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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 dihydrofolic acid 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

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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, when combined with clavulanate (9). The MICs for drug-susceptible and a few MDR isolates were well within the therapeutic range, less than 1 μg/ml. Meropenem plus clavulanate sterilized aerobic cultures within 14 days, and the combination inhibited anaerobically grown cultures. Meropenem-clavulanate inhibited 13 isolates of XDR *M. tuberculosis* at the same concentrations as for drug-susceptible strains. Unfortunately, both imipenem and meropenem require parenteral administration, so the practicality of this approach, let alone combining either carbapenem with clavulanate, may be limited to more-serious cases of disease. Since there is precedent for the therapeutic use of at least one of the carbapenems, an approximation of this particular approach and an evaluation of members of this class as components of an antituberculosis regimen are also called for in the same manner as the reassessment of SXT. The advantages of an established, licensed agent is that the pharmacologic properties and potential for drug interactions are likely to be well understood, although the pharmacodynamic effects versus mycobacteria may well be an interesting subject for further investigation.

My colleagues and I noted a number of years ago that mefloquine, a licensed antimalarial that is active against chloroquine-resistant strains, has bactericidal activity against MAC, the most common nontuberculous mycobacterial infection (1, 5). A single human case report described successful treatment of a patient with refractory MAC disease by the addition of linezolid and mefloquine to other anti-MAC agents, but the former compound has limitations in long-term therapy (12). It would appear that mefloquine also has an effect against *M. tuberculosis*; a presentation reporting in vivo activity was presented at the 49th Interscience Conference on Antimicrobial Agents and Chemotherapy (10). Mefloquine was bactericidal against *M. tuberculosis* alone and in murine tuberculosis could substitute for both isoniazid and rifampin. Mefloquine has its own set of clinical limitations, not the least of which is its central nervous system toxicity, but mefloquine analogues have been prepared by several laboratories, and assessment of their efficacy against mycobacterial pathogens also seems warranted.

From the perspective of antimicrobial development, it is gratifying that new resources have been mobilized and expedited against the global threat of tuberculosis. Totally new molecular entities such as PA-824, OPC-67683, and TMC207 are already in the clinic and have generated considerable excitement (6, 7). Spurred by the laboratory demonstration of the effect of metronidazole against *M. tuberculosis* in the Wayne model, two nitroimidazopyrans, PA-824 and OPC-67683, were discovered by extensive chemical analoging. Other new molecular entities, such as the more recently described benzothiazinones (11) and capuramycin derivatives (13), are supported by in vitro and in vivo data but as yet have not been evaluated in human trials. Nonetheless, more than a decade has elapsed since the first description of PA-824. It has been a matter of frustration to many workers in tuberculosis clinics that new agents such as PA-824 and TMC207 are not more readily available for clinical trials. To this end, compounds like SXT, amoxicillin/clavulanate, carbapenems like imipenem and meropenem, and mefloquine are available licensed agents that could be the subjects of carefully controlled assessments of antituberculosis activity in animal models and humans.

REFERENCES

1. **Bermudez, L. E., P. Kolonoski, M. Wu, P. A. Aralar, C. B. Inderlied, and L. S. Young.** 1999. Mefloquine is active in vitro and in vivo against *Mycobacterium avium* complex. Antimicrob. Agents Chemother. **43:**1870–1874.
2. **Chambers, H. F., T. Kocagoz, T. Sipit, J. Turner, and P. C. Hopewell.** 1998. Activity of amoxicillin/clavulanate in patients with tuberculosis. Clin. Infect. Dis. **26:**874–877.
3. **Chambers, H. F., J. Turner, G. F. Schecter, M. Kawamura, and P. C. Hopewell.** 2005. Imipenem for treatment of tuberculosis in mice and humans. Antimicrob. Agents Chemother. **49:**2816–2821.
4. **Cynamon, M. H., and G. S. Palmer.** 1983. In vitro activity of amoxicillin in combination with clavulanic acid against *Mycobacterium tuberculosis*. Antimicrob. Agents Chemother. **24:**429–431.
5. **Danelishvili, L., M. Wu, L. S. Young, and L. E. Bermudez.** 2005. Genomic approach to identifying the putative target of and mechanisms of resistance to mefloquine in mycobacteria. Antimicrob. Agents Chemother. **49:**3707–3714.
6. **Diacon, A. H., A. Pym, M. Grobusch, R. Patientia, R. Rustomjee, L. Page-Shipp, C. Pistorius, R. Krause, M. Bogoshi, G. Churchyard, A. Venter, J. Allen, J. C. Palomino, T. De Marez, R. P. van Heeswijk, N. Lounis, P. Meyvisch, J. Verbeeck, W. Parys, K. de Beule, K. Andries, and D. F. McNeeley.** 2009. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. N. Engl. J. Med. **360:**2397–2405.
7. **Donald, P. R., and P. D. van Helden.** 2009. The global burden of tuberculosis—combating drug resistance in difficult times. N. Engl. J. Med. **360:** 2393–2395.

8. **Forgacs, P., N. L. Wengenack, L. Hall, S. K. Zimmerman, M. L. Silverman, and G. D. Roberts.** 2009. Tuberculosis and trimethoprim-sulfamethoxazole. Antimicrob. Agents Chemother. **53:**4789–4793.
9. **Hugonnet, J.-E., L. W. Tremblay, H. I. Boshoff, C. E. Barry III, and J. S. Blanchard.** 2009. Meropenem-clavulanate is effective against extensively drug-resistant *Mycobacterium tuberculosis*. Science **323:**1215–1218.
10. **Lenaerts, A. J., L. K. Woolhiser, V. Gruppo, I. M. Orme, R. C. Goldman, and C. Lambros.** 2009. Mefloquine, moxifloxacin and pyrazinamide is a triple-drug alternative to isoniazid- and rifampin-containing regimens for treatment of tuberculosis in mice, abstr. B-1873. Abstr. 49th Intersci. Conf. Antimicrob. Agents Chemother., San Francisco, CA.
11. **Makarov, V., G. Manina, K. Mikusova, U. Mollmann, O. Ryabova, B. Saint-Joanis, N. Dhar, M. R. Pasca, S. Buroni, A. P. Lucarelli, A. Milano, E. De Rossi, M. Belanova, A. Bobovska, P. Dianiskova, J. Kordulakova, C. Sala, E. Fullam, P. Schneider, