CME CREDIT

Treatment strategies for hepatitis C: Making the best of limited options

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ABSTRACT

Data from two recent major trials suggest that several changes in clinical practice would benefit hepatitis C patients, including viral genotyping to more accurately determine the duration of therapy, and timely RNA measurement to predict treatment response. Although the combination of interferon alfa-2b and ribavirin therapy has proved superior to interferon alone, the success of interferon-based therapies in eradicating hepatitis C is limited, and the quest for new strategies and treatments continues.

Combination therapy produces a response in about 40%

EACH NEW DEVELOPMENT in hepatitis C treatment has improved our ability to treat patients successfully; as recently as 10 years ago, no treatment was available. With the advent of interferon therapy, we were able to eradicate the hepatitis C virus in approximately 10% to 15% of patients. Now, combination interferon alfa-2b and ribavirin therapy helps us achieve sustained viral eradication in about 40%.[1,2] Yet even the two-drug regimen obviously leaves a large number of patients for which no effective treatment is available.

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Findings of two recent trials build on what we already know about hepatitis C treatment and suggest that patients receiving combination treatment would benefit from viral genotyping to determine the duration of therapy and measurement of HCV RNA at week 24 to predict virologic response.[1,2]

WHAT WE KNOW ABOUT TREATMENT

Patient selection

The minimal criteria recommended by the National Institutes of Health[3] for candidates for interferon-based therapy are:

- Elevated liver enzyme levels for at least 6 months
- The presence of HCV RNA in serum
- Portal fibrosis or moderate to severe liver inflammation on liver biopsy
- Compensated liver disease
- No contraindications to treatment
- Patient compliance and acceptance of therapy
- Abstinence from alcohol
- Abstinence from illegal drugs.

Combination interferon and ribavirin treatment is not approved in children and is contraindicated in patients who have anemia, hemolysis, renal insufficiency, coronary artery disease, cerebral vascular disease, or gouty arthropathy, or who are unable to practice contraception. However, some of these patients may be suitable candidates for interferon monotherapy.

The recommended dose of interferon alfa-2b is 3 million units three times a week and ribavirin 1,000 to 1,200 mg/day for 24 or 48 weeks, based on the viral genotype and the serum HCV RNA level measured at week 24.

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To prevent liver disease progression, patients treated with antiviral therapy should abstain from alcohol.

Drawbacks of combination therapy

Although interferon-and-ribavirin therapy has proved more effective than interferon alone, the two-drug regimen has its drawbacks:

- From 10% to 21% of patients discontinue treatment due to lack of tolerance
- It may cause profound hemolytic anemia
- Common adverse effects include rash, itch, insomnia, dyspnea, and cough
- Therapy may be teratogenic
- Combination treatment cannot be used in certain subgroups (see contraindications list above).

NEWER STUDY RESULTS

The exact optimal dose or duration of ribavirin therapy, the long-term durability of sustained virologic response, and the reliability of predictors of response are not entirely known. Although a recent economic analysis suggests that combination therapy is cost-effective,[4] more studies are needed.

Two comparative trials of interferon monotherapy and combination interferon and ribavirin that provide 2-year results for a cohort of 1,744 patients provide much of the data to date.[1,2] Ongoing studies continue to address these issues and to shed new light on directions we can take in clinical practice. Among them are new formulations of interferon, such as pegylated interferon, with or without ribavirin.

Predicting the sustained response rate

Genotype was found to be the most useful determinant of response. Patients with genotype 2 or 3 had an excellent response rate: almost 60% achieved virologic clearance with combination therapy (FIGURE 1). Furthermore, their response rate with 6 months of treatment was often as good as their response rate with 12 months of therapy.

Comparatively, genotype 1 patients were found to be the most difficult to treat. Very few of them had responses to treatment with interferon alone, but a relatively high proportion—about 29%—achieved virologic clearance with 12 months of therapy with the two-drug combination.

