Agents in Pipeline May Help Combat MRSA

BY ROBERT FINN

FROM THE ANNUAL MEETING OF THE INFECTIOUS DISEASES SOCIETY OF AMERICA

VANCOUVER, B.C. – New compounds in preclinical stages of testing may eventually help combat the surge in methicillin-resistant *Staphylococcus aureus* and other multidrug-resistant organisms, Dr. Ronald N. Jones said at the meeting.

Fusidic acid was discovered in the 1960s and used widely in Europe, Australia, and Canada. However because it was never released in the United States, domestic MRSA strains have built up little resistance to it, which makes it something of "an old drug in new clothing," said the chief executive officer of JMI Laboratories, a contract research organization in North Liberty, Iowa.

Dr. Jones and his colleagues tested the compound against 7,340 *S. aureus* isolates collected from 51 hospitals in every region of the country. Fusidic acid inhibited 99.6% of the isolates at a concentration of 1 mcg/mL or less. The compound also showed comparable activity against *S. aureus* strains in eight different resistance groups, including strains resistant to five or more other compounds including oxacillin, erythromycin, clindamycin, and the fluoroquinolones.

"This is pretty exciting, because it also has no cross-resistance with any other class of antibiotic," Dr. Jones said. "It could be used widely if we could deliver it in such a way that would prevent any emerging resistance from happening in what I call the naïve population of United States *Staph aureus*."

In addition, Dr. Jones said, "it's been conservatively stated that tens of millions of patients have been treated with fusidic acid over the period of the 4-plus decades. The drug is considered safe, and it's usually administered orally for the treatment of serious staphylococcal infections. It also has been applied in some countries topically."

A second agent, JNJ-Q2, is a broad-spectrum fluoroquinolone developed by Johnson & Johnson and Furiex Pharmaceuticals.

"One of the things that was noted very early on is that quinolone resistance, particularly among methicillin-resistant *staphylococci*, became quite common over a decade ago," Dr. Jones said. "New compounds have been tried for a number of years, [but] what's novel about this is it's 16 times more potent than the best of the existing marketed fluoroquinolones."

JNJ-Q2 is moving into phase II and phase III clinical trials. In preclinical studies, "We challenged it with the worst of the MRSA and the fluoroquinolone-resistant MRSA that we could find in our surveillance systems all around the planet. And this new compound came out quite well and covered essentially 90%-100% of the strains, depending upon the geography."

Compared with other fluoroquinolones, JNJ-Q2 was 16 times more potent than moxifloxacin, 64 times more potent than levofloxacin, and 128 times more potent than ciprofloxacin when tested against 511 *S. aureus* isolates.

A third agent, ceftaroline, is a broad-spectrum cephalosporin from Forest Laboratories. It is being tested in combination with NXL104, a beta-lactamase inhibitor being developed by Novexel.

Dr. Jones pointed out that ceftaroline alone is active against MRSA and multidrug-resistant pneumococci, but when combined with NXL104, it could also be used against the growing population of Enterobacteriaceae that produce derepressed AmpC beta-lactamase.

In studies, Dr. Jones and his colleagues determined that the combination, which they refer to as CXL104, inhibited 96% of ceftazidime-resistant strains of *Enterobacter, Citrobacter*, and *Serratia* at concentrations of 4 mcg/mL or lower.

"It's probably not going to be on the market until 2013 or 2014, [but will probably have labeling] against a large number of indications if everything goes well in clinical trials," Dr. Jones said. ■

VITALS

Major Finding: Fusidic acid inhibited 99.6% of 7,340 isolates of *Staphylococcus aureus*. Tested against 511 *S. aureus* isolates, JNJ-Q2 was 16 times more potent than moxifloxacin, 64 times more potent than levofloxacin, and 128 times more potent than ciprofloxacin. Ceftaroline is highly active against methicillin-resistant *S. aureus* itself, but when combined with NXL104 it is also at least as active as carbapenems and fourth-generation cephalosporins against Enterobacteriaceae producing derepressed AmpC beta-lactamase.

Data Source: Three separate in vitro studies.

Disclosures: The study on CXL104 was supported by Forest Laboratories, and the study on JNJ-Q2 was supported by Furiex Pharmaceuticals. JMI Laboratories conducts studies supported by Forest, Furiex, and other pharmaceutical companies.

M. genitalium Urethritis: Tx Guidelines Seen as Problematic

BY BRUCE JANCIN

EXPERT ANALYSIS FROM THE ANNUAL CONGRESS OF THE EUROPEAN ACADEMY OF DERMATOLOGY AND VENEREOLOGY

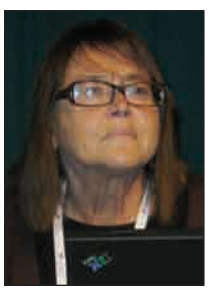
GOTHENBURG, SWEDEN – The treatment regimens currently recommended for nongonococcal urethritis and cervicitis by the Centers for Disease Control and Prevention have significant drawbacks for infections caused by *Mycoplasma genitalium*, according to Dr. Carin Anagrius.

