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Treatment of Severe Sepsis—An Advance At Last!

ABSTRACT & COMMENTARY

Synopsis: *Therapy with drotrecogin alfa activated (DRA—Zovant), a recombinant human activated protein C, was associated with significantly improved survival in patients with severe sepsis.*

Source: Bernard GR, et al. *N Engl J Med.* 2001;344:699-709.

Bernard and colleagues, in a double-blind, placebo-controlled trial, randomized 1690 patients with severe sepsis at 164 centers in 11 countries to receive adjunctive therapy with either placebo or drotrecogin alfa activated (DRA—Zovant™), a recombinant human activated protein C (aPC). Patients were eligible for randomization if they had known or suspected infection with 3 or more signs of systemic inflammation and sepsis-induced organ dysfunction of no more than 24 hours duration; treatment was initiated within 24 hours of having met inclusion criteria. DRA was given intravenously as a continuous infusion at a dose of 24 mg/kg/h for 96 hours. The infusion was temporarily interrupted 1 hour before percutaneous procedures or major surgery and was resumed, respectively, 1 and 12 hours later. Other therapies, including fluids, antibiotics, vasopressors, etc., were not specified by protocol. The primary efficacy end point was death from any cause by 28 days after the start of the infusion.

Protein C deficiency was detected in 87.6%, plasma d-dimer was present in 99.7%, and IL-6 in 98.5%. At 28 days, the all-cause mortality was 30.8% in the placebo group and 24.7% in the DRA recipients (P = .005). The reduction in relative risk of death was 19.4% (95% CI, 6.6-30.5%). Plasma d-dimer and IL-6 levels were significantly lower through day 7 in DRA recipients.

The overall incidence of serious adverse events was similar in the 2 groups, although serious bleeding occurred in 3.5% of DRA and only 2.0% of placebo recipients (P = .06). Fatal intracranial hemorrhage occurred in 2 DRA recipients during infusion and in 1 placebo recipient 6 days after the end of infusion. Neutralizing antibody against aPC was not detected.

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INSIDE

COMMENT BY STAN DERESINSKI, MD, FACP

This trial, the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis study (PROWESS) was terminated on June 28, 2000, prior to completion of the total planned enrollment at the time of a scheduled interim analysis when it became apparent that statistical significance had been reached. Given the repeated failure of similar trials in the treatment of severe sepsis, even some of the investigators were probably surprised to find something that worked.

Severe sepsis is associated with a procoagulant, as well as a generalized inflammatory response.[1,2] The procoagulant state in sepsis may result in the depletion of 1 or more of the 3 primary endogenous inhibitors of coagulation: aPC, antithrombin III, and tissue factor pathway inhibitor. The activation of protein C, which normally occurs in the microcirculation following the binding of thrombin to the endothelial receptor thrombomodulin, is a critical defense mechanism against excess fibrin formation.[3]

Sepsis may cause impairment of the conversion of protein C to the activated state as a result of decreased production of thrombomodulin in response to proinflammatory cytokines. As a consequence, the majority of septic patients have reduced protein C levels and there is an association between increased mortality and the extent of protein C depletion.[4] In patients with meningococcemia, failure of this system is associated with the development of purpura fulminans. In fact, the administration of a protein C concentrate was associated with improved survival, relative to matched historical controls, in patients with severe meningococcemia.[5]

Restoration of balance in the coagulation system is, however, probably not the only reason for the efficacy of DRA: aPC also inhibits monocyte production of IL-1b and TNF-a in response to exposure to lipopolysaccharide.[6] It also inhibits LPS-induced nuclear translocation of NFkB, inhibits neutrophil activation, downregulates the expression of several endothelial cell adhesion molecules, including ICAM-1, E-selectin, and VCAM-1.[7]

Bernard et al have demonstrated the efficacy of aPC infusion in patients with severe sepsis. Now the challenge will be to learn how to optimally use this advance in therapy. ❖

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Dapsone for Children

ABSTRACT & COMMENTARY

Synopsis: *The bioequivalence of a proprietary liquid dapsone preparation and commercially available dapsone tablets makes dapsone available to children and others who are unable to ingest tablets.*

Source: Mirochnick M, et al. Bioequivalence of a propylene glycol-based liquid dapsone preparation and dapsone tablets. *Am J Health Syst Pharm*. 2000;57(19):1775-1777.

In a bioequivalence study, 12 adult volunteers received dapsone doses (either in liquid or tablet form) with 8 ounces of water 1-2 hours after breakfast.

Each volunteer initially received a 100-mg dose of a propylene glycol-based liquid preparation of dapsone with blood sampling before each dose and up to 96 hours after administration of each dose. This was repeated in each individual 2 weeks later with a 100-mg dapsone tablet.

The area under the concentration-vs.-time curve and maximum serum concentration for the 2 formulations met the specifications for bioequivalence. While the time to maximum serum concentration tended to be lower for the liquid preparation, it was not significant. Both preparations could be used interchangeably.

COMMENT BY THOMAS G. SCHLEIS, MS, RPh

Dapsone is a versatile agent that has been used in the areas of infectious diseases, immunology, and dermatology (*see Table*). Its use as a prophylactic agent for *Pneumocystis carinii* pneumonia (PCP), either alone or with pyrimethamine, or as treatment of PCP in combination with trimethoprim is well documented.[1-3] Advances in the treatment of pediatric HIV and oncology patients have resulted in a higher population of children at risk for PCP, and a pediatric formulation of dapsone would be desirable for those patients that cannot tolerate trimethoprim-sulfamethoxazole, which is a first-line agent for PCP prophylaxis. Previous liquid formulations of dapsone either demonstrated poor bioavailability or did not have adequate stability information available.[4,5]

This new preparation, which is available for compassionate use in patients who cannot tolerate trimethoprim-sulfamethoxazole, is an advance in treating the pediatric population. Once FDA approved and released, it will also be useful in administering to those patients who are not able to swallow tablets. ❖

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Recent Outbreak of Oral Poliovirus-1 Vaccine-Derived Viral Infection in Haiti and the Dominican Republic

SPECIAL FEATURE

Synopsis: *The recent occurrence of an outbreak of poliovirus infection due to a mutant strain of vaccine-derived OPV-1 in the Dominican Republic and Haiti, which has left at least 6 children paralyzed, should provoke reconsideration of current OPV vaccine programs in developing countries.*

Health care experts around the world have been stunned by the recent news of an outbreak of an infection with an unusual strain of mutant Sabin-derived oral poliovirus-1 (OPV-1) in the Dominican Republic and Haiti. Although reports first began surfacing in December following the recognition of the unusual mutant OPV-1 strain by the PAHO Poliovirus Laboratory in the Caribbean Epidemiology Center in October, a finding was subsequently confirmed by the Poliovirus Laboratory at the Centers for Disease Control and Prevention, although the first case probably occurred in July

Table

Disorders Treated with Dapsone

Infectious Diseases	Immunology	Dermatology
Leprosy	Relapsing polychondritis	Actinomycotic mycetoma
PCP prophylaxis and treatment	Relapsin systemic lupus erythematosus	Dermatitis herpetiformis
Malaria prophylaxis		Pemphigoid
		Subcorneal pustular dermatosis
		Granuloma annulare
		Pyoderma gangrenosum

2000.[1] In all, 6 cases of vaccine-derived poliovirus type-1 have been identified in the Dominican Republic and 1 case in Haiti (which share the mountainous Island of Hispaniola). All of the cases occurred in individuals who were previously either unvaccinated or incompletely vaccinated. No further cases have been reported, although additional cases of acute flacid paralysis (AFP) in both countries are being investigated.

The virus is unusual because, although it is derived from OPV-1 vaccine virus, it shares only 97% genetic similarity to the parent strain, whereas most oral vaccine-derived viruses share more than 99.5% homology. Based on these results, the virus may have been replicating for up to 2 years either in an immunodeficient host or within the community. Studies demonstrate reversion of the virus with enhanced neurovirulence and transmissibility.

These cases serve as a grim reminder of the potential risks posed by inadequate OPV vaccine programs resulting in low rates of vaccination in some countries. Haiti, which has fairly low vaccine coverage (varying from 20-32% in 1993-1998), has been considered polio-free since 1990. The last known case of wild polio infection in Haiti occurred in 1989. The Dominican Republic, which has better vaccine coverage (73-82%), has been polio-free since 1985, although 43 cases of acute flacid paralysis were reported in 1997 and 1998. Two cases of AFP were reported in 1998 in Haiti.

