

drug therapy topics supplement

A Timely Discussion of Contemporary Issues

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CLINICAL PRACTICE

Hemophilia Drug Shortage Will Persist into 2002

Kogenate (recombinant antihemophilic factor), the leading brand of recombinant clotting factor VIII, intended for use in the therapy of classical hemophilia (hemophilia A), will remain in short supply until the beginning of next year due to manufacturing problems at Bayer's factory in California. Bayer halted shipments of *Kogenate* in January after an FDA inspection found, for the second time in three years, bacteria in some of the manufacturing stages [*Reuters Health*, 12 June 2001].

Drug shortages are becoming more common. Recent shortages include albuterol inhalers, phentermine, injectable dexamethasone, naloxone, fentanyl, succinylcholine, and tetanus vaccines. There are several reasons for these problems, but none is easy to fix. There are fewer manufacturers for some staple drugs because of mergers or decisions to drop unprofitable lines. Drug manufacturers have had to stop production because of shortages of raw materials or violations of FDA good manufacturing practices. Pharmacies and wholesalers are forced to carry smaller drug inventories because of financial pressure. There is now a Web site devoted to the drug shortage situation: www.ashp.org/shortage/. The ASHP site not only lists those drugs in short supply but also provides suggestions as to alternative therapy [*Prescriber's Letter* 2001;8(5):30].

Editor's Note: The FDA also maintains a Web site for information on drug shortages (www.fda.gov/cder/drug/shortages/default.htm) and operates a Drug Shortages listserver where practitioners can sign up for e-mail notification of drug shortages (<http://list.nih.gov/cgi-bin/wa?SUBED1=drug-shortages&A=1>).

Delayed Distribution of Influenza Vaccine

One of the four remaining influenza vaccine manufacturers has dropped out of the competition and, as a result, the vaccine will likely be delayed again this fall, but the delay should not be as troublesome as it was last year [*Reuters Health*, 15 August 2001]. Based on last year's unpleasant experience, the Centers for Disease Control and Prevention has developed a plan to ensure that physicians and high-risk individuals have priority access to the limited supply of vaccine early in the season. Manufacturers project that 20 million fewer doses of influenza vaccine will be available by the end of October 2001, compared with the supply at the end of October 1999. However, this is about twice the amount of vaccine that was available at the same time last year. The projected total vaccine to be produced by

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CLINICAL PRACTICE (continued)

Delayed Distribution of Influenza Vaccine (continued)

December 2001—about 83.7 million doses—is greater than the 70.4 million doses ultimately distributed during the 2000-2001 flu season. The CDC advises high-risk individuals—people aged 65 years and older or those with chronic medical conditions—to seek vaccination in Sep-

tember and October. Those who are not in a high-risk category are advised to seek immunization in November or later, when additional supplies will be available. Updates on the 2001-2002 flu season will be posted at www.cdc.gov/nip/flu.

Pilocarpine Eye Drops Orally to Treat Severe Dry Mouth

Here is a neat suggestion from the people who write *Prescriber's Letter*: using pilocarpine eye drops orally to treat severe dry mouth. Chronic dry mouth can lead to dental caries, oral candidiasis, periodontal disease, and difficulty with eating and talking. *Salagen* (pilocarpine) tablets or *Evoxac* (cevimeline) capsules are often used to ameliorate dry mouth, but they are expensive, costing more than \$120 per month. Pilo-

carpine eye drops taken orally seem to be equally effective and cost much less. The editors of the newsletter report that some physicians direct patients to take four to five drops (0.25 ml) of 2% pilocarpine ophthalmic solution in four ounces of water four times daily. They suggest that physicians consider this approach for patients who cannot afford *Salagen* or *Evoxac* [*Prescriber's Letter* 2001;8:40].

DRUG SAFETY

Anthracyclines After *Herceptin* May Also Pose Problems

Genentech and the FDA are discussing revisions to *Herceptin* (trastuzumab) labeling following the submission of data that suggests the half-life of trastuzumab is much longer than previously thought. Preliminary information from an ongoing clinical trial indicates that the half-life of trastuzumab is 25 days, rather than 5-6 days as stated in earlier studies. The U.S. label for *Herceptin* says that trastuzumab has a mean half-life of 5.8 days (range 1-32 days) when a loading dose of 4 mg/kg is used followed by a weekly maintenance dose of 2 mg/kg. The longer half-life may affect how breast cancer patients are treated after they discontinue *Herceptin*. Concomitant treatment with *Herceptin* and anthracyclines is associated with cardiac toxicity.

Anthracycline administration was thought to be free of excess toxicity when initiated four weeks after discontinuing *Herceptin*; this may not be true. The new data prompted the European Medicines Evaluation Agency (EMA) to issue a statement warning that the use of anthracyclines after stopping *Herceptin* may carry a higher risk of cardiac toxicity. "*Herceptin* may persist in the circulation for more than 18 weeks (range 15-22 weeks) after stopping treatment," the EMA stated. The agency recommended that if possible, anthracycline-based therapy should be avoided for up to 22 weeks after stopping *Herceptin* therapy. Roche, which markets *Herceptin* in Europe, has notified physicians there of the new data and their possible implications.

Fenofibrate, Gemfibrozil, Plasma Homocysteine, and Renal Function

Fenofibrate (*Tricor*) increases plasma homocysteine, now regarded as an independent cardiovascular risk factor. Plasma homocysteine depends, in part, on renal function. Investigators have postulated that increases in plasma homocysteine are a result of the known impairment of renal function caused by fenofibrate. Gemfibrozil (*Lopid*), another fibrate, does not affect renal function. In a crossover study, researchers tested whether gemfibrozil, like fenofibrate, would

raise homocysteine levels. Twenty-two patients with elevated triglyceride levels received gemfibrozil 900 mg or fenofibrate 200 mg daily for six weeks. Both drugs reduced triglycerides and elevated HDL cholesterol, but only fenofibrate raised homocysteine and creatinine levels. Based on these findings, the investigators proposed that gemfibrozil should be the fibrate of choice [*Lancet* 2001;358:39-40].

NEW DRUGS AND INDICATIONS

New Applications for *Remicade*

Preliminary data suggest that periodic use of the monoclonal antibody *Remicade* (infliximab) can prolong remission in moderate-to-severe Crohn's disease. The results mean that *Remicade* could become the first therapy for Crohn's disease to allow long-term management of the disease, rather than dealing solely with episodic flare-ups. The data also show that ongoing treatment with infliximab can allow patients to reduce or eliminate steroid use.

The new information derives from a study of 573 patients with active disease. All patients received an initial treatment course of *Remicade*, and those who responded, about 60%, were randomized to one of three treatment groups: infliximab infusion 5mg/kg at weeks 2, 6, 14, 22, and 30; infliximab infusion 5 mg/kg at weeks 2 and 6 followed by 10mg/kg infusions at weeks 14, 22, and 30; and placebo infusions. By week 30, patients in the two treatment groups were twice as

likely to be in remission than were those who received placebo. About 40% of patients on the lower infliximab dose and 45% on the higher dose had no symptoms compared with 21% of patients assigned to placebo. At the outset of the study, 50% of patients were on steroids, but the majority who received infliximab were able to stop use completely. Those in the placebo group had to continue using steroids [*Scrip*, 8 June 2001].

Another study has demonstrated that patients with moderate to severe plaque psoriasis also appear to benefit from therapy with *Remicade*. Treatment with intravenous doses, initially, and at weeks 2 and 6, led to clearance of lesions by week 10 in more than 80% of patients. The median time to response was four weeks [*Lancet* 2001;357:1842-47]. Centocor is seeking FDA approval of *Remicade* for psoriasis and plans to initiate phase III trials by the autumn.

TAILORED DRUG THERAPY

C-Reactive Protein Measurement Permits Targeting of Statin Therapy

Current guidelines recommend that statins be prescribed for primary prevention of heart disease when LDL cholesterol levels exceed 160 mg/dl. Half of all coronary events, however, occur in persons without overt lipidemia. C-reactive protein is an independent risk factor for coronary heart disease. A single measurement in the high-normal range predicts an increased long-term risk of angina, myocardial infarction, and death, even in persons whose blood lipids are below median levels in the population.

