) which causes pulmonary fibrosis. Activation of TH1 lymphocytes and cytokines may cause crisis similiar to astma. Interferon-induced interstitial pneumonitis can be life-threatening, although it usually resolves with withdrawal of interferon. However, the most common cause for cough and shortness of breath is likely ribavirin-induced (49). Shortness of breath may occur only on exertion or, in some patients, may be present even at rest. In our study pulmonary side effects were reported in 27.65% of patients.

Interferon use is associated with sensory and autonomic neuropathies related with an autoimmune phenomenon neuronal injury caused by interferon stimulation of the immune system. (51). Neuropathy usually resolves with the termination of interferon treatment, but additional steroids and/or cyclophosphamide may be beneficial (25). Rare cases of myasthenia gravis have been reported. In such cases, interferon therapy is withdrawn and pyridostigmine therapy is initiated (52).

In such cases interferons use have been associated with retinopathy (retinal hemorrhages and cotton wool spots) particularly in patients with diabetes and hypertension (53, 54). None of our patients reported neurologic or ophthalmologic adverse events.

Time to onset of common adverse effects

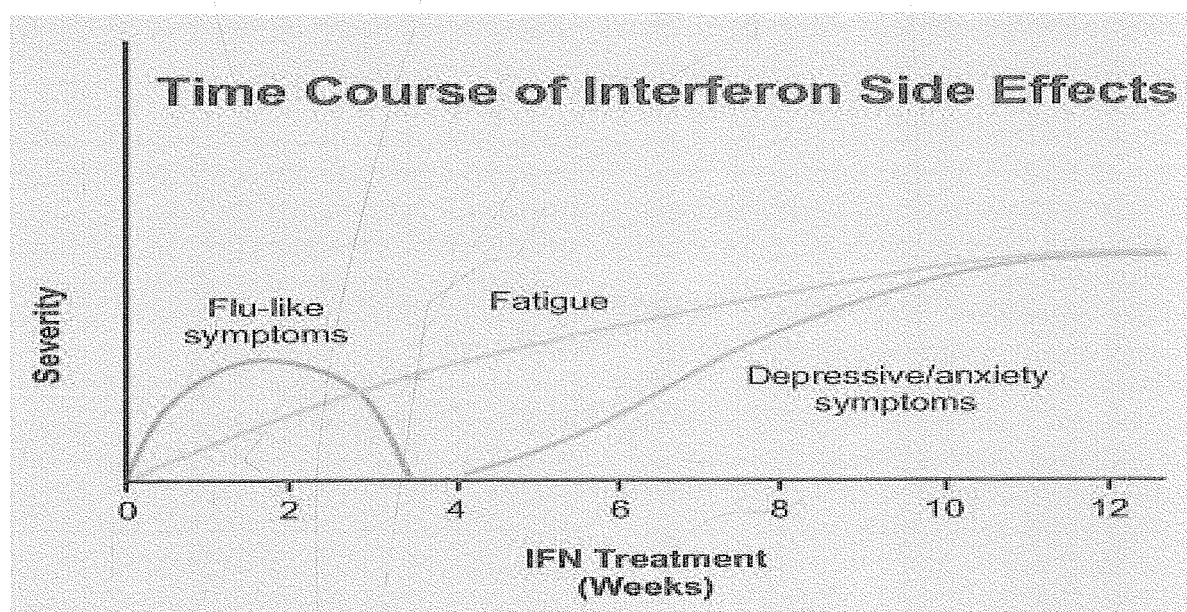| Symptoms	Typical time of onset
Constitutional symptoms	
Fever, myalgias, headache, arthralgias, nausea	minutes to day
Neuropsychiatric symptoms	
Depression	12 weeks to 6 months
Dermatological symptoms	
Rash	minutes to day
Hematological symptoms	
Neutropenia	2–6 weeks
Anemia	1 day to 4 weeks
Thrombocytopenia	1–14 days

Figura 3: Wentworth, CL. Managing Therapeutic Challenges in Hepatitis C. Clinical Care Options

Hematologic Effects

Hematological side effects are the most important effects of treatment which may lead to dose reduction of interferon and ribavirin or premature interruption of treatment, especially in patient with cirrhosis characterized by low count of thrombocytes before starting the therapy (24). The bone marrow suppressive effects of interferon observed for pluripotent progenitor cells of all lineages resulted in anemia, neutropenia and thrombocytopenia (61). Immune mediated haematological toxicity and capillary sequestration of platelets and white blood cells have been proposed as additional causes for severe thrombocytopenia and leucopenia during IFN therapy. For most patients treated with combination therapy,

the etiology of anemia is "mixed," incorporating both hemolysis and inhibition of erythroprogenitor cells. Ribavirin is taken into the red blood cells (RBCs), where it is converted to ribavirin triphosphate. Since RBCs lack the enzymes needed to hydrolyze ribavirin triphosphate, it is "trapped" in the RBCs, where it depletes the cells' adenosine triphosphate (ATP).

The resulting ATP deficiency impairs antioxidant defense mechanisms and induces RBC oxidative membrane damage, which causes premature extravascular hemolysis by the reticuloendothelial system (60).

In our study resulted: anemia in 25 (53.1%) patients, thrombocytopenia in 16 (34%) and leucopenia in 25 (53.1%) patients.

Other effects

An important side effect related with ribavirine is nausea reported in studies in 25% to 40% of patients (55, 23, 25). In our study was experienced in 40.4% of patients.

Ribavirin therapy is often associated with a dry, nonproductive cough, which resolves only upon termination of treatment. However, if the cough becomes productive or other clinical indications are present, a chest radiograph should be considered.

Ribavirin according to FDA (Food and Drug Administration) belong to pregnancy category X of teratogenicity so it is contraindicated in pregnant woman and in the male partners of women who are pregnant. Also it is imperative for patients to avoid pregnancy during ribavirin treatment and for 6 months after treatment completion.. Two reliable forms of effective contraception are recommended to be used during this time. (56,57).

Conclusiones

The current treatment regimen for chronic hepatitis C involves pegylated interferon in combination with ribavirin, which is associated with significant side effects. Recognition of the period and incidence of expected occurrence of these effects is important for good management of them, increase patients quality of life during treatment and increase the chances of achieving SVR, because chances to achieve an SVR significantly decrease when the patients receive less than 80% of the total dose of peg-IFN and/or less than 80% of the total RBV and/or during less than 80% of the total treatment duration (58).

Given this fact, in our study, early recognition and appropriate treatment of side effects made that 43 of 47 patients (89.5%) fully complete the scheme of treatment with INF/ribavirin. More frequent adverse events at the beginning of treatment were weakness/ fatigue, high temperature and muskulo-skeletal pain, and most important implication was thrombocytopenia, which when severe, leaded to the cessation of treatment, especially in patients, with established liver cirrhosis.

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