Multiple studies – reported since the Centers for Disease Control and Prevention's guidelines were released in 2006 – indicate that *M. genitalium* is the second most common cause of nongonococcal urethritis (NGU), with a prevalence about half that of *Chlamydia trachomatis*, Dr. Anagrius said at the congress.

The first-line treatment options recommended by the CDC for NGU and presumptive treatment of cervicitis (doxycycline and azithromycin) both have problems, said Dr. Anagrius of Falu Hospital in Falun, Sweden. Doxycycline at 100 mg twice daily for 7 days has an unacceptable eradication rate for *M. genitalium,* and azithromycin in a single 1-g dose promotes emergence of macrolide-resistant organisms.

For this reason, she said, a revision of the guidelines is in order. The best solution would be to elevate azithromycin given over 5 days to preferred first-line therapy status. This regimen consists of 500 mg of azithromycin on day 1 followed by 250 mg on days 2-5. Studies found it has a 95% *M. genitalium* eradication rate and a substantially lower risk of inducing azithromycin resistance than with a single 1-g dose, she said.

An observational study by Dr. Anagrius and coworkers showed that eradication rates in symptomatic *M. genitalium* NGU in Scandinavia were about 85% for azithromycin 1 g and less than 30% for doxycycline (Sex. Transm. Infect. 2008;84:72-6). Similar rates have been confirmed by other investigators, she noted.



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DR. ANAGRIUS

For example, University of Mississippi investigators randomized men with known *M. genitalium* urethritis at a New Orleans STD clinic to doxycycline (100 mg twice a day for 7 days) or azithromycin (1 g as a single dose). The cure rates at the first follow-up visit were 87% with azithromycin, compared with 45% with doxycycline; 47% of those who were initially cured experienced clinical relapse in the next 2-6 weeks (Clin. Infect. Dis. 2009;48:1649-54).

The latest data from large population studies suggest *M. genitalium* causes about 15% of all NGU, noted Dr. Anagrius. Since there is as no commercially available diagnostic assay for *M. genitalium* infections, for every 1,000 patients with NGU who are treated with doxycycline, roughly 84 will return with persistent symptomatic *M. genitalium* urethritis. However, if the 1,000 patients were treated with single-dose azithromycin at 1 g, only 18 would return with persistent symptomatic *M. genitalium* urethritis.

Dr. Anagrius's studies indicate roughly 70% of these unsuccessfully treated patients would as a consequence of this unsuccessful treatment develop resistance to azithromycin in the form of a single base mutation in domain V of the 23S rRNA gene. Extended azithromycin as second-line therapy is unlikely to be successful in these patients. For them the only effective second-line antimicrobials are moxifloxacin and gatifloxacin. And there is as yet no third-line therapy.

If, on the other hand, 1,000 NGU patients were treated with 1.5 g of azithromycin over a 5-day period, only 6 would return because of persistent *M. genitalium* urethritis, she said. Thus, the number of individuals with azithromycin-resistant *M. genitalium* infections would be reduced by two-thirds, compared with the count if azithromycin 1 g were used.

The impact of using azithromycin 1 g as first-line therapy for NGU is illustrated by the markedly contrasting prevalence of macrolide-resistant *M. genitalium* in Sweden and neighboring Denmark. In Sweden, where using 1 g of azithromycin to treat NGU is uncommon, Dr. Anagrius and coworkers found the prevalence of azithromycin resistance to be only 1.6% among 181 patients presenting with new confirmed *M. genitalium*.

In Denmark, where azithromycin 1 g is widely prescribed as first-line therapy, Dr. Anagrius's Danish collaborators found a 40% prevalence of macrolide resistance in 415 patients presenting with new confirmed *M. genitalium* urethritis.

Dr. Anagrius noted that discussion about screening for *M. genitalium* infection in asymptomatic individuals in high-prevalence settings is starting to occur among venereologists and public health officials. The problem is the lack of a commercial polymerase chain reaction assay, which must be a high developmental priority. In the meantime, Dr. Anagrius urged physicians to "think *M. genitalium*" in patients with repeated urinary tract infections, abnormal bleeding, lower abdominal pain, persistent discharge, epididymitis, prostatitis, and what is often labeled treatment-resistant candidiasis.

And since *M. genitalium* NGU and cervicitis are sexually transmitted infections, optimal care includes treatment of the patient's partner or partners, she stressed.

Dr. Anagrius said she had no financial conflicts of interest. ■