Since statins lower the blood levels of C-reactive protein—a recent report provides an example [*JAMA* 2001;286:64-70]—as well as LDL cholesterol, investigators asked whether the measurement of C-reactive protein could identify patients who might benefit from statin therapy despite having relatively low levels of LDL cholesterol. They measured C-reactive protein at baseline and after one year in 5742 participants in a five-year randomized trial of lovastatin for primary prevention of acute coronary events.

Coronary-event rates increased significantly with increases in baseline C-reactive protein levels. Lovastatin reduced the C-reactive protein level by about 15%. Regardless of C-reactive protein level, lovastatin prevented coronary events in participants whose ratio of total cholesterol to HDL cholesterol at baseline was higher than the median ratio. One coronary event was prevented for every 47 people treated for five years. Lovastatin was also effective among those with a ratio of total to HDL cholesterol that was lower than the median and a C-reactive protein level that was higher than the median. One coronary event was prevented for every 43 people treated for five years. In contrast, lovastatin was ineffective among participants with a ratio of total to HDL cholesterol and a C-reactive protein level that were both lower than the median. In this group, the results suggest that 983 people needed treatment for five years to avoid one coronary event [*N Engl J Med* 2001;344:1959-65]. The results call for prospective, randomized trials to determine whether C-reactive protein testing can be used to identify persons whose coronary risk can be reduced by statin therapy [*Ibid*, 2016-18].

DRUG EVALUATION

Role of Glycoprotein IIb/IIIa Inhibitors in Acute Coronary Syndromes and Acute MI

Therapy directed against platelet aggregation with platelet glycoprotein IIb/IIIa receptor blockers can reduce procedure-related complications in patients with acute coronary syndromes (ACS) undergoing coronary angioplasty. Available drugs include abciximab, eptifibatide, and tirofiban. Are there differences among them?

A comparison of abciximab and tirofiban in eligible patients has shown that the primary end point—a composite of death, nonfatal MI, or urgent target vessel revascularization at 30 days—occurred more frequently among the 2398 patients in the tirofiban group than in the 2411 patients in the abciximab group (7.6% vs. 6.0%, $p=0.038$) [*N Engl J Med* 2001;344:1888-94]. A related report demonstrated that these patients—when treated with aspirin, heparin, and tirofiban and assigned either to early coronary angioplasty or, more conservatively, to angioplasty only in the event of recurrent ischemia—fared significantly better with the more aggressive strategy [*Ibid*, 1879-87].

Many patients with ACS do not undergo early revascularization. Therefore, evaluation of the value of a glycoprotein IIb/IIIa receptor blocker for medical

treatment of ACS is of interest. To this end, a placebo-controlled trial assessed abciximab in 7800 eligible patients who were not undergoing early revascularization. In light of evidence-based guidelines for the management of ACS from the American College of Cardiology/American Heart Association that support the addition of tirofiban or eptifibatide for ACS patients at risk of progression to acute MI or death, the results were disappointing. There was no difference in the occurrence of death or MI at 30 days between the placebo group and the abciximab group [*Lancet* 2001;357:1915-24].

Patients with acute MI may also benefit from treatment with a glycoprotein IIb/IIIa receptor blocker. Yet another study has shown that the administration of both aspirin and abciximab at presentation facilitates acute reperfusion. At 30 days, in 300 patients with acute MI assigned to abciximab plus stenting or placebo plus stenting, the primary end point—a composite of death, reinfarction, or urgent revascularization of the target vessel—had occurred in 6.0% of patients in the abciximab group, as compared with 14.6% of those in the placebo group [*N Engl J Med* 2001;344:1895-903].

Complete Viral Suppression Is Not Required to Derive Benefit from HAART

While highly active antiretroviral therapy (HAART) does not achieve complete HIV suppression for all patients, treatment can still provide durable virologic and clinical benefit, according to the findings of two recent reports. These observations are not consistent with the conceptual framework of HIV infection and treatment, which holds that ongoing viral replication in the presence of therapy should result in the rapid selection of drug-resistant mutations and subsequent virologic rebound and treatment failure.

One study involved children and adults who had achieved and maintained undetectable plasma HIV RNA levels (<50 copies/ml). By means of techniques to amplify plasma viral RNA, virus was identified in

plasma from 10 of 20 patients. Genotype analysis of the isolate viral RNA showed no evidence of new mutations related to the treatment regimen. Therefore, the low-level viremia that was measured in some patients appears to result from HIV strains that were present before HAART was initiated rather than from mutated strains that occurred as a result of treatment. The findings indicate that viral replication can be identified in patients apparently responding to combination therapy, but that this level of replication appears to be insufficient to select for drug resistance [*JAMA* 2001;286: 196-207].

In another investigation, investigators addressed a similar question in a totally different way. Patients enrolled in a long-term treatment study were identi-

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Complete Viral Suppression Not Required for HAART Benefit (continued)

fied and stratified into two groups: those whose plasma HIV RNA levels remained consistently below 50 copies/ml and those whose plasma HIV RNA levels were transiently detectable (>50 copies/ml) with a subsequent measured level of <50 copies/ml and who were categorized as having intermittent viremia. Despite evidence of higher levels of viral replication in the intermittent viremia group, both groups had similar rates of virologic failure—the occurrence of two

consecutive HIV RNA levels >200 copies/ml [*Ibid*, 171-79].

A related editorial comments on reassessing definitions of success or failure with antiretroviral therapy [*Ibid*, 224-26]. The author told *Reuters Health* [11 July 2001], “These articles call into question the concept that complete viral suppression is necessary in order to achieve a durable clinical benefit from antiretroviral therapy.”

Correcting Anemia with EPO and Iron in Congestive Heart Failure

Anemia is common in patients with congestive heart failure (CHF) and is associated with a poor prognosis. In a recently reported 32-patient, randomized trial, investigators studied the effect of correction of mild anemia in severe, resistant CHF using erythropoietin (EPO) and iron. All patients had moderate to severe CHF (New York Heart Association class III to IV), a left ventricular ejection fraction (LVEF) of less than 40%, despite optimal treatment, and hemoglobin levels between 10 g/dl and 11.5 g/dl. One group of patients received subcutaneous EPO, 4000 units per week with the dose increased or decreased to achieve the target hemoglobin levels of 12.5 g/dl, and intravenous iron, 200 mg every two weeks until serum fer-

ritin, iron saturation, or hemoglobin reached target levels, and then as needed to maintain these levels. The other group did not have their anemia treated. The mean NYHA class improved in the treated group and worsened in the untreated group. LVEF increased in treated patients and decreased in untreated patients. Serum creatinine did not change in treated patients, but increased by nearly 30% in untreated patients. The authors concluded: “In patients with severe CHF, treatment of anemia . . . results in a marked improvement in cardiac function. This is associated with less hospitalization, less renal impairment, and a reduced need for diuretics” [*J Am Coll Cardiol* 2001;37: 1775-80].

No Long-Term Benefits of Extended Oral Anticoagulation in Idiopathic DVT

The optimal duration of treatment with warfarin after deep vein thrombosis (DVT) reflects a balance between the risk of recurrence when treatment is stopped and the risk of bleeding as a result of continued anticoagulation. The results of two recent studies indicate that longer anticoagulant therapy should be considered for patients with idiopathic thrombosis. However, whether the advantage observed in patients for whom therapy is continued for an extended period is maintained after that therapy is discontinued remains unclear. Accordingly, researchers conducted a multicenter, randomized trial to evaluate the long-term clinical benefits of extending to one year the recommended three-month course of warfarin therapy after a first episode of idiopathic proximal DVT. The primary outcome was the confirmed recurrence of venous thromboembolism during at least two years of follow-up. Continuing therapy was asso-

