Shorter, Simpler TB Regimen Considered a Priority

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LISBON — Tuberculosis experts now generally agree that the top priority for improving TB therapy is to shorten and simplify the regimen for active disease, Dr. Ann Ginsberg said at the 12th International Congress on Infectious Diseases.

"This will have the greatest impact on the epidemic as compared to trying specifically to improve treatment of MDR [multidrug-resistant] TB and of TB/HIV-coinfected patients. Those are also extremely important problems, but epidemiologically speaking they don't involve the same number of patients as standard active disease," noted Dr. Ginsberg, head of clinical development at the Global Alliance for TB Drug Development, New York.

A short-course treatment for latent infection—the norm today remains 9 months of isoniazid—would probably have the biggest impact of all on the epidemic. But it's not yet feasible. Not enough is understood about the biology underlying TB latency to permit rational drug development, she said.

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DR. GINSBERG

Treatment for active drug-responsive TB today typically involves a minimum of 6 months of therapy with complex combinations of four drugs: isoniazid, rifampicin, pyrazinamide, and ethambutol. The length and complexity of this regimen result in poor compliance, which promotes increased drug resistance. Treatment of TB patients coinfected with HIV—a large and growing population—is essentially the same, with the added complication that rifampicin interacts adversely with key antiretroviral agents.

The near-term goal of the Global Alliance and other groups is to replace the current regimen, which entails taking up to 14 pills per day for 6 months, with 2-3 months of once-weekly therapy.

The longer-term goal is to shrink treatment to 2 weeks or less, much as other respiratory infections are treated. That must likely await better understanding of the mechanisms involved in TB persistence, Dr. Ginsberg explained at the congress, which was sponsored by the International Society for Infectious Diseases.

The last new class of TB drugs was introduced in the 1960s. Drug development then stagnated for more than 3 decades. That began to change a few years ago. Today the TB drug development pipeline is richer than at any point in the last half-century.

New compounds being developed target the TB bacillus. Most are still in preclinical development. However, at least a half-dozen are in clinical trials, including gatifloxacin, now in phase III trials, and moxifloxacin, slated to begin phase III studies within several months. Both fluoroquinolones have pharmacokinetics amenable to weekly dosing, as does rifapentine, a long-acting rifamycin developed in the 1990s.

Animal studies suggest a shorter, simpler 2- to 3-month regimen of weekly therapy is probably achievable with drugs now in development, perhaps used in combination with some current drugs. However, all of the current first-line drugs have suboptimal profiles, and none may wind up in a new optimized regimen, according to Dr. Ginsberg.

Developing a truly novel TB drug regimen in a timely fashion will require new guidelines from the Food and Drug Administration and other regulatory agencies. The conventional development process evaluates one new drug at a time, substituting it in studies for one of the agents in the current regimen. With the conventional process, a regimen with multiple new drugs could take 30 years to gain approval. "Given the urgency of the global TB epidemic, this is not acceptable," she said.

The Global Alliance has supported an alternative pathway to clinical development, one in which whole new regimens would be tested against the standard combination. In this way, a more efficacious optimized regimen could be established in a 6-year clinical development period if all goes smoothly, Dr. Ginsberg said. ■