THE EFFECTIVE PHYSICIAN

# Acute Liver Failure

BY WILLIAM E. GOLDEN, M.D., AND ROBERT H. HOPKINS, M.D.

## Background

Nearly 2,000 patients suffer acute liver failure annually in the United States. The American Association for the Study of Liver Diseases recently published a practice guideline on this condition, which causes high morbidity and mortality in a young population.

## Conclusions

Acute liver failure (ALF) is defined as hepatic disease of less than 26 weeks' duration that results in some encephalopathy and impaired coagulation (international normalized ratio > 1.5) in patients without previous evidence of cirrhosis. Common causes include viruses, toxins, autoimmune conditions, and hypoperfusion. Drugs other than acetaminophen rarely cause dose-related toxicity.

Viral hepatitis has become an infrequent cause of ALF, with hepatitis B being twice as common as hepatitis A. Hepatitis C is not considered to be a cause of the condition. Hepatitis E is an important cause of ALF in endemic areas. Wilson's disease is an uncommon cause of ALF, but is uniformly fatal without transplantation.

Cerebral edema with intracranial hypertension is one of the most serious complications of ALF. Grade I-II encephalopathy carries minimal risk for cerebral edema, but risk for cerebral edema increases to 25%-33% in grade III encephalopathy and up to 75% in patients with grade IV. No uniform treatment protocol currently exists. Blood ammonia levels above 200 mcg/dL are associated with cerebral herniation.

No single agent or therapy is useful for all forms of ALF. Corticosteroids are ineffective. *N*-acetylcysteine cannot be justified in all cases of ALF based on currently available clinical study data.

Survival in the past was less than 15%, but varied according to the underlying cause of the organ failure. Cases of ALF due to acetaminophen, hepatitis A, shock liver, and pregnancy-related conditions have transplant-free survival rates better than 50%.

Overall, nearly two-thirds of patients now survive because of the success of liver transplantation. Many patients die while waiting for an organ on the transplant list.

Existing prognostic scoring systems do not reliably predict the outcomes of episodes of ALF.

## Implementation

The history should focus on exposure to toxins or ingestion of specific medications.

During the examination, failure to palpate a liver edge or percuss a normal liver span could indicate massive hepatocyte loss and reduced liver volume.

Because the condition can progress rapidly, patients with ALF complicated by mental impairment and prolongation of the INR should be admitted to the hospital for ongoing observation and supportive treatment.

Extensive serum testing and liver biopsy via the transjugular route is mandatory to determine the cause and severity of the liver dysfunction.

Patients with grade I or II encephalopathy should have active, ongoing planning for transplantation, and those with grade III or IV encephalopathy should be transported to the appropriate unit to avoid morbidity associated with moving patients in extreme states of liver failure. Surveillance cultures are useful in patients who have ALF, but prophylactic antibiotics have not been shown to improve outcomes.

Patients with ALF in the ICU should receive prophylaxis for gastrointestinal bleeding.

Nutrition is important, but protein restriction should not go below 60 g per day. Branched-chain amino acids have not been shown to offer advantages over other types of nutritional support.

Although there is no evidence of improved survival, lactulose can reduce ammonia levels. It can also increase intestinal distention, however, which could interfere with liver transplantation.

Patients with severe encephalopathy can benefit from elective intubation for airway protection, sedation, elevation of the head of the bed to 30 degrees, and avoidance of straining. Endotracheal lidocaine prior to suctioning might be beneficial.

Management of seizures with phenytoin can also avoid increases in intracranial pressure (ICP). Monitoring of ICP is not uniformly recommended, but is more common in patients scheduled for transplantation.

Patients with acetaminophen poisoning can have transaminase levels over 3,500 U/L. Activated charcoal can be helpful within 4 hours of ingestion. It does not interfere with *N*-acetylcysteine, which should be given to all patients with suspected acetaminophen poisoning, up to and possibly after 48 hours of presentation. Those patients with an arterial pH under 7.3 should be placed on a list for potential liver transplantation.

Mushroom poisoning (especially with *Amanita phalloides*) should be considered in presentations of ALF. There is no diagnostic blood test for this ingestion. *N*-acetylcysteine has not been effective in animal studies. Penicillin G and silibinin are accepted antidotes, despite the lack of data on their use from controlled trials.

Acute fatty liver of pregnancy can be seen with low platelet counts and hemolysis. Coincident features of preeclampsia are common. Prompt delivery is important, with rapid recovery typically seen post partum.

