PREVENTION

The best treatment is prevention, which should begin in the early teenage years with adequate dietary calcium and reasonable physical activity. Strong bones and a vigorous lifestyle in the early years should enhance the efficacy of estrogen in the menopausal years.

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EVALUATING TREATMENT OPTIONS FOR CHRONIC LIVER DISEASE

Newer options for treating chronic liver disease are accepted by most experts, and have found their way to many internists' offices. Nevertheless, they represent a grey area, in that they have yet to appear in standard textbooks.

Three areas are of particular interest: the use of colchicine to treat primary biliary cirrhosis (PBC); alpha interferon for the treatment of chronic non-A non-B hepatitis; and nadolol therapy to prevent first variceal bleeds.

TREATING PRIMARY BILIARY CIRRHOSIS

Despite a limited number of studies that demonstrate efficacy, colchicine has been accepted for five or six years for treatment of primary biliary cirrhosis. The beneficial effects of colchicine include decreased collagen synthesis and increased collagenase activity. The drug is also safe and inexpensive. In a recent study (Kaplan et al. N Engl J Med 1986; 315:1448–54) that compared colchicine, 0.6 mg bid, with placebo, the 45 patients who received the drug showed improvements in serum albumin, bilirubin, alkaline phosphatase, cholesterol, and aminotransferases. The cumulative mortality after four years of study was 21% in the colchicine group *v* 47% in the untreated patients.

Ursodeoxycholic acid also is potentially useful for treatment of primary biliary cirrhosis. The rationale is that the underlying cause of primary biliary cirrhosis is an autoimmune process, and the accumulation of bile acids in portal areas may contribute to worsening of the disease. The replacement of these bile acids by ursodeoxycholic acid may lead to improvement in liver lesions. A recent trial (Poupon et al. Lancet 1987;1:834–6) of 15 patients showed improvements in alkaline phosphatase, transaminases, bilirubin, and pruritus, but no change in histology.

The Cleveland Clinic Foundation is now formulating a trial that will compare colchicine with ursodeoxycholic acid.

INTERFERON

Alpha interferon may be helpful in patients with chronic non-A non-B hepatitis. A recent multicenter trial (Davis et al. Hepatology 1989;9:in press), that included the Cleveland Clinic Foundation, addressed this question. Patients in one group received either 1 million or 3 million units of alpha interferon three times weekly for 24 weeks; treatment was delayed in the second group. A preliminary analysis showed marked improvement in SGPT in the treatment group, from 175 before therapy to 95 after treatment. SGPT levels normalized in 36% of the treatment group, compared to 5% of the delayed therapy group. Improvement was unlikely in patients who did not respond within 10–12 weeks. Unpublished data suggest that the lower dosage may be inadequate.

In patients with chronic active hepatitis B, alpha interferon appears to eliminate viral replication in some patients. Those patients who have active disease characterized by e antigen positivity and higher SGPT and SGOT levels are more likely to respond to therapy than are homosexuals or patients with minimally elevated enzymes, childhood onset of disease, and HIV positivity. High-dose prednisone therapy, which temporarily worsens the disease, seems to enhance the effects of alpha interferon.

Despite the potential for benefits, interferon is not easy to use. Most patients who take it have a flu-like illness for the first week or two; depression may warrant cessation of therapy; and leukopenia is potentially dangerous. The drug, which is expensive, must be administered parenterally.

PREVENTION OF FIRST VARICEAL BLEEDS

The mortality from bleeding esophageal varices may be as high as 60%–65%.

With proper patient selection, beta blocker therapy has the potential to prevent first bleeds because it re-

duces portal pressure in patients with alcoholic cirrhosis. In patients considered to be good risks (no ascites, Childs Class A), propranolol therapy is associated with less bleeding, but it does not significantly affect survival. The drawbacks of propranolol therapy are side effects and its reliance on hepatic metabolism for elimination.

Nadolol may be a more logical choice because it does not rely on hepatic elimination. A recent study (Ideo et al. Hepatology 1988;8:6–9) compared nadolol (30 patients) with placebo or ranitidine (49 patients). Nadolol was associated with significantly fewer episodes of bleeding, and endoscopic evaluation showed reduced variceal size in 63% of the nadolol-treated patients, compared to only 29% of control patients. Only 3% of the patients withdrew because of side effects—a much lower figure than observed in propranolol studies.

Although beta blocker therapy may benefit patients who have large esophageal varices that have never bled, the effect on mortality is less clear. For patients who are at the terminal end of disease (Childs Class C), transplantation may be the more appropriate course.

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METHOTREXATE TREATMENT OF RHEUMATOID ARTHRITIS

Dihydrofolate inhibitors including methotrexate (MTX) have been used to treat inflammatory arthritis since 1951. Following numerous reports of retrospective and prospective open trials in the late 1970s and early 1980s, five controlled, double-blind studies have confirmed its effectiveness as treatment for rheumatoid arthritis. In October 1988 the FDA approved methotrexate for that indication.

MTX is given in pulse fashion, preferably as one oral dose (7.5–15 mg) each week. Clinical improvement of rheumatoid disease is often seen within 2–4 weeks and plateaus at about six months. Because MTX is not significantly metabolized in the liver, and its half-life depends almost entirely on renal excretion, patients with elevated serum creatinine should not be given the drug.

Mild, acute adverse effects include nausea, diarrhea, minor alopecia, and oral ulcers, which occur in 10%–40% of patients, depending on the length of follow-up. These effects are usually dose related and respond to manipulation of the dose. Cytopenia is rare, occurring in less than 1% of patients reported. Acute pulmonary toxicity, which may occur in as many as 6% of patients in one report, is worrisome and does not seem to be dose related. Long-term use can result in hepatic fibrosis in a small number of patients treated for rheumatoid arthritis. For this reason, alcoholic beverages are proscribed for patients receiving the drug.

Controversy still exists in the medical literature regarding the necessity and timing of liver biopsy in patient follow-up, the mechanism(s) of action of the drug in rheumatoid arthritis, and its place on the treatment pyramid (whether it should be considered at the same time gold therapy is initiated or only after failure or intolerance to gold therapy). As further metabolic and prospective comparison studies are reported, the answers to these issues will become clearer.

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