Health care experts descended on the two countries before Christmas to initiate a mass 3-day vaccination program.

COMMENT BY CAROL A. KEMPER, MD, FACP

It is well known that the administration of live attenuated virus in OPV vaccine results in the excretion of virus in stool. Although potentially advantageous to individuals in countries with high rates of vaccination, where household or environmental contact with excreted virus can provide an additional source of "booster" vaccination, this becomes a potential liability to countries with poor vaccine rates. This liability is further increased by the possible reversion of attenuated virus to a more neurovirulent form during replication in the gut. A longer period of circulation, either within a single individual or within the community, can increase the risk of further genetic mutation and reversion to wild-type virus. Circulation of vaccine virus in the community is known to occur for about 2-3 months following a mass vaccination program. This may be prolonged by continuous vaccine programs. Furthermore, excretion of virus can be prolonged in certain immunodeficient hosts; for example, 1 immunoincompetent individual has reportedly excreted vaccine-derived virus for 16 years.[2]

The Western Hemisphere is believed by most experts to have been free of wild-type polio virus since 1991 when the last case was reported in Peru (about 7100 cases were reported worldwide last year, mostly in Africa and Asia). New infections in the Western Hemisphere are, therefore, invariably due to transmission of vaccine-derived virus from a recent vaccinee to an inadequately vaccinated or immunodeficient host. These cases are believed to be separate vaccine-related events. There is growing evidence, however, that some of these poliovirus infections may be due to actual "outbreaks" with person-to-person transmission of a variant strain of vaccine-derived virus, as occurred in the Dominican Republic and Haiti.

Based on nucleic acid sequencing studies, a highly divergent strain of vaccine-derived OPV-2 virus may have been circulating in 1 or more people in Israel and Palestine for approximately 6 years during the late 1990s.[3] The unusual mutant virus was first isolated from sewage during routine environmental screening in Israel and Palestine in 1998. One of 25 environmental OPV strains identified in sewage was found to be highly divergent from OPV-2 vaccine virus; 4 additional isolates were recovered in 1999. All 5 isolates had reverted at neurovirulence attentuation sites, and 3 were found to be highly virulent for transgenic (PVR-Tg21) mice expressing poliovirus receptor. Sequence analysis found only 90% homology with OPV-2 vaccine-derived virus.

Circulation of OPV-2 vaccine-derived virus is now known to have occurred between 1982-1993 in Egypt, resulting in 32 cases of polio in that country.[4] The cases were originally believed to be separate vaccine-related events, but further analysis conducted in 1999 found that all of the viruses were related based on nucleic acid sequencing. Similar analyses suggest that a second outbreak of OPV-derived type-2 infection probably occurred in China in the 1990s.

Such outbreaks are more likely to occur in countries with low vaccine rates. Mass vaccination campaigns, which limit the period of community exposure, may be more optimal in such countries than continuous vaccine programs, although mass vaccination programs require greater effort and expense. Vaccination with IPV has been proposed as an alternative, but the cost is much greater. In addition, IPV may not provide as effective mucosal protection from oral-fecal transmission of virus. Some experts have, therefore, proposed a combined OPV/IPV program, which could enhance safety, improve overall immunogenicity, and limit costs. A large-scale Omani study of 1025 infants aged 9 months

assessed the response to a single supplemental dose of 1 of 4 different poliovirus vaccines.[5] All of the children had received 5 doses of OPV and were randomized to receive IPV, trivalent OPV, either manufactured in the United States or Europe, or monovalent type 3 OPV. Overall, there was a significantly greater antibody response to type 3 OPV in patients receiving the single booster dose of IPV.

The current outbreak in Haiti and the Dominican Republic probably poses no significant threat to travelers to these countries. A booster dose is generally recommended for any adult traveler to an endemic country (1 lifetime booster with IPV is probably sufficient). Unvaccinated adults should receive the whole series of 3 doses of IPV, and children (in the United States) currently receive 4 doses (at ages 2 and 4 months, 6-18 months, and 4-6 years).

The recent outbreak in the Dominican Republic and Haiti will no doubt stir debate among world health care experts regarding the optimal vaccine program for developing countries. Certainly the continued administration of OPV in areas where wild-type poliovirus has been eradicated poses significant questions, especially in countries with meager resources and poorer rates of vaccination.[2] Furthermore, OPV-vaccine programs do not necessarily prevent the circulation of wild-type or variant vaccine-derived virus within a population, as virus can be transmitted from a healthy vaccinated child, who is protected, to an unvaccinated one.