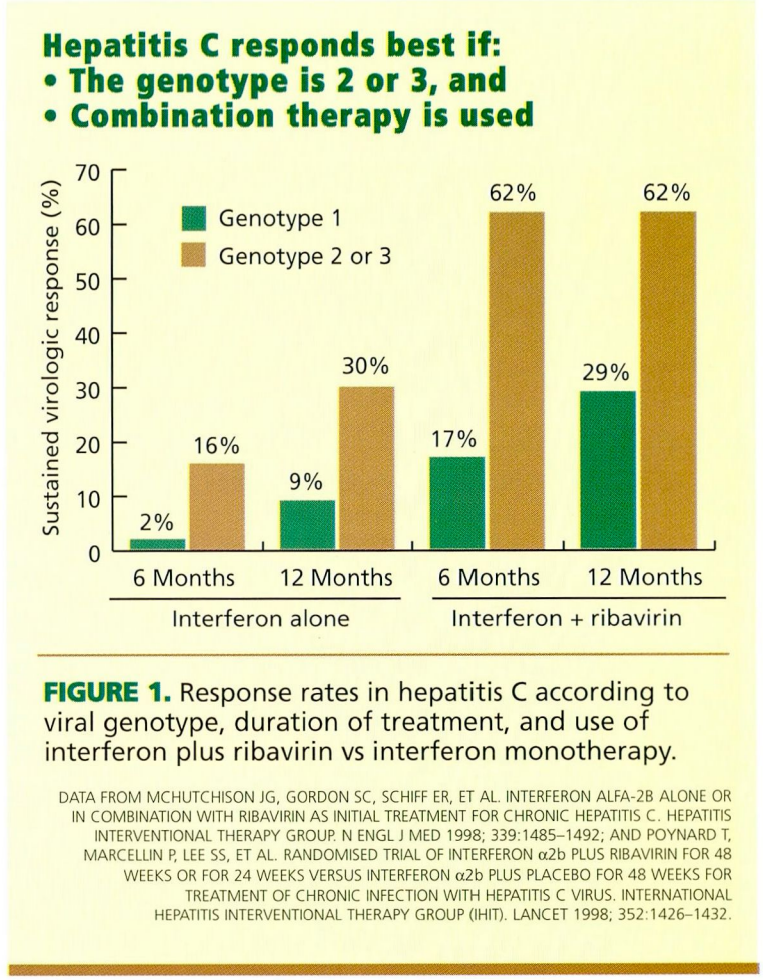

FIGURE 1. Response rates in hepatitis C according to viral genotype, duration of treatment, and use of interferon plus ribavirin vs interferon monotherapy.

DATA FROM MCHUTCHISON JG, GORDON SC, SCHIFF ER, ET AL. INTERFERON ALFA-2B ALONE OR IN COMBINATION WITH RIBAVIRIN AS INITIAL TREATMENT FOR CHRONIC HEPATITIS C. HEPATITIS INTERVENTIONAL THERAPY GROUP. N ENGL J MED 1998; 339:1485–1492; AND POYNARD T, MARCELLIN P, LEE SS, ET AL. RANDOMISED TRIAL OF INTERFERON α2b PLUS RIBAVIRIN FOR 48 WEEKS OR FOR 24 WEEKS VERSUS INTERFERON α2b PLUS PLACEBO FOR 48 WEEKS FOR TREATMENT OF CHRONIC INFECTION WITH HEPATITIS C VIRUS. INTERNATIONAL HEPATITIS INTERVENTIONAL THERAPY GROUP (IHIT). LANCET 1998; 352:1426–1432.

Predicting earlier response

These trials found that, if a patient's serum is HCV RNA-positive at week 24, his or her chance of going on to achieve a sustained response is very low. Only 2% of patients in that group did so. If therapy were to be discontinued at 12 weeks, the error rate would be unacceptably high; 5% of patients treated for 6 months and 11% of patients treated for 12 months would unnecessarily have been denied the benefits of treatment.

Is the response to combination therapy durable?

Although the response rate to interferon monotherapy is low, and response to combi-