ciated with a reduced incidence of recurrent thrombosis during therapy. During the initial nine months after randomization (after all patients received three months of treatment), one patient had a recurrence while receiving warfarin (0.7%), as compared with 11 of the patients assigned to discontinuation of warfarin (8.3%). The clinical benefits of extending the duration of anticoagulant therapy, however, were not maintained. Of the patients assigned to extended warfarin therapy, 15.7% had a recurrence after an average follow-up of 37.8 months; of the patients assigned to the discontinuation of warfarin after three months, 15.8% had a recurrence after an average follow-up of 37.2 months [*N Engl J Med* 2001;345:165-69]. It would seem that for patients to remain free of recurrent DVT they must receive anticoagulant therapy indefinitely, a discouraging prospect at this time.

BIOTECHNOLOGY

Gene Therapy Demonstrates Promise for Hemophilia Patients

Two investigational gene-therapy treatments for hemophilia have made progress in early studies. Hemophilia A and B are X-linked hereditary disorders caused by the absence or defect of clotting factors VIII and IX, respectively. Current treatment calls for replacing the missing clotting factor. Gene therapy is an attractive alternative.

Preliminary data from a two-year phase I study in patients with severe hemophilia A show that a nonviral somatic-cell gene-therapy system was safe and well tolerated. In the study, dermal fibroblasts obtained from each patient by skin biopsy were grown in culture and transfected with a plasmid containing sequences of the gene that encodes factor VIII. Cells that produced factor VIII were selected, cloned, and propagated *in vitro*. The cloned cells were then harvested

and administered into the patients' peritoneal cavities. The investigators found detectable levels of factor VIII in four of six patients who received such cells; two patients had levels greater than 1% of normal, the threshold generally thought to be therapeutic. However, levels decreased and were undetectable by ten months after administration [*N Engl J Med* 2001;344:1735-42].

At a recent American Society of Gene Therapy meeting, researchers reported that a proprietary adeno-associated virus gene-therapy product delivers the factor IX gene via infusion into a portal artery. The procedure was safe and well tolerated in eight patients with hemophilia B. The investigators have received FDA approval to conduct additional studies [*Scrip*, 22 June 2001].

CONTROVERSIES AND DILEMMAS

More Concerns Over Antimicrobial-Resistant Streptococcus and Staphylococcus

Rates of antimicrobial resistance in the U.S. among *Streptococcus pneumoniae* isolates continue to increase at an alarming rate. Researchers at the University of Iowa who have undertaken three national surveillance projects have provided the sobering evidence. Each survey tracked the scope and magnitude of antibiotic resistance in *S. pneumoniae*.

In the first survey, conducted during 1994 to 1995, 23.6% of *S. pneumoniae* isolates collected were resistant to penicillin and 9.1% were resistant to multiple antimicrobials. In the second surveillance, conducted during 1997 to 1998, rates of penicillin resistance had increased to 29.5% and the rate of multiresistant *S. pneumoniae* increased to 16.0%. By 1999 to 2000, when the third survey was carried out, *S. pneumoniae* resistance to penicillin exceeded 34%; 22.4% of *S. pneumoniae* isolates were resistant to at least three different classes of antimicrobials [*Antimicrob Agents Chemotherap* 2001;45:1771-1729]. The principal investigator told *Reuters Health* [5 July 2001], "These results show unequivocally

that this problem continues to grow and shows no sign of abating any time soon."

In another frustrating development, investigators in Boston reported the first case of *Staphylococcus aureus* resistance to the newly introduced, novel antimicrobial linezolid (Zyvox) in an 85-year-old man undergoing peritoneal dialysis [*Lancet* 2001; 358:207-08]. Linezolid has been consistently active against multiresistant gram-positive pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). *In vitro*, staphylococci and enterococci resistant to linezolid can be selected only with difficulty. Resistance to linezolid has emerged rarely during treatment of complicated VRE infections, but, up until now, linezolid resistance has not been reported in isolates of staphylococci. A dire situation lies ahead if this first report is a harbinger of the emergence of resistance to linezolid, because MRSA is a virulent and major pathogen [*Reuters Health*, 20 July 2001].