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Management of adverse reactions to chronic hepatitis C treatment

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Most patients with chronic hepatitis C virus (HCV) infections are asymptomatic or display few symptoms, but some experience adverse reactions to therapy. The severity of these adverse effects depends mainly on drug dosage, frequency of administration, and route of administration. Severe reactions to treatment are experienced in 10%–15% of cases.[1]

The practical significance of the adverse effects of drugs is that they lower the quality of life of patients, which results in fewer adherences to anti-HCV therapy and a lower virological response. Systemic side effects occur in 30%–50% of cases and include flu-like symptoms, fatigue, headache, thyroid dysfunction (hypothyroidism or hyperthyroidism), anorexia, digestive disorders, central nervous system disorders including depression, hematological disorders because of bone marrow dysfunction, and anemia. In most cases, the symptoms only cause slight discomfort or are easy to manage with symptomatic treatments, dose adjustments, or adjustment of the duration of therapy. About 10%–15% of patients discontinue treatment with interferon plus ribavirin because of adverse effects. The rate of discontinuation of treatment increases as the duration of treatment increases and is elevated when interferon plus ribavirin treatment is used.[1]

The principal adverse effects of interferon are pseudo-flu symptoms, fatigue, anorexia, weight loss, diarrhea, alopecia, insomnia, depression, anemia, neutropenia, thrombocytopenia, retinopathy, thyroiditis, and Hashimoto thyroiditis.

Adverse effects of ribavirin. The most frequent side effect of ribavirin is hemolytic anemia, which occurs in up to one-third of patients. Ribavirin causes hemolysis because ribavirin triphosphate is concentrated by erythrocytes.[2] The second most frequent side effect is pruritus, which rarely results in discontinuation of treatment. H_1-antihistamines should be administered when pruritis occurs. During treatment with ribavirin, bilirubin and uric acid levels increase in about 10%–25% of patients. These side effects disappear 4–7 weeks after discontinuation of therapy. Other side effects of ribavirin are teratogenicity, cough, dyspnea, and rash.[1]

The adverse effects of pegylated interferon alfa plus ribavirin are the same as those of standard interferon alfa plus ribavirin. Pseudo-flu symptoms are more frequent when pegylated interferon alfa is administered in high doses, probably because the dose of interferon is greater. As with pegylated interferon alfa monotherapy, pegylated interferon alfa plus ribavirin results in a higher incidence of localized erythema, which is generally light and does not require discontinuation of treatment. The occurrence of anemia, an adverse effect of ribavirin, is similar when ribavirin is given in combination with pegylated interferon alfa or regular interferon alfa. The dose of ribavirin is reduced in 20%–25% of patients because of anemia, in 20% of patients because of neutropenia, and in less than 5% of patients because of thrombocytopenia, but discontinuation of ribavirin treatment is rare.

Neutropenia

Neutropenia is an exclusion criterion for treatment protocols and is reversible after discontinuation of treatment. About 30% of patients develop an absolute neutrophil count (ANC) of less than 1000 cells/mL during treatment, and about 2% of patients develop an ANC of less than 500 cells/mL. The dose of pegylated interferon alfa should be halved if the ANC is less than 750 cells/mL. If the ANC is less than 500 cells/mL, pegylated interferon alfa treatment should be discontinued until the leukocyte count is more than 1000 cells/mL, following which, treatment can be resumed beginning with half of the dose. However, a recent study failed to detect a higher incidence of infection in hepatitis C patients with neutropenia, except in cirrhotic, immunosuppressed, or transplanted patients. Granulocyte colony-stimulating factor (Neupogen) is often used at a dose of 300 mg three times weekly, but there is no solid evidence to support this practice.[2-4]

Anemia

Ribavirin is an analogue of guanosine. Ribavirin causes anemia by inducing hemolysis and bone marrow

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dysfunction. Hemoglobin levels are reduced below baseline in 70% of patients treated with interferon plus ribavirin; in 15% of cases, hemoglobin levels are less than 10 g/dL. The decrease in hemoglobin concentration begins after the first week of treatment, reaches a nadir of 2.5–3.0 g/dL below baseline levels in the fourth week of treatment, and stabilizes thereafter. Anemia is fully reversible upon discontinuation of treatment. The dose of ribavirin should be halved if hemoglobin levels decrease from 10 g/dL to 8.5 g/dL in hepatitis C patients or if hemoglobin levels decrease by more than 2 g/dL in hepatitis C patients with heart disease. Ribavirin treatment should be discontinued if, after administration of a reduced the dose of ribavirin for 4 weeks, hemoglobin levels are less than 8.5 g/dL in hepatitis C patients or less than 12 g/dL in hepatitis C patients with heart disease. It has been suggested that simultaneous administration of erythropoietin should be considered for these patients to enable the dose of ribavirin to be maintained. The usual dose of erythropoietin is 40,000–60,000 IU per week. However, some studies have recommended lower doses. Erythropoietin treatment is indicated when hemoglobin levels are less than 12 g/dL or when they decrease by more than 3 g/dL below baseline.[1,4]

Thrombocytopenia

Thrombocytopenia is rare and occurs in less than 5% of cases. When the platelet count is less than or equal to 50,000 cells/mm^3, the dose of pegylated interferon should be halved. If the platelet count is less than or equal to 25,000 cells/mm^3, therapy should be discontinued.

Depression

Depression occurs during treatment of 20%–39% of patients. Variation in the reported incidence of depression is attributable to variations in criteria for the detection and diagnosis of depression.[5-7] There is a lower frequency of depression in patients treated with pegylated interferon plus ribavirin than those treated with standard interferon. Depression is associated with patients who experienced alcoholism, drug addiction, or had a history of comorbidity prior to treatment. Some studies reported that treatment with antidepressives before commencement of antiviral therapy significantly reduced the incidence of psychiatric symptoms. Therefore, it is advisable to establish whether the patient has a history of depression and, if so, to initiate prophylactic treatment with antidepressives such as selective serotonin recapture inhibitors, which have few adverse effects, are not hepatotoxic, and have no effect on cytochrome P450. Citalopram (5 mg/d), paroxetine (5–30 mg/d), or sertraline (25–100 mg/d) may be considered.

Recommendations of the consensus panel

Should antidepressant treatment be used during treatment for HCV infection?

Evaluations before and during treatment are recommended in order to detect possible neuropsychological changes. The use of antidepressants before or during treatment is recommended when necessary.

Evidence quality: 2

Should drug doses be adjusted according to changes in biochemical or hematological parameters during treatment?

The use of protocols for the reduction of doses of drugs according to biochemical and/or hematological protocols is recommended.

Evidence quality: 1

What is the most frequent cause of dosage modification during antiviral treatment?

Although it is not possible to identify a predominant cause of modification of doses of drugs used for combined antiviral treatment, the most frequent are those of a hematological nature (anemia, 50%; neutropenia, 32%; thrombocytopenia, 12%), followed by depression (6%).

Evidence quality: 1

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