Drug Monitor

Simvastatin for MS?

Statins may have earned yet another gold star. Results from a multicenter, open-label, study suggest that statins' newly identified immunomodulatory effects could be useful in treating relapsing-remitting multiple sclerosis (MS).

Researchers enrolled 30 patients who hadn't been treated with interferon or glatiramer in the previous three months or with corticosteroids in the previous 30 days. They monitored the patients for three months, performing monthly magnetic resonance imaging brain scans. Patients found to have at least one gadolinium (Gd) enhancing lesion during the monitoring phase were given oral simvastatin 80 mg/day for six months. In the treatment phase, brain scans were repeated at four, five, and six months.

Simvastatin reduced the number and volume of Gd enhancing lesions by 44% and 41%, respectively. It had no effect, however, on yearly relapse rates or disability status scores.

There were no serious adverse events. Two of the treated patients had a clinically important change in liver function and one had a clinically relevant creatinine phosphokinase concentration at one month, which subsequently normalized. Three patients reported muscle weakness possibly related to simvastatin.

Although the researchers acknowledge that, due to their study design, improvements from baseline could represent regression to the mean, they say their findings support calls for randomized, controlled trials investigating the use of statins in relapsing-remitting MS.

Source: *Lancet*. 2004; 363:1607–1608.

Natural vs. Artificial Colloids

Are all colloids interchangeable? Not when it comes to safety, say researchers from the University of Miami School of Medicine, Miami, FL and Hygeia Associates, Grass Valley, CA. They reviewed data from 113 studies of the natural colloid albumin and the artificial colloids hydroxyethyl starch (HES), dextran, and gelatin. Their conclusion: Albumin appears to be the safest of the four. Albumin infusion resulted in a low rate of total adverse events (3.1 to 8.6 per 10^5 infusions) and serious adverse events (1.29 per 10^6 infusions).

Bleeding was reported widely with the artificial colloids, particularly in cardiac surgery, the researchers say. Anaphylactoid reactions were relatively infrequent for all the colloids, but compared to albumin, dextran more than doubled the incidence of such reactions, HES more than quadrupled it, and gelatin raised it more than 12-fold. HES exposure also significantly increased the odds of developing pruritus. Although this effect was dose-related, many patients were receiving less than the maximum HES dose.

All three artificial colloids have been associated with renal impairment. In one study, HES was an independent risk factor for acute renal failure. In patients who'd undergone renal transplantation, HES reduced urinary output, increased creatinine levels and dopamine requirement, and increased the need for hemodialysis or hemodiafiltration. In a study of patients with acute ischemic stroke receiving dextran, nearly 5% experienced acute renal failure. Gelatin, compared with albumin as pump prime in cardiac surgery, elevated creatinine levels. The artificial colloids also were linked to circulatory and hepatic dysfunction.

The researchers note that, in some settings, factors such as desirability of anticoagulant activity "might militate in favor of artificial colloids." Nonetheless, they emphasize the importance of considering the contrasting safety profiles in clinical decision making.

Source: *Arch Surg*. 2004; 139:552–563.

New HCV Drug Shows Promise

If interferon-based treatment isn't working for your patient infected with hepatitis C virus (HCV), there may be some help on the way. NM283, a new once daily oral treatment that works by inhibiting the HCV RNA polymerase, has just passed its first human trial with flying colors.

All patients enrolled in the randomized, multicenter study had chronic genotype 1 HCV infection,

serum HCV RNA levels greater than 100,000 IU/mL, alanine aminotransferase levels lower than five times the upper limit of normal, and compensated liver disease without cirrhosis. All had either failed to respond to prior interferon-based therapy or had been previously untreated.

The researchers grouped patients into cohorts of 12 patients each, with two receiving placebo and 10 receiving the study drug. The study design included eight cohorts distinguished by drug dosage: five taking 50, 100, 200, 400, or 800 mg once daily, one taking 200 mg twice daily, one starting with 100 mg/day and titrating to 800 mg/day, and one starting with 400 mg/day and titrating to 800 mg/day. The last group received antiemetic medication on the first two days and then for one day during each of the two dosage increases.

Thus far, a total of 82 patients from seven cohorts have completed the trial (68 receiving NM283 and 14 receiving placebo). Analysis of data from these patients revealed that NM283 had a consistent, dose-related effect on serum HCV RNA levels. Patients who received the highest cumulative dose of NM283 over the 15-day treatment period saw the greatest antiviral effect, with a mean HCV RNA reduction of 92%.

In this dosing group, HCV RNA dropped in all 10 patients by between 79% and 99%. Nine of the 10 patients had tried interferon-based therapies previously without success. Furthermore, average antiviral responses in the three highest dose groups exceeded those observed in patients with HCV who respond to the current standard of therapy: ribavirin plus pegylated interferon.

At the higher doses, some patients experienced adverse gastrointestinal effects that were mild to moderate, tended to appear in the first two days of treatment, and typically resolved quickly. No patients changed or stopped treatment due to adverse effects. Pharmacokinetics data indicated that patients absorbed NM283 well, with no significant drug accumulation by the end of the treatment period.

The once daily 800 mg cohort is ongoing. The next clinical trial will evaluate the combination of NM283 and pegylated interferon over a four-week treatment period, with longer-term trials to follow later this year. ●

Source: Indenix Pharmaceuticals News Release. May 18, 2004.