CLINICAL ADVANCES IN BIOTECHNOLOGY

CHICAGO—A survey of the recent literature on clinical trials of biotech-derived therapeutics turned up the following highlights:

• *More Good News on Alpha-Interferon.* Hepatitis B virus (HBV) infection represents a major public health problem worldwide. The Centers for Disease Control (CDC, Atlanta, GA) estimates that over 300,000 people in the U.S. alone will become infected annually, of whom 5,000 will die. Moreover, roughly one million people are carriers, with as many as 200 million worldwide. HBV infection can lead to cirrhosis of the liver and liver cancer.

Therapeutic intervention has proven elusive. Clinical responses to various drugs have been described but cures are rare. To successfully treat the disease, it is necessary to eradicate all circulating virus. It now appears that alpha-interferon (IFN)—which has a dual effect as an anti-viral agent and as an immune system stimulant—may prove a successful therapeutic.

The following study from the *British Medical Journal* (**299:**652, Sept. 9, 1989) summarizes the positive effects of alpha-interferon in chronic HBV infection. The study involved a randomized, controlled trial of three months of alpha-IFN treatment, followed by a 12-month observation period. Treatment was on an outpatient basis; 37 men (34 in the untreated control group) received a subcutaneous injection of 5–10 million units daily (per meter squared of body size) for five days. This therapy was then followed by 10 million units per meter squared three times per week for 11 weeks.

Among the 37 treated patients, 12 became persistently negative for circulating hepatitis antigen and viral DNA, comparing favorably to the results in the control group where only one in 30 had a spontaneous recovery. Thus, the excess response rate was 29 percent for the treatment group.

• *G-CSF in Dose-Intensive Chemotherapy—Moving in the Right Direction.* Both GM- and G-CSF (granulocyte macrophage- and granulocyte-colony stimulating factor, respectively) have been shown to reduce the severity of granulocytopenia in patients undergoing chemotherapy at standard doses. And trials have now begun on the use of the CSFs in high-dose, or dose-intensifying, chemotherapy regimens. A variety of studies have shown that dose-intensive chemotherapy can produce significant anti-cancer responses in tumors traditionally refractory to standard doses. Such dose-intensive protocols—used in the treatment of lymphoma, breast, and lung cancer—are often given in combination with bone marrow transplantation to restore functional white blood cells (WBCs).

A study presented in the *Journal of Clinical Oncology* (**7:**1685, November 1989) examined whether G-CSF could reduce morbidity in dose-intensive chemotherapy without the support of bone marrow transplantation. Patients were judged incurable and terminal. G-CSF doses included 20, 40, or 60 micrograms/kilogram body weight and were administered from day 6 to day 26. The patients received chemotherapy—toposide, cyclophosphamide, and cisplatin—for three days at the beginning of each cycle.

G-CSF significantly reduced the duration of granulocytopenia and increased the speed and degree of recovery. Patients receiving chemotherapy without G-CSF became severely granulocytopenic roughly four days following treatment and slowly became "normal" by day 28. On the other hand, G-CSF therapy at 60 micrograms/kilogram returned WBC counts to normal by day 15; the mean duration of granulocytopenia was 5.5 days versus 8.5 days in the control group. Additionally, G-CSF significantly shortened the recovery time of granulocyte counts to six days in the treatment group versus 12 days in the control group. The duration of granulocytopenia was not prolonged after repeated chemotherapy cycles and G-CSF.

Although these data are highly encouraging, the question of optimal time to initiate G-CSF therapy in relation to chemotherapy has not been determined.

• *Broadening the Clinical Applications for EPO—And the Band Plays On.* Autologous blood donation is a relatively common practice for patients undergoing elective surgery. But previous clinical studies have indicated that, although most patients could donate three units, 40 percent could not donate four, due to anemia. The current study addresses erythropoietin's (EPO) effectiveness in preventing this anemia, as well as whether the drug increases the volume of red blood cells (RBCs) that can be collected before surgery.

The New England Journal of Medicine (**321:**1163, October 26, 1989) contains an important paper describing the effectiveness of EPO in increasing the pre-operative collection of autologous blood. The experimental protocol involved the following: An autologous unit of blood was collected from each patient twice a week for three weeks. At each visit, patients received either intravenous EPO (600 units/kilogram body weight) or placebo. Fifty-four patients were enrolled and 47 completed the study (24 in the placebo group and 23 in the EPO group). EPO's effectiveness was remarkable—treated patients were able to donate a total of 125 units (5.4 units/patient) versus 99 units in the placebo group (4.1 units/patient). Only one treated patient was unable to donate four units, compared to seven placebo-treated patients. RBC volume was significantly higher than in the placebo group. Adverse reactions such as fatigue, dizziness, and nausea were similar to the placebo group and there were no differences in blood pressure.

• *The t-PA Dosing Story—Faster is Better.* Historically, reperfusion rates with tissue plasminogen activator (t-PA) ranged from 55–75 percent using the currently recommended dose of 100 milligrams infused over a three-hour period. This protracted infusion time related to the pharmacokinetics of injected t-PA: with a short circulating half-life, it was assumed that a shorter infusion time would lead to an unacceptably high rate of reocclusion. But various animal data now suggest there is a direct correlation between thrombolytic efficacy and infusion rate.

The Journal of the American College of Cardiology (**14:**1566, November 15, 1989) contains an article describing significantly improved thrombolytic activity when t-PA is infused more rapidly than under FDA-approved protocols. The current study investigated the effect of a more rapid infusion regimen on overall thrombolytic activity: there was an initial bolus injection of 15 milligrams of t-PA, followed by 50 milligrams over 30 minutes, and a final 30 milligrams over the following 60 minutes. All patients received a bolus injection of heparin and a vast majority received coronary angiograms to accurately monitor reperfusion rates. Results indicate that at 60 minutes, reperfusion was evident in 74 percent of the infarct-related arteries and over 90 percent at both 90 minutes and 24 hours. At 48 hours post-infarct, the reinfarction rate was 8 percent and reocclusion was 11 percent. There was no unusual bleeding. **—Peter F. Drake**