## Reference

J. Polson and W.M. Lee. AASLD Position paper: The management of acute liver failure. Hepatology 2005;41:1179-97.

*Dr. Golden (right) is professor of medicine and public health and Dr. Hopkins is associate director of the medicine/pediatrics residency program at the University of Arkansas, Little Rock.*

# Certolizumab Achieves Good Clinical Response In Crohn's Patients

BY BRUCE JANCIN
*Denver Bureau*

HONOLULU — Certolizumab pegol, a novel anti–tumor necrosis factor-α agent, proved effective for both induction and maintenance of clinical remission in patients with Crohn's disease in a pivotal phase III, 26-week randomized trial, Dr. William J. Sandborn reported at the annual meeting of the American College of Gastroenterology.

Certolizumab (Cimzia) is a humanized monoclonal Fab fragment conjugated to polyethylene glycol, giving it a lengthy plasma half-life of nearly 2 weeks. It is considered far less likely to engender an immune response than infliximab (Remicade), at present the sole anti-TNF agent approved for Crohn's disease.

Also, unlike the intravenously administered infliximab, certolizumab is given by subcutaneous injection, a route that offers the potential for more convenient self-treatment, explained Dr. Sandborn, professor of medicine at the Mayo Medical School, Rochester, Minn.

He reported on 668 patients with moderate to severe Crohn's disease who participated in the PRECiSE 2 trial, sponsored by UCB Pharmaceuticals Inc., manufacturer of certolizumab.

All patients received an open-label induction regimen of 400-mg certolizumab at weeks 0, 2, and 4. The 64% who showed a significant clinical response by week 6 were then randomized to double-blind maintenance therapy with 400-mg certolizumab or placebo once a month.

The primary end point in PRECiSE 2 was maintenance of a clinical response, defined as at least a 100-point drop in the Crohn's Disease Activity Index at week 26, compared with baseline. The clinical response rate in the certolizumab group was 63%, significantly better than the 36% rate in controls.

In addition, the remission rate, defined by a Crohn's Disease Activity Index of 150 or less at 26 weeks, was 48% with certolizumab and 29% with placebo.

Certolizumab's efficacy was equally robust in patients with or without an elevated baseline C-reactive protein level, unlike the findings of an earlier trial in which only patients with a baseline CRP of at least 10 mg/L showed significant improvement.

The efficacy of certolizumab in PRECiSE 2 was similar in patients who were on immunosuppressive therapy and those who weren't. Certolizumab was significantly more effective than placebo, both in patients who had previously been on infliximab and those who hadn't. However, the 69% clinical response rate in anti-TNF–naive patients was markedly greater than the 44% rate among those previously on infliximab, Dr. Sandborn continued.

A single case of tuberculosis occurred in the certolizumab-treated group during the 26 weeks. The overall rate of significant infections was 1.8% during the 4-week induction phase and 2.8% during maintenance therapy. Antibodies to certolizumab developed in 8% of patients.

PRECiSE 3 and 4 are ongoing, 24-month, open-label trials designed to provide additional safety and tolerability data. UCB plans to file for marketing approval for certolizumab early next year.

Certolizumab is one of three new biologic agents that clinicians will likely be able to offer their Crohn's disease patients in 2007, according to Dr. Sandborn. The other two are adalimumab (Humira), a fully human monoclonal antibody directed against TNF-α with very low immunogenicity, and natalizumab (Tysabri), a humanized monoclonal antibody directed against α4 integrins.

Dr. Sandborn was principal investigator in the positive phase III Clinical Assessment of Adalimumab Safety and Efficacy Studied as an Induction Therapy in Crohn's Disease (CLASSIC-II) trial of adalimumab, as well as in the Efficacy of Natalizumab as Active Crohn's Therapy-1 and -2 (ENACT-1 and -2) trials.

Natalizumab was developed initially for the treatment of multiple sclerosis but was quickly taken off the market after three cases of progressive multifocal leukoencephalopathy occurred.

In September, the drug's manufacturer filed an application to resume marketing, since no more cases of leukoencephalopathy were ascertained.

Dr. Sandborn is a consultant to Centocor Inc., UCB, Abbott Laboratories, and Biogen Idec, the manufacturers of infliximab, certolizumab, adalimumab, and natalizumab, respectively.

Although all of the biologics are expensive to manufacture, the subcutaneous route of administration for certolizumab and adalimumab could spell substantial savings because prescribers won't need to set up an office infusion center, Dr. Sandborn said. ■