TRIALS UPDATE

CLINICAL ADVANCES IN BIOTECHNOLOGY

NEW YORK—A survey of the recent clinical literature supports the impression that biotechnology and pharmaceutical companies have made major gains in developing new drugs. Selected highlights from the journals include the following:

• *Clinical Advances Using the Colony Stimulating Factors (CSFs)—The More the Merrier.* The clinical literature has been flooded with reports describing the safety and efficacy of the CSFs. In a variety of trials, these agents—granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and macrophage colony-stimulating factor (M-CSF)—increase the concentration of circulating white blood cells (WBCs). The most advanced application of the CSFs is in the area of cancer.

Roughly 700,000 patients in the U.S. undergo cancer chemotherapy each year, but only about 25 percent of them receive a full-course regimen due to the treatment's severe side effects. The major dose-limiting side effect is a severe reduction in WBCs (neutropenia), which compromises the immune system and renders cancer patients vulnerable to life-threatening infectious diseases.

An article in *The New England Journal of Medicine* (1988, **319:**593) contains the first publication on the use of GM-CSF (from Genetics Institute, Cambridge, MA; Sandoz, New York, NY; and Schering-Plough, Madison, NJ) in combination with chemotherapy in cancer patients. Sixteen patients (non-randomized) with advanced cancer were treated with GM-CSF before and immediately after a first cycle of chemotherapy with MAID (mesna, doxorubicin, isophosphamide, and dacarbazine). A follow-up cycle of chemotherapy was administered without GM-CSF.

Given before chemotherapy, GM-CSF was well tolerated at doses from 4–32 micrograms/kilogram body weight, and produced a dose-dependent increase in WBC levels. Of the original 16 patients, 12 completed both cycle 1 (with GM-CSF) and cycle 2 (without GM-CSF). GM-CSF significantly reduced the duration of neutropenia—from 7.4 days to 3.5 days. In addition, WBC and platelet counts were higher after cycle 1 than after cycle 2.

• *Epidermal Growth Factor (EGF) in Wound Healing—Learning to Walk Before We Run.* The process of wound healing represents a series of diverse biological events: inflammation, replication of fibroblasts and epithelial cells, angiogenesis, matrix formation, and tissue remodeling. The role of growth factors in promoting cell replication *in vitro* has led to speculation that they may have applications in accelerating wound healing.

The first clinical prospective study of the use of growth factors in treating wounds was published in *The New England Journal of Medicine* (1989, **321:**76). This randomized, double-blind study addressed the safety and efficacy of EGF (from Chiron, Emeryville, CA, and Johnson & Johnson, New Brunswick, NJ). The tests used paired skin-graft donor sites on 12 patients requiring skin grafts. Physicians applied a topical silver sulfadiazine cream containing EGF (10 micrograms/ml) to one site, and placebo (silver sulfadiazine cream alone) to the other site.

The results were consistent and striking. Wound sites treated with EGF showed accelerated wound healing compared with controls. Moreover, EGF was without side effects and the healed tissue was normal histologically.

Although considerable additional testing will be required to obtain FDA approval for EGF, the current study underscores the potential benefit of growth factors in treating clinically relevant wounds.

• *Zidovudine (AZT) and Alpha-Interferon in AIDS—The Cocktail Party Begins.* New approaches to AIDS treatment have come from both academic and industrial scientists. To date, only one drug, AZT, has been shown to prolong survival in HIV-infected patients. In addition, recombinant alpha-interferon from Biogen (Cambridge, MA)/Schering-Plough and Genentech (So. San Francisco, CA / Hoffmann-La Roche (Nutley, NJ) recently received FDA approval for the treatment of Kaposi's sarcoma. Since AZT and alpha-interferon exert their antiviral activities via different biological mechanisms (by inhibiting reverse transcriptase and by interfering with viral assembly, respectively), researchers are looking into the combination of the two drugs in a "cocktail" approach to treat AIDS and Kaposi's sarcoma.

A recent issue of the *Annals of Internal Medicine* (1989, **111:**280) describes the use of AZT and alpha-interferon in a non-randomized, open clinical trial on 39 patients with HIV and Kaposi's sarcoma. The study design was a dose escalation regimen beginning with AZT therapy, followed six weeks later by alpha-interferon.

The results were encouraging and distinct from use of either agent alone. Of 22 patients who received a stable dose of both drugs for 12 weeks, 11 had complete or partial tumor response and eight showed an anti-retroviral effect—in fact, six became culture-negative for HIV. Dose-limiting toxicities included neutropenia (57 percent), fatigue (16 percent), thrombocytopenia (14 percent), and hepatic dysfunction (10 percent).

This study portends the use of the "cocktail" approach to AIDS treatment and hints of the potential importance of alpha-interferon in HIV treatment regimens.

• *Gamma-Interferon in Rheumatoid Arthritis—Getting Closer to a Moving Target.* Rheumatoid arthritis (RA) has long been linked to an immune system dysfunction; thus researchers are considering biological agents to treat the condition. One immunomodulator—gamma-interferon (from Biogen)—has been approved for the treatment of RA in West Germany.

A recent issue of *Arthritis and Rheumatism* (1989, **32:**964) contains the most recent published data on gamma-interferon's use in a 12-week, randomized, prospective, double-blind, placebo-controlled trial in 105 RA patients. Fifty-four patients received five subcutaneous injections of gamma-interferon (100 micrograms /injection) each week for 12 weeks, while 51 received placebo. Concurrent antirheumatic medications were permitted (e.g., non-steroid antiinflammatory drugs, aspirin, gold, and D-penicillamine). Clinical data included joint tenderness and swelling, grip strength, and pain severity.

The data showed a clear trend for the utility of gamma-interferon therapy, though most of the results were not statistically significant. Joint tenderness and swelling was reduced by 50 percent or more, and morning stiffness was significantly less in treated patients. Ten percent of the treated patients reported adverse reactions, primarily fever, chills, nausea, headache, fatigue and dizziness.

Thus, while several studies have demonstrated the safety of gamma-interferon in treating RA, they have not consistently shown significant efficacy; larger and longer-term trials, currently underway, may succeed in doing so.

—Peter F. Drake