

Shorter, Simpler TB Regimen Considered a Priority

BY BRUCE JANCIN
Denver Bureau

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



The goal is to shrink treatment to 2 weeks or less, similar to other respiratory infections.

DR. GINSBERG

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.

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 coinfecting 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. ■

new



Introducing Levemir®: a long-acting basal insulin with a light touch

New Levemir: for your patients who need a safe and effective way to improve A1C control

With proven reductions in A1C and FPG levels over time, Levemir can help your patients get to goal with up to 24 hours of glycemic control. Patients with diabetes can experience a consistent blood glucose response from injection to injection. Less weight gain was observed with Levemir in 12 of 12 clinical trials.* And Levemir is available in the Levemir® FlexPen®. FlexPen is the world's #1 selling prefilled insulin pen. So start your patients with diabetes on Levemir, and help them experience the light side of basal insulin.

Levemir is indicated for once- or twice-daily subcutaneous administration for the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

Important safety information
Levemir should not be diluted or mixed with any other insulin preparations. Levemir is contraindicated in patients hypersensitive to insulin detemir or one of its excipients.

Hypoglycemia is the most common adverse effect of all insulin therapies, including Levemir. As with other insulins, the timing of hypoglycemic events may differ among various insulin preparations. Glucose monitoring is recommended for all patients with diabetes. Any change of insulin dose should be made cautiously

and only under medical supervision. Concomitant oral antidiabetes treatment may require adjustment.

Levemir is not to be used in insulin infusion pumps. Inadequate dosing or discontinuation of treatment may lead to hyperglycemia and, in patients with type 1 diabetes, diabetic ketoacidosis. Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy. Dose and timing of administration may need to be adjusted to reduce the risk of hypoglycemia in patients being switched to Levemir from other intermediate or long-acting insulin preparations. The dose of Levemir may need to be adjusted in patients with renal or hepatic impairment.

Other adverse events commonly associated with insulin therapy may include injection site reactions (on average, 3% to 4% of patients

in clinical trials) such as lipodystrophy, redness, pain, itching, hives, swelling, and inflammation.

*Whether these observed differences represent true differences in the effects of Levemir and NPH insulin is not known, since these trials were not blinded and the protocols (eg, diet and exercise instructions and monitoring) were not specifically directed at exploring hypotheses related to weight effects of the treatments compared. The clinical significance of the observed differences in weight has not been established.



new Levemir®

insulin detemir (rDNA origin) injection
Lighter years ahead



Reference: 1. IMS Health, IMS MIDAS [12 months ending September 2005]. Please see brief summary of Prescribing Information on adjacent page. FlexPen and Levemir are registered trademarks of Novo Nordisk A/S.

© 2006 Novo Nordisk Inc. 130299R1 May 2006