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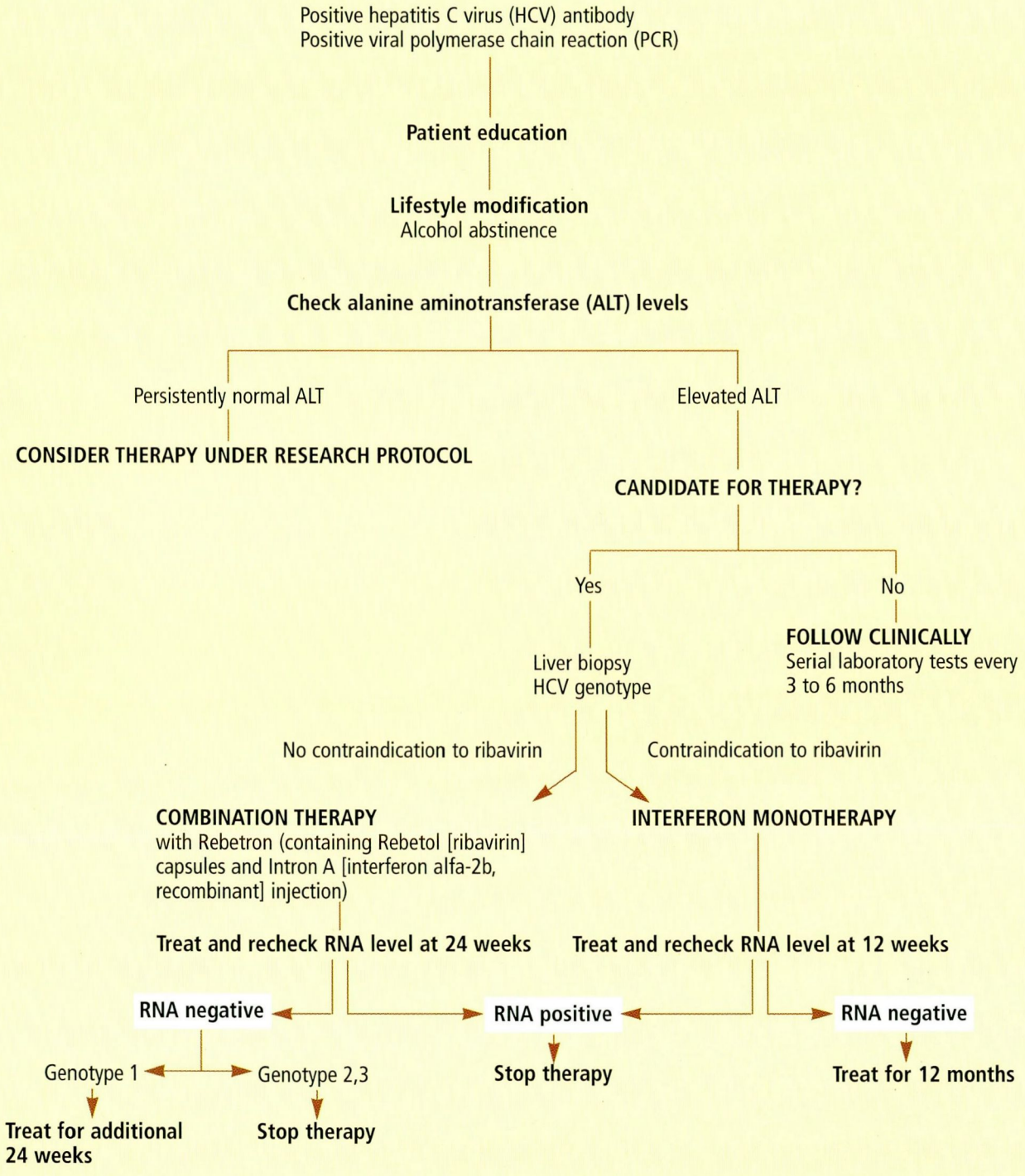
Algorithm for the treatment of hepatitis C infection



ADAPTED FROM SARBAH SA, YOUNOSSI ZM. HEPATITIS C. AN UPDATE ON THE SILENT EPIDEMIC. J CLIN GASTROENTEROL 2000; 30:125–143.

FIGURE 2

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nation therapy is still modest, those patients who have a sustained response to therapy will have a durable response. Follow-up studies of patients treated with interferon monotherapy indicate that 95% remain in remission 5 to 10 years later. Extrapolating from this and similar findings of interferon monotherapy trials, we anticipate that the 5-year viral clearance rate for those who respond to combination therapy will be about 95%.

Are we overtreating with combination therapy?

Should certain individuals still be treated with interferon alone? When five factors associated with enhanced response rate were considered (presence of genotypes 2 or 3, low viral load [≤ 2 million copies/mL], absence of cirrhosis, female gender, and age younger than 40 years), across the board, patients achieved a significantly better sustained response rate when treated with the two-drug combination. Interferon monotherapy should still be considered for those patients with a contraindication to ribavirin.

Progression and prevention of fibrosis

The data demonstrated that only 8% of patients who achieved a sustained response had progression of fibrosis from one stage to the next, compared with 22% of patients who had no response to therapy. Although preliminary, these data suggest that combination therapy may have a positive effect on fibrosis.

African-American patients

As in previous studies, African-American patients did not respond to interferon monotherapy in the two recent trials. An explanation may be that significantly more African-Americans are infected with HCV genotype 1 than are whites. Yet, when the results were adjusted for genotype, African-American patients responded equally to interferon/ribavirin combination as well as white patients. The issue of ethnic differences in regard to the efficacy of interferon-based therapies remains unsettled.

IMPLICATIONS FOR TREATMENT

Data from these trials suggest that making the following changes in clinical practice would benefit hepatitis C patients receiving combination treatment (FIGURE 2)[5]:

- Consider ordering HCV genotype testing to determine the duration of therapy. Treat patients with genotype 1 for 12 months (if HCV RNA is undetectable after 6 months of therapy) and patients with genotypes 2 or 3 for 6 months.
- Measure HCV RNA at week 24 to predict virologic response.
- Monitor the hemoglobin level, because ribavirin treatment causes hemolytic anemnia, which can be managed with dose modifications.
- Order pregnancy testing and have the patient use contraception, because ribavirin is potentially teratogenic.
- Monitor for neuropsychiatric side effects of interferon, such as depression and anxiety.

Retreatment of relapse patients

The study data also suggest three guidelines for retreating patients who initially respond to interferon treatment but who suffer a relapse (FIGURE 3)[6]:

Monitor hemoglobin, as ribavirin causes hemolytic anemia

Add ribavirin. Adding ribavirin to interferon significantly enhances the response rate in patients who have experienced a relapse.

Choose patients who are likely to respond. Relapse patients infected with HCV genotype 2 or 3 and a small proportion of patients with genotype 1 will respond well.

Treat longer. Extrapolating data from these two studies indicates that patients who relapse might do better if treated with the two drugs for 12 months. A study conducted by DiMarco et al and presented at the 1999 American Association for the Study of Liver Disease meeting found that longer treatment does, in fact, improve sustained response rates in relapse patients. However, these data need to be confirmed with larger studies, and at this point we can only justify 6-month therapy for patients who relapse.

Retreatment of nonresponders

Typically, patients in whom interferon therapy did not eradicate the virus do not respond well

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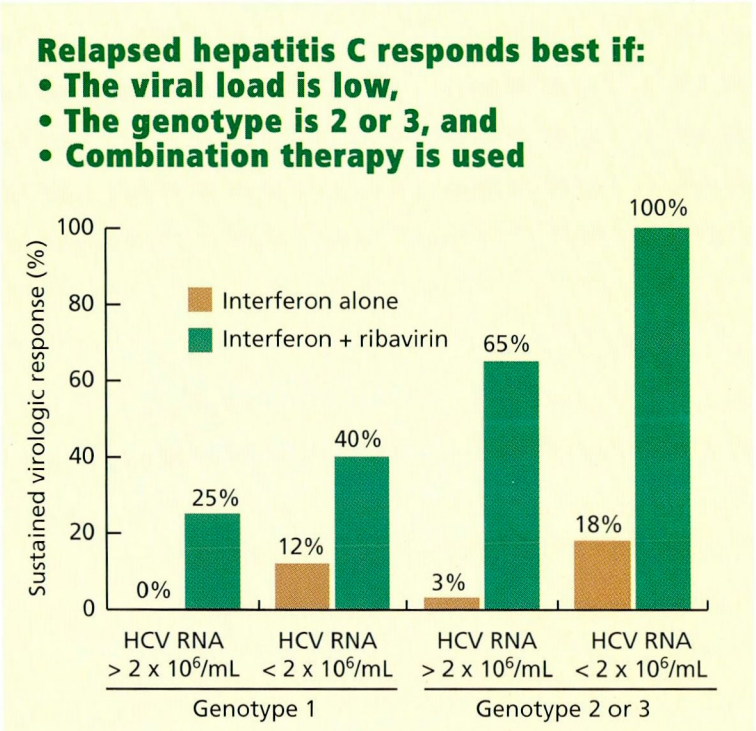

FIGURE 3. Response rates in cases of relapsed hepatitis C infection according to viral genotype, viral load, and use of interferon plus ribavirin vs interferon alone.

DATA FROM DAVIS GL, ESTEBAN-MUR R, RUSTGI V, ET AL. INTERFERON ALFA-2B ALONE OR IN COMBINATION WITH RIBAVIRIN FOR THE TREATMENT OF RELAPSE OF CHRONIC HEPATITIS C. INTERNATIONAL HEPATITIS INTERVENTIONAL THERAPY GROUP. N ENGL J MED 1998; 339:1493–1499.

to retreatment, including fixed and extended doses of interferon, induction regimens, and combination regimens with agents other than ribavirin. Although findings are preliminary, a small portion of patients who do not respond to interferon therapy appear to respond to retreatment with interferon and ribavirin. This means that there remains a large group of patients for whom no effective treatment is available.

Retreatment of patients who did not respond to combination therapy is difficult. Because results from ongoing trials are not yet available, we do not know whether induction, fixed-dose, or maintenance-dose regimens of combination therapy are beneficial. Other retreatment options for this group include alternative medicine or waiting for newer, more-effective therapies to become available.

WHAT LIES AHEAD?

Many innovative approaches to the treatment of HCV are being developed. They include:

- **Pegylated interferon,** a long-acting, synthetic form of interferon that would be more convenient for the patient because it is given by depot injection.
- **Viral enzyme inhibitors** that could block the HCV enzymes protease, helicase, and polymerase to prevent viral replication.
- **Molecular-based approaches,** including hammerhead ribozymes and antisense oligonucleotides, which also prevent replication of the virus.
- **Immunotherapy approaches,** including T-cell-based immunotherapy, either antigen specific or nonspecific; DNA-based immunization; and strategies that efficiently deliver antiviral cytokines to the liver by adenoviral vectors or by liposomes.

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