COMMENTARY

Reconsidering Some Approved Antimicrobial Agents for Tuberculosis

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The case report in this issue by Forgacs and colleagues (8) is particularly timely in view of the resurgence of tuberculosis and the promise of new therapeutic approaches (15). Much of the current attention on tuberculosis has focused on the close association of tuberculosis and human immunodeficiency virus, particularly in sub-Saharan Africa and Asia, where a huge proportion of the population has latent tuberculosis (7). Still, totally new drug treatments or even those that are modest improvements within well-known classes, such as the fluoroquinolone moxifloxacin, will not be easily introduced into resource-limited clinical settings. It is clear that the affordability of and accessibility to “standard” current antituberculosis medications are major factors leading to the emergence of multiple-drug resistant (MDR) and extensively drug resistant (XDR) tuberculosis.

Forgacs and colleagues’ observation of a single immune-suppressed patient responding to trimethoprim-sulfamethoxazole (SXT) appears to be a prescient clinical observation that reopens the subject of sulfonamides plus folate antagonists as therapeutic options for the treatment or prevention of tuberculosis. Clinical evidence of defervescence in the absence of any other antimicrobial intervention, along with some improvement in laboratory parameters (with equivocal changes in the imaging studies), led this group of clinicians and microbiologists to reexamine the susceptibility of Mycobacterium tuberculosis strains to the SXT combination. The overall profile of susceptibility (98% of 44 isolates) appears quite encouraging with the total number of isolates tested, although the number of MDR-M. tuberculosis strains (six in all) was more limited and was probably insufficient to draw conclusions from. The inference of susceptibility was logically made by using laboratory criteria for susceptibility testing of M. kansasii and M. marinum to SXT; no standardized guidelines are available for M. tuberculosis testing since, as the authors indicate, tuberculosis isolates have long been considered to be resistant to this combination.

That the fixed combination of SXT may have activity against M. tuberculosis should not come as a major surprise. A fixed combination of a sulfonamide and a folate antagonist is already recognized to be effective therapy for some types of nontuberculous mycobacteria. The early clinical studies cited in the paper by Forgacs and colleagues summarize the initial evidence that sulfonamides alone have modest in vivo activity against tuberculosis disease but for good reasons were supplanted by more-effective therapies a half century ago. The same fate was met by para-aminosalicylic acid with the advent of isoniazid and rifampin combination therapy. Sulfones have long been used for the treatment of leprosy, and it is well recognized that the molecular targets of sulfonamides and folate antagonists, dihydropteroate synthetase and dihydrofolate reductase, are present in mycobacteria. Working with another common disease-causing species of mycobacteria, the M. avium-M. intracellulare complex (MAC), my colleagues and I have screened a number of folate antagonists provided to us from both industrial and governmental sources. Some compounds, such as trimetrexate, had potent activity in vitro but proved to be toxic in the beige mouse model of MAC disease. Systematic screening of other folate antagonists identified other compounds with in vitro activity, but pharmacologic limitations (solubility, oral absorption, etc.) precluded assessment of in vivo effects (14).

Given the importance of the case observation by Forgacs and colleagues in leading us to reexamine the potential of SXT in tuberculosis therapy, it still seems premature to suggest initiation of a clinical trial to establish efficacy. What would be justified and fully indicated at this point are additional enhanced screening of MDR/XDR isolates from widely dispersed geographical sources, some attempt to vary in vitro culture conditions and media for optimizing the drug activity, and an examination of the effect of anaerobiosis on the activity of the fixed combination. The latter has been utilized to create a state analogous to latent tuberculosis (the so-called Wayne model [16]) in which tubercle bacilli are viable but nonreplicating. Activity in such an anaerobic in vitro test system could provide further insights into the potential application of SXT. Drugs with sterilizing activity in human clinical trials, such as rifampin, appear active versus both replicating and nonreplicating M. tuberculosis. Before a large clinical trial is even contemplated, however, an evaluation of the early bactericidal effect in sputum of the fixed-agent combination alone would be appropriate in cases of pulmonary tuberculosis. This has been a standard approach in looking at new antituberculosis therapies. The short observation period in which the bactericidal effect of any monotherapeutic compound is evaluated in human patients, using quantitative mycobacterial counts in sputum, does not appear to jeopardize the ultimate course of treatment and could provide valuable initial information about
the therapeutic potential of any compound against tuberculosis being considered.

The observation of Forgacs and colleagues is clearly encouraging from the perspective that SXT is already a licensed compound for antimicrobial therapy worldwide and is no longer subject to patent protection. However, it would be unfortunate if such an agent were employed for tuberculosis therapy without first establishing a well-founded basis for its therapeutic use, beginning with broadened in vitro screening and assessment of its therapeutic efficacy in various animal models. Various murine species may be the most expedient in vivo test systems, but important pharmacologic parameters (e.g., trimethoprim and folate levels) will have to be worked out.

Are there any other examples of licensed antimicrobial agents showing promise as antituberculosis therapies analogous to the experience detailed in the report by Forgacs? Interestingly, the answer is yes. M. tuberculosis as well as other mycobacteria elaborate beta-lactamases, and in a report more than two decades ago Cynamon observed the effect of amoxicillin plus clavulanate (4). Chambers and colleagues showed that this same fixed combination exerted an early bactericidal effect against M. tuberculosis in human respiratory disease, but interestingly, except for scattered reports there has been no extended follow-up in the 10 years since this report (2). Chambers and coworkers subsequently reported the therapeutic efficacy of imipenem for tuberculosis disease in mice and humans (3). The experimental studies of imipenem in mice showed it to be bactericidal but not as potent as isoniazid. The human studies comprised a small series of 10 patients with MDR tuberculosis who were therapeutic failures on standard chemotherapy. Evaluation of the clinical effect was complicated by the use of imipenem in combination with other therapies such as aminoglycosides and fluoroquinolones. However, in selected cases the single addition of imipenem appeared to have a beneficial effect. More recently, Hugonnet and colleagues from the National Institute of Allergy and Infectious Diseases published in vitro (only) studies on the potent activity of meropenem, a carbapenem closely related to imipenem, D. Danelishvili, L., M. Wu, L. S. Young, and L. E. Bermudez. 2009. Mefloquine is active in vitro and in vivo against Mycobacterium avium complex. Antimicrob. Agents Chemother. 43:1870–1874.


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