Early Repeat *C. difficile* Testing Rarely Useful

BY ROBERT FINN

SAN FRANCISCO — Repeating a negative stool cytotoxicity assay for *Clostridium difficile* rarely returns a different result if done within the first 3 days, according to a retrospective study involving more than 10,000 patients.

This is true even during a *C. difficile* epidemic, Dr. Joe Dylewski said in an interview at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy. Dr. Dylewski of St. Mary's Hospital, Montreal, presented his results during a poster session.

The study involved 10,882 patients and 16,665 stool specimens submitted for toxin testing between January 2001 and March 2008. Dr. Dylewski divided the samples into two time periods to reflect an epidemic of *C. difficile*–associated diarrhea that began in April 2002.

Overall, the positivity rate of the cytotoxicity assay was 27% during the epidemic and 15% during the nonepidemic period. Among samples that initially tested negative, fewer than 1% changed to positive if tests were repeated within the first day. Repeat testing of negative results yielded positive results in 6% during day 2 and in 3% during day 3.

After day 3, the percentage of positive results after initial negative findings rose to 7%, 9%, 12%, and 13% on days 4, 5, 6, and 7, respectively.

"Repeat testing during the first 3 days is probably not beneficial even during an epidemic," Dr. Dylewski said in the interview at the meeting, sponsored by the American Society for Microbiology. He was particularly critical of repeat testing on the same day of the initial test, which occurred in 698 cases. It takes about 2 days to return a negative result from the *C. difficile* cytotoxicity assay, so most of these repeat stool samples were sent to the lab before results from the initial sample could have been received.

He attributed these decisions to an erroneous belief among physicians that a second test always is necessary. But even that doesn't explain why he sometimes received three samples from the same patient within that first day. "The order is '*C. diff.* times three,'" he said. "So [the patient has] three bowel movements on the same day, and they send all three [samples] down on the same day."

Of the 698 cases of same-day repeat testing, the initial test was positive in 225 cases and negative in 473. On repeat testing, no results switched from positive to negative, and only two (0.4%) switched from negative to positive.

"It makes sense to retest after 3 days if the patient is still symptomatic and your index of suspicion is high and you haven't started empiric therapy," he said.

If, after 3 days, the result is still negative but the index of suspicion remains high, there are two ways to proceed. One is to start empiric therapy, and the other is to refer the patient to colonoscopy.

"It's a little bit different when you're in an epidemic situation … because patients get really sick really quickly," Dr. Dylewski said. During an epidemic, patients with an initial negative result must be followed closely if the index of suspicion is high. "You still need to follow them, potentially treat empirically, or repeat the test after a certain number of days, because you can be wrong, but it's not often."

But even during an epidemic, he advised, "it should not be routine to say, 'I'm going to do multiple specimens in order to detect it.' "

Dr. Dylewski reported no conflicts of interest related to his study. ■

Phase III Data Show Safety of Fidaxomicin for C. difficile

BY DOUG BRUNK

SAN FRANCISCO — Fidaxomicin appears to be just as safe as vancomycin for the treatment of *Clostridium difficile* infection, results from a multicenter randomized trial showed.

The finding comes from the first phase III study of fidaxomicin (Dificid), a first-in-class macrocyclic antibiotic for the treatment of *C. difficile*. A second phase III trial that is underway is expected to be completed by the end of the year, Pamela Sears, Ph.D., said in an interview during a poster session at the annual meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy.

Any treatment-emergent event occurred in 62% of patients on fidaxomicin and 60% of those on vancomycin.

DR. SEARS

The drug's safety profile is "very similar to oral vancomycin, which is a very safe drug," said Dr. Sears, executive director of biology and preclinical trials at Optimer Pharmaceuticals Inc., San Diego, which developed the drug.

Dr. Sears and her associates said fidaxomicin has "potent bactericidal activity against *C. difficile* infection with a prolonged postantibiotic effect but minimal activity against much of the other commensal gut flora. The narrow spectrum of activity allows fidaxomicin to kill *C. difficile* while sparing much of the normal gut flora. Importantly, fidaxomicin is also minimally absorbed from the gastrointestinal tract."

In a multicenter trial supported by Optimer, the researchers compared two regimens for *C. difficile*: fidaxomicin 200 mg twice a day (300 patients) and vancomycin 125 mg four times a day (323 patients). Both agents were taken for 10 days. The mean age of the patients was 62 years. At baseline and after 10 days of therapy, the researchers collected plasma and urine samples, obtained 12-lead electrocardiograms, and conducted physical exams.

Any treatment-emergent event occurred in 62% of patients in the fidaxomicin group and in 60% of patients in the vancomycin group. Gastrointestinal disorders were most common (25% vs. 22%), followed by infections (21% vs. 20%, primarily urinary tract infections and pneumonia) and general disorders and administration site conditions (15% vs. 16%, primarily fever, chills, edema, and fatigue).

The incidence of serious adverse events also was similar between groups: 25% in the fidaxomicin group, compared with 24% among the vancomycin group. The most common serious adverse events were infections, including *C. difficile,* pneumonia, sepsis, or bacteremia (7% vs. 9%, respectively), and GI disorders (4% vs. 3%). Fewer than 3% of patients in both groups developed abnormal liver, blood, and renal tests while on therapy, and mortality was similar in both groups (5% vs. 7%). No death was considered to be related to the study drug.

A limitation of the study was that it did not compare fidaxomicin with metronidazole. For *C. difficile*, vancomycin "appears to be the marketed compound that performs the best, but most people use metronidazole. We may explore that comparison in phase IV," she said.

Dr. Sears expects Optimer to file for new drug approval with the Food and Drug Administration by early 2011. ■

Fidaxomicin Reduced *C. difficile* Recurrence Rate by 45%

BY DOUG BRUNK

SAN FRANCISCO — Patients with *Clostridium difficile* infection who were treated with the novel macrocylic antibiotic fidaxomicin had a 45% lower rate of recurrence, compared with those who received vancomycin.

"It's encouraging because fidaxomicin is an easier drug to take compared with the current therapies," Dr. Yoav Golan said in an interview during a poster session at the annual meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy. "It's only twice a day dosing versus three and four times a day for metronidazole and vancomycin. Also, it seems to have a much smaller impact on emergence of resistance among gut pathogens."

The analysis involved 432 patients in a multicenter, randomized trial to compare fidaxomicin, 200 mg every 12 hours, with vancomycin, 125 mg every 6 hours for 10 days, in patients with *C. difficile*. The mean age of patients was 62 years.

Fidaxomicin (Dificid), a minimally absorbed, narrow spectrum antibiotic with limited impact on gut flora, was developed by Optimer Pharmaceuticals, which sponsored the trial. Dr. Golan disclosed that his relationship with Optimer is limited to functioning as an investigator in the fidaxomicin clinical trials. Pamela Sears, Ph.D., executive director of biology and preclinical trials at Optimer, expects the company to file for new drug approval with the Food and Drug Administration by early 2011.

'It's encouraging because fidaxomicin is an easier drug to take compared with the current therapies.'

DR. GOLAN

Overall, recurrence of diarrhea and positive toxin within 4 weeks after the end of therapy occurred in 19% of patients. The rate was significantly lower among the 211 patients in the fidaxomicin group (13%) than among the 221 patients in the vancomycin group (24%). This represented a relative reduction of 45% with fidaxomicin, compared with vancomycin.

Recurrence rates were highest in patients aged 75 years and older (31%) and in those aged 65-74 years (18%), and in those who were hospitalized (22% vs. 15% in outpatients).

Of the 81 patients with recurrent *C. difficile*, recurrence developed later in patients who took fidaxomicin. For example, 25% of patients in the fidaxomicin group had recurrence within 10 days after initial treatment completion vs. 57% of patients in the vancomycin group, while 36% of patients in the fidaxomicin group developed recurrence within 21-30 days after initial treatment vs. 15% of patients in the vancomycin group.

The recurrence rate was significantly lower for patients in the fidaxomicin group who had not received any *C. difficile* infection-active antibiotics 24 hours prior to study enrollment (11%, compared with a rate of 24% for their counterparts in the vancomycin group). This finding suggests the potential for a high clinical benefit for fidaxomicin when used as a first-line therapy, said Dr. Golan, assistant professor of medicine at Tufts Medical Center, Boston.

"The future for treating *C. diff.* is [to use] very narrow spectrum antibiotics, compared to the very broad spectrum antibiotics we've been using," he concluded. ■