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The Management of Adverse Effects with PEG-Interferon/Ribavirin Combination Therapy is a Significant Challenge

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Review of data from a large multicenter trial looking at PEG-Intron combination therapy (PEG-interferon alfa-2b/ribavirin) shows equal or worse adverse effects in almost all areas compared to standard interferon-ribavirin combination.¹ The most prominent among these adverse effects were injection site reactions and dose reductions for neutropenia. A similar comparison of adverse events with PEG-interferon alfa-2a combination therapy (Peg-interferon alfa-2a and ribavirin) shows somewhat less side effects than standard combination therapy.² It is difficult to determine the importance of these trial differences in clinical practice until a significant clinical experience with both compounds has accumulated.

The hematologic adverse events require specific close investigation. There are three major problems encountered: neutropenia, thrombocytopenia, and anemia.

Neutropenia:

Patients receiving Peginterferon alfa-2a combination or monotherapy experience significant

neutropenia approximately 20% of the time. Dose reductions occurred in monotherapy and combination therapy trials of Peginterferon alfa-2a and ribavirin in 17-20% of individuals. Patients receiving PEG-Intron and ribavirin were noted to have dose modifications for neutropenia in 18% of patients receiving 1.5 mcg/g of PEG-Intron (the currently recommended dose schedule). Currently, dose reduction is the only safe management for neutropenia, although a number of individuals have used G-CSF at a dose of 300 mcg three times a week for control of neutropenia. There have been no publications showing this approach to be safe and effective to date.

Thrombocytopenia:

Roughly 4-6% of patients receiving Peginterferon alfa-2a and ribavirin required dose reductions for thrombocytopenia during treatment. This is comparable to patients treated with PEG-Intron/ribavirin combination (3%) and standard interferon/ribavirin (1%). In general, dose reduction is recommended when platelet counts fall below 50,000. Although discontinuation of therapy is usually unnecessary,

it would be recommended if platelet counts fell below 30,000. The use of IL-11 for treatment of thrombocytopenia has been shown to be associated with lower extremity edema and is currently not recommended.³

Anemia:

Most patients treated with combination interferon/ribavirin experience anemia of grade 1-2 severity (mild to moderate). Conventional management of anemia and that recommended in the package insert, is to reduce ribavirin dose for hemoglobins less than 10 g/dl, and obtain blood count levels every two weeks or more frequently, if indicated. Patients with cardiac function abnormalities may require discontinuation of ribavirin, if they become anemic. Ribavirin dosing is recommended to be discontinued if hemoglobin falls below 8.5 g/dl.

Looking at a large population treated with combination Peginterferon alfa-2a and ribavirin, 19-22% of patients required reduction of ribavirin dose during therapy. This was somewhat more than patients requiring dose reduction in the trial with peginterferon alfa-2b/

ribavirin (12-13%). This is likely due to the lower dose of ribavirin used in this F trial, which has been shown to be inadequate for genotype 1 patients.⁴ Weight-based ribavirin dosing at 1000-1200 mg/day is mandatory for patients who are genotype 1, whereas a

gests that dose reduction is certainly preferable to discontinuation of ribavirin.

The anemia associated with interferon/ribavirin therapy is likely due to a combination of reversible hemolysis and hematopoietic suppression of bone marrow by interferon. It is

to maintain their initial dose of ribavirin as opposed to 62.5% of patients receiving placebo ($p \leq 0.01$).⁸ The mean ribavirin dosage maintained on treatment significantly improved within the first 8 weeks of therapy in patients receiving epoetin alfa, and hemoglobin

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Because there is a clear relationship between ribavirin concentration and sustained virologic response rate, it is preferable not to dose reduce ribavirin if possible, especially in genotype 1 patients.⁵

lower dose of ribavirin (800 mg/kg/day) is acceptable in genotype 2,3 patients.⁴

Because there is a clear relationship between ribavirin concentration and sustained virologic response rate, it is preferable not to dose reduce ribavirin if possible, especially in genotype 1 patients.⁵ In Manns, et al., a regression analysis of sustained virologic response rate and ribavirin dosage shows a clear direct relationship between SVR and dose with a definitive cutoff at a critical dose of 10.6 mg/kg.¹ This has led to the argument that adherence to ribavirin dosage improves sustained virologic response rate, although this remains an unproven point to date.⁶

A recent study by Fried et al. shows that full dose scheduling of both PEG-interferon and ribavirin permits 75% of early virologic responders to have an ultimate SVR. Dose reduction results in a fall to 67% of those individuals, but discontinuation results in a loss of SVR in all but 12%. This sug-

gests that the triphosphate metabolite of ribavirin accumulates in red blood cells and causes oxidative injury to red blood cell membranes, thereby resulting in hemolysis. Patients who develop an anemia on ribavirin therapy have a responsive reticulocytosis. However, DeFranceschi et al. have shown that the compensatory reticulocytosis in patients treated with combination therapy is much less than that seen in patients treated with ribavirin alone, suggesting that interferon bone marrow suppression prevents an adequate reticulocytosis.⁷ Epoetin alfa has now been shown to effectively overcome this effect—this inadequate reticulocytosis—and to improve the anemia in patients treated with combination therapy.

A recent study presented at AASLD in 2002 has shown that epoetin alfa given at 40,000-60,000 international units weekly significantly improves hemoglobin levels in patients receiving combination therapy. Approximately 96% of patients receiving epoetin alfa were able

improved from 10.6 ± 0.9 g/dl to 13.2 ± 1.2 g/dl in those patients receiving epoetin ($p \leq 0.0001$).⁸ This resulted in a significant improvement in overall quality of life in patients receiving epoetin in the first 8 weeks of therapy ($p=0.0019$), and specifically in energy and activity levels ($p \leq 0.0001$ and $p=0.0003$ respectively).⁸ It is hoped that this will translate into improved adherence for these patients and thereby ultimately improve sustained virologic response rate, although this information is currently still conjectural. The safety of epoetin in this trial suggested that the majority of patients tolerate epoetin alfa without adverse events. Therefore, it appears to be an acceptable method to maintain ribavirin dosing and improve quality of life in patients receiving combination therapy. The cost of epoetin alfa is substantial and must be considered in making these decisions.