Looming on the horizon, as well, is the possibility of a polio-free earth. Current vaccine programs should be reevaluated in light of these recent outbreaks. Health care experts are going to have to start addressing the challenging questions of how to provide adequate and safe vaccine programs in a world with fewer and fewer cases of wild-type polio, and when these programs may be safely discontinued altogether. ❖

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More on Malaria Prophylaxis with Malarone

ABSTRACT & COMMENTARY

Synopsis: *Malaria prophylaxis with Malarone (atovaquone plus proguanil) was effective and well tolerated in nonimmune travelers.*

Source: Hogh B, et al. Atovaquone-proguanil versus chloroquine-proguanil for malaria prophylaxis in non-immune travellers: A randomised, double-blind study. *Lancet*. 2000;356: 1888-1894.

Hogh and colleagues, in a double-blind, placebo-controlled trial, randomised 1083 individuals travelling to a malaria-endemic area to receive prophylaxis with either daily atovaquone-proguanil (Malarone™; 250 mg atovaquone plus 100 mg proguanil hydrochloride) or weekly chloroquine phosphate (500 mg) plus daily proguanil hydrochloride (Paludrine™, 100 mg), each together with appropriate placebos. Malarone was administered beginning 1-2 days prior to travel, during travel, and for 7 days after. Chloroquine was started 7 days before travel, while proguanil was started 1-2 days before; both were continued for 28 days after completion of travel.

Patients 14 years of age and older weighing at least 50 kg were enrolled at 21 travel clinics in northern Europe, the United Kingdom, Canada, and South Africa. The study was powered only to detect equivalence; 1008 completed the trial.

Compliance during pretravel, travel, and post-travel periods was, respectively, 95%, 96%, and 93% for Malarone; 94%, 91%, and 80% for chloroquine; and 90%, 94%, and 87% for proguanil. Thus, compliance (at least 80% of prescribed doses) during the post-travel period was significantly greater for Malarone than for either chloroquine ($P = .001$) or proguanil ($P = .003$).

Adverse events (excluding those occurring while individuals were receiving only placebo) were reported in 58% of Malarone recipients and in 64% of those given chloroquine-proguanil. Treatment-related adverse events, as determined by site investigators, occurred, respectively, in 22% and 28% ($P = .024$), with the difference mostly the result of more frequent gastrointestinal side effects among patients given chloroquine-proguanil. Moderate-to-severe adverse events were also more frequent in the latter group—11% vs. 7% in Malarone recipients ($P = .05$).

A diagnosis of *Plasmodium falciparum* malaria was made in 3 chloroquine-proguanil recipients; 1 probable

case of *P ovale* infection occurred 28 days after completion of Malarone prophylaxis. Each of the 3 *P falciparum* isolates were found to have the *K76T* mutation in the pfcrt gene associated with chloroquine resistance, the *S108N* mutation in dhfr associated with pyrimethamine resistance as well as increased resistance to cycloguanil, and *N51I* and *C59R* mutations also associated with pyrimethamine resistance (high level). One isolate also contained a mutation *N86Y*) in pfmdr1.

Seven Malarone recipients and 8 chloroquine-proguanil recipients (including only 1 of the 3 with clinical malaria) developed antibody to *P falciparum* circumsporozoite antigens. Considering the number of individuals who developed antibody and/or clinical malaria as having been at high risk for malaria and using this number as the denominator, the minimal efficacy of Malarone was calculated to be 100% (95% confidence interval [CI], 59-100%) while that of chloroquine-proguanil was 70% (95% CI, 35-93%).

COMMENT BY STAN DERESINSKI, MD, FACP

Atovaquone is a hydroxynapthoquinone that inhibits electron transport and alters mitochondrial membrane potential; proguanil enhances the ability of atovaquone to cause a collapse of that potential.[1] Thus, the dominant activity of proguanil in this combination is as a biguanide, rather than via its DHFR-inhibiting metabolite, cycloguanil. *P falciparum* resistant to cycloguanil by virtue of mutations in *DHFR* do not exhibit reduced susceptibility to Malarone.[2]

While either component of Malarone given alone is poorly effective in the treatment of *P falciparum* malaria, the combination, which is synergistic in vitro, has potent blood schizonticidal activity and has been associated with an overall efficacy rate in excess of 98%. Therapy with Malarone has been demonstrated, in comparative trials, to be superior to mefloquine in Thailand, to amodiaquine in Gabon, and to chloroquine plus pyrimethamine/sufladoxine in the Philippines. The combination has been effective in all geographic areas in which it has been subject to examination and has been effective in generally nonimmune, as well as semi-immune, populations and has also been effective in the treatment of multiresistant malaria.[3-5] Malarone is also effective in the treatment of *P vivax* infection, when followed by primaquine administration.[6]

In addition, studies in semi-immune populations have demonstrated that Malarone administration is effective as antimalaria prophylaxis. For instance, adults in an area of Zambia highly endemic for *P falciparum* malaria were initially treated with a curative therapeutic regimen of Malarone to eradicate existing infection due to this protozoan.[7] They were then randomized to receive either placebo or Malarone daily for at least 10 weeks. Forty-one (37%) of 111 placebo recipients, but only 2 (2%) of 102 A/P recipients developed parasitemia ($P < .001$). While adverse effects overall were more commonly reported by placebo recipients, headache occurred approximately twice as frequently (9% vs 4%) in the A/P recipients. The efficacy rate of A/P prophylaxis in a semi-immune population in Kenya was 100% compared to a rate of only 48% ($P < .001$) for placebo recipients.[8] Semi-immune African children living in a hyperendemic area were randomized, after initial curative therapy with A/P, to receive either placebo or Malarone for prophylaxis. Twenty-five (18%) of 140 children in the placebo group and none of the 125 children in the A/P group had detectable parasitemia during chemoprophylaxis ($P < .001$).[9]

Prophylactic efficacy in semi-immune populations does not, however, predict similar efficacy in non-immunes, such as travelers from nonendemic regions. Until now, there previously had been only very limited published data indicating efficacy in non-immune populations. This trial by Hogh et al is, therefore, the first large-scale randomized trial to fully demonstrate its efficacy and safety in such a population.[10] The case of *P ovale* infection in a Malarone recipient is, however, indicative that this product, like mefloquine and chloroquine, lacks activity against hypnozoites. As a consequence, follow-up primaquine administration should be considered for travellers who have had unusually prolonged and/or intense potential exposure to *P vivax* or *P ovale*. ❖

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CME Questions

19. Which one of the following is correct?

a. Activated protein C has anti-inflammatory properties as a result, at least in part, of inhibition of the monocyte production of proinflammatory cytokines.
b. Protein C levels are elevated in sepsis, accounting for the procoagulant state seen in this circumstance.
c. DRA is a recombinant human antithrombin III molecule.
d. The incidence of intracranial hemorrhage in patients receiving recombinant human protein C in the PROWESS trial was more than 20%.

20. Which one of the following is correct?

a. Dapsone in a liquid preparation is FDA approved and commercially available.
b. Dapsone is available for compassionate use in certain patients.
c. All liquid dapsone preparations are stable and bioequivalent.
d. Dapsone is not safe for use in the pediatric population.

21. Which one of the following is *false*?

a. Polio vaccine virus circulates in a community for 1 week following mass vaccination.
b. A healthy vaccinated child can serve as a vector for wild-type poliovirus infection.
c. Immunodeficient hosts can have prolonged excretion of vaccine virus.

22. Malarone:

a. is a combination of dapsone and pyrimethamine.
b. is effective prophylaxis against falciparum malaria for semi-immune, but not nonimmune, travelers.
c. eliminates plasmodial hypnozoites from the liver.
d. prophylaxis given daily, beginning 1-2 days prior to travel and continuing for 7 days after leaving the endemic area.

In Future Issues:

Gut Feelings About Salmonellosis

UPDATES

By Carol A. Kemper, MD, FACP

Fecal Carriage of VRE

Source: Donskey CJ, et al. Effect of antibiotic therapy on the density of vancomycin-resistant enterococci in the stool of colonized patients. *N Engl J Med.* 2000;343:1925-1932.

Donskey and associates examined the effect of various antibiotic regimens on the fecal carriage of vancomycin-resistant enterococcus (VRE) in 55 patients with pre-existing colonization. The density of VRE in stools was significantly increased within 1 week of administration of agents with antianaerobic activity, including such agents as amoxacillin-clavulanate, ampicillin-sulbactam, piperacillin-tazobactam, imipenem-cilastin, cefoxitin, ceftriaxone, clindamycin, metronidazole, and vancomycin. High levels of fecal colonization with VRE were maintained in these patients as long as the antibiotics were continued (mean, 7.8 logs of VRE/g of stool), irrespective of the mode of administration (oral vs parenteral).

Once the antibiotics were discontinued, the density of VRE in stool began to fall in all subjects within 4 weeks. But it took an average of 17.4 weeks (range, 6-20) after the discontinuation of antibiotics before VRE were no longer detectable in stools. In addition, colonization with VRE decreased among 10 patients who received agents with minimal antianaerobic activity, including dicloxacillin, cephalexin, levofloxacin, ciprofloxacin, and trimethoprim-sulfamethoxazole.

Environmental samples collected from the rooms of patients with fecal incontinence were significantly more likely to be positive for VRE if the patient had high levels of VRE in stool. Sets of environmental samples had at least 1 positive specimen in 83% of patients with high levels of fecal carriage (≥ 4.0 logs/g) vs. only 11% of those with lower levels.

The good news from this report is that fecal carriage of VRE does eventually go away. The bad news is that these patients may present a transmission risk for up to 5 months—and that's if they don't receive any more "bad" antibiotics with anaerobic activity. For this reason, patients admitted to the hospital with a history of fecal colonization with VRE should be isolated with contact precautions, at least until they are cleared. Clinicians should presume that the immediate surroundings of these patients, especially those who are incontinent, are contaminated. The use of antibiotics with anaerobic activity (not just vancomycin!) should be limited and of the shortest duration as possible in patients with known fecal carriage of VRE. ■

Nonmeningeal Cocci: Is One Azole Better?

Source: Galgiani JN, et al. Comparison of oral fluconazole and itraconazole for progressive, nonmeningeal coccidioidomycosis. A randomized, double-blind trial. Mycoses Study Group. *Ann Intern Med.* 2000;133:676-686.

Galgiani and associates conducted a large-scale, randomized, double-blind, placebo-controlled trial of fluconazole vs. itraconazole in the treatment of nonmeningeal coccidioidomycosis. A total of 191 patients with chronic pulmonary (n = 70), soft tissue (n = 71), or skeletal (n = 50) cocci were randomized to receive either fluconazole 400 mg daily or itraconazole 200 mg twice daily for 12 months. Patients who had received more than 4 mg/kg of amphotericin B or more than 8 grams of an azole were excluded from study. HIV-infected patients were eligible if their CD4 count at the time of enrollment was greater than 250/mm^3 (7 patients with HIV/AIDS were enrolled). Eighteen patients with both skeletal and soft tissue infection (5 of whom also had pulmonary involvement) were assigned to the skeletal group.

Both agents were similarly effective at 8 and 12 months of therapy, although there was a trend toward slightly greater efficacy with itraconazole. At 12 months, 57% of patients responded to fluconazole, whereas 72% responded to itraconazole (P = .05). This was largely the result of the poorer response of patients with skeletal infection to fluconazole compared with itraconazole (37% vs 69%; P = .03). In contrast, there was no apparent difference in the response between the two treatment groups for patients with soft tissue or pulmonary infection. In multivariate analysis, patients with soft tissue infection, a lack of dermal erythema overlying skeletal lesions, and no prior therapy for cocci infection were associated with higher rates of response.

A longer duration of therapy was associated with a greater likelihood of response, although a few patients responded to only 4 months of therapy. Serum azole concentrations, which were assessed after the close of study, were not associated with response.

Both drugs were well tolerated. One possible difference between the 2 therapies was unanticipated: alopecia and dry lips were reported in 15% and 11% of patients receiving fluconazole, compared with only 4% and 0% of patients receiving itraconazole. Earlier reports have suggested that cheilitis and xerosis may be related to the administration of fluconazole. These data suggest that about 63-79% of patients with nonmeningeal cocci may respond to either itraconazole or fluconazole, although itraconazole may be a better choice for the treatment of skeletal disease due to coccidioidomycosis. ■