HIV Entry Inhibitors Running Into Trouble in Trials; One Withdrawn

BY ROBERT FINN
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SAN FRANCISCO — Efforts to develop entry inhibitors, which constitute the first new class of anti-HIV drugs in years, have hit snags that could delay the entry of these novel agents into the pharmaceutical marketplace.

The debut of entry inhibitors has been eagerly awaited because of preclinical hints that they may be highly effective and have few side effects. But all three entry inhibitors in clinical trials have run into difficulty, and one has now been withdrawn from development, Dr. Steven W. Deeks said at a meeting on HIV management sponsored by the University of California, San Francisco.

GlaxoSmithKline has discontinued development of Aplaviroc, which appears to have caused at least five cases of liver toxicity. Schering-Plough's vicriviroc did not perform as well as efavirenz in a head-to-head comparison on treatment-naive patients, and is now being developed only for salvage therapy. And a patient taking Pfizer's maraviroc developed liver failure and required a transplant, although there are indications that other drugs the patient was taking might have been to blame.

Entry inhibitors don't attack the HIV virus directly, explained Dr. Deeks of UCSF. Instead they block a coreceptor on the surface of T cells that the virus requires for entry. Two such coreceptors are known, CCR5 and CXCR4, which are popularly called R5 and X4, respectively. All three current investigational drugs target the R5 receptor.

Some people are known to lack the R5 coreceptor because of spontaneous genetic mutations. They seem to harbor no ill effects from this, leading to speculation that agents that block that receptor are unlikely to have serious side effects. No humans are known to lack the X4 coreceptor, on the other hand, and deleting it in mice is lethal. For that reason, there has been a reluctance to develop drugs that bind to the X4 receptor.

R5 viruses are associated with slow disease progression and are common in early HIV disease. X4 viruses are associated with rapid disease progression and emerge in late disease. One of the worries in using R5 inhibitors is that they may encourage the earlier emergence of X4 viruses. Indeed, this has apparently happened in five or six patients in the clinical trials, Dr. Deeks said, and this is likely to be associated with more rapid disease progression.

The difficulties that aplaviroc, vicriviroc, and maraviroc have run into are not related to this, however. Aplaviroc has been associated with five cases of liver toxicity, all of which involved a threefold increase in ALT and a 1.5-fold increase in bilirubin. In all cases, this elevation in enzymes declined when the drug was removed, and in the one case in which the patient was rechallenged with aplaviroc, the liver toxicity recurred. Further development of aplaviroc has been stopped.

There was hope that entry inhibitors might be a good first-line therapy in treatment-naive patients. But a study comparing Combivir plus efavirenz with Combivir plus vicriviroc in patients who were treatment naive was terminated early because of the clear superiority of efavirenz. Vicriviroc is no longer being developed as a first-line therapy; its use will be only for salvage in patients who have failed earlier regimens.

The case of liver failure in a patient taking maraviroc originally caused concern that studies on this medication would have to be terminated as well. This was despite the fact that the drug has been used in hundreds of treatment-naive and salvage patients with no ill effects. But the patient, a 24-year-old woman, had also been receiving isoniazid and cotrimoxazole for HIV-associated infections. Her ALT levels increased more than fivefold during the 7-week screening period, and her AST increased as well.

On the fifth day of taking maraviroc plus Combivir the patient developed rash and fever, and maraviroc was discontinued. The next day her liver enzymes were significantly elevated (32 times normal). For some reason, despite the known potential for additional liver toxicity, she was given a high dose of acetaminophen (11 g IV) at this time. Her liver enzymes continued to worsen, and on day 16 she received a liver transplant.

"Most people think this Pfizer case is highly, highly unlikely to be related to maraviroc, and I agree," Dr. Deeks said. "There are a couple of reasons for the liver disease here, so all studies are going forward, at least for the Pfizer drug, for now."

Dr. Deeks disclosed relationships with several pharmaceutical companies, including being a recipient of research support from GlaxoSmithKline and working as a consultant for Pfizer. ■

MINDFUL PRACTICE

Decision Tools for Antibiotic Prescribing

BY JON O. EBBERT, M.D., AND ERIC G. TANGALOS, M.D.

The Problem

At a monthly staff meeting, one of your group members complained about the inappropriateness of antibiotic prescribing for presumed respiratory tract infections. She described the case of a patient with persistent cough who had received two courses of antibiotics from other practitioners in your collective. After stopping the patient's ACE inhibitor, the cough resolved. At the meeting, your group discussed the diverse approaches taken to antibiotic therapy and asked the question, would implementation of clinical decision support decrease inappropriate prescribing?

The Question

Does the implementation of a clinical decision support system (CDSS) decrease inappropriate antibiotic prescribing?

The Search

We used PubMed (www.pubmed.gov) and entered the terms "decision support" and "antibiotics."

Our Critique

This remarkable study provides compelling evidence that CDSS tools can reduce inappropriate antibiotic prescribing at a population level. Overall, the pharmacy and chart review results were consistent and showed a greater reduction in antibiotic use and improved appropriateness of antibiotic prescriptions in the CDSS communities. Interestingly, this specific CDSS tool was developed by a vendor for the purpose of this study and is not available for sale or use. The inability to evaluate this tool makes it difficult to assess whether it can be exported and implemented in other practice settings. Additional information regarding whether the paper-based or personal digital assistant–based tool was more effective would have been interesting. Questions remain regarding the impact on patient outcomes and on the overall question of whether such innovations will decrease antimicrobial resistance patterns.

Patient Preferences and Clinical Decision

The group agrees to explore the use of CDSS in order to decrease inappropriate antibiotic use.

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M.H. Samore, et al.

Clinical decision support and appropriateness of antimicrobial prescribing: a randomized trial. (JAMA 2005;294:2305-14).

▶ **Design and Setting:** Population-based randomized trial with communities as the unit of randomization; conducted in 12 rural communities in Utah and Idaho.

▶ **Subjects:** The study included 407,460 patients and 334 primary care clinicians.

▶ **Intervention:** Six communities received a community intervention plus a CDSS targeted to primary care clinicians, and six control communities received a community intervention only. The CDSS consisted of support tools on paper and PDAs designed to guide diagnosis and management of acute respiratory tract infection. The CDSS tools covered a wide variety of acute respiratory tract infections, sinusitis, pneumonia, croup, and influenza. The paper version was either a flow chart designed to lead the clinician to the correct diagnosis or a patient-completed chart-documentation tool. The PDA generated diagnostic and therapeutic recommendations based upon the data entered. The community intervention involved two waves. The first wave consisted of meetings with community leaders, news releases, mailings, and distribution of educational materials at pharmacies and physician offices. The second wave focused on self-management of respiratory tract infections and improving communication with physicians.

▶ **Outcomes:** Retail pharmacy volume and chart review were the sources of information about antimicrobial prescribing. Diagnoses recorded by the primary care clinician were categorized according to the appropriateness of antibiotic use: never indicated (acute bronchitis, upper respiratory tract infections); sometimes indicated (sinusitis, otitis media, and pharyngitis); or always indicated (strep pharyngitis, acute otitis media, and pneumonia).

▶ **Results:** Of the primary care clinicians, 71% used the CDSS tools. Of that group, 54% used the PDA, 23% used paper algorithms, and 24% used both. A total of 20,727 respiratory tract infection cases were completed. Antibiotic prescribing rates were not significantly different across study arms before the intervention. According to the retail pharmacy data, the overall antimicrobial prescribing rate declined significantly more in the CDSS group than in the control group from baseline to the second year of the intervention. This translated into an expected reduction of 93 antimicrobial prescriptions per month. In CDSS communities, macrolide prescriptions decreased by 12% during the first year and 28% during the second year—both differences were significant—and remained stable in the other communities. According to chart review data, antimicrobial prescribing during clinical encounters in which antibiotic prescribing was "never indicated" decreased significantly more in the CDSS group (35%-24%), compared with the community intervention alone (40%-38%). In the CDSS communities, a significant 50% reduction in the odds of prescribing macrolides relative to penicillins was observed. Within CDSS communities, physicians who used the algorithms showed a greater decrease in antimicrobial use than clinicians who did not use the tools.