Review Article

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New Drugs for Tuberculosis

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There are good drugs to treat drug-sensitive tuberculosis in otherwise healthy, compliant patients, but everyone who treats tuberculosis knows that many of our patients fall outside of this group. Even in this "perfect setting", therapy is too long and intolerance too frequent.

After decades with few or no new medicines for tuberculosis, many drugs and drug-candidates are now being developed, tested, and marketed (1).

The first strategy to find new medications is to look at the currently used antituberculous drugs. Most currently agents have reached their maximal benefit-toxicity dosing (2). That is, giving higher doses has not been shown to render additional benefit, or higher doses are more toxic. The exception to this may be the rifampicins. Several studies have shown that blood levels of about half the patients taking these drugs are below the recommended maximum therapeutic blood levels; and the levels seem to be lower in sicker patients (3). Several studies in mice and humans indicate that higher doses of rifamycins hasten culture conversion. Rifapentine is a promising drug, whose high potency, long duration of activity, ability to kill latent as well as active bacilli, and low toxicity suggest that it will have expanded use in the future (4). Developing the best treatment for latent tuberculosis is still in evolution.

Other drugs in current use that were not primarily designed for tuberculosis include the quinolones. Moxifloxacin, gatifloxacin, and levofloxacin have now taken a place as the standard treatment of drug-resistant tuberculosis (5). Moxifloxacin is the most studied drug and appears to be able to replace isoniazid (6) or ethambutol (7), but it cannot replace rifampin or pyrazinamide. Linezolid is an oxazolidinone whose antimycobacterial properties were known before it was marketed. It is used for resistant Gram-positive bacterial infections. Limited studies on drug-resistant tuberculosis show it to be very effective, but very toxic (8). When given for a prolonged period for drug-resistant tuberculosis, more than half of the patients developed serious side effects to it. Some of side effects were fatal or resulted in permanent loss of function. Lower doses and shorter intervals are being considered. Other oxazolidinones are in development.

A problem with the strategy of using existing for tuberculosis is that pharmaceutical manufacturers are not likely to spend large amounts of their research money to develop currently available drugs because they could not sell them exclusively. Most of the evidence for potential drugs, such as metronidazole and phenothiazines, is too scant for clinicians to rely on. Many studies show increased incidence and severity of tuberculosis with vitamin D deficiency, which should prompt its replacement in anyone with tuberculosis.

Most new drugs are coming from screened metabolites of existing drugs. The strategy of developing drugs from plants or natural products is much less efficient than screening large data banks of compounds. It appears that large pharmaceutical companies already have many good candidate drugs. The bottleneck of development is human

trials and bringing them to market, not in the initial phase of drug discovery.

Several new drugs are near marketing. Bedaquiline was approved for use in the USA on December 31, 2012 for treating drug-resistant tuberculosis. It is a diarylquinolone, which inhibits bacterial ATP synthetase. ATP, of course, is required for both the active and dormant stages of mycobacterial life. This new class of agents has no cross-resistance with other agents. Bedaquiline has a long half-life and high tissue binding. Mice studies have been impressive, and the early bactericidal activity is significant (9,10).

PA-824 is a nitro-imidazole derived from metronidazole that appears to work by several means. It is an NO donor that is important in killing anaerobically metabolizing bacteria. But it also blocks ketomycolates that are required for mycobacterial cell wall synthesis (11). Delamanid is a nitro-dihydro-imidazooxazole also derived from metronidazole. It may work by the same mechanism and is effective for both replicating and nonreplicating bacteria. It has very low minimum inhibitory concentration (0.006-0.024 µg/mL) and excellent intracellular activity (12). Both PA-825 and delamanid have delayed killing and appear to be well-tolerated.

Even when drugs are marketed, availability, cost, unforeseen toxicity, and their role among other medicines are factors to be considered before they reach a place in therapy against tuberculosis. Vaccines and immunotherapy are also being studied and may impact the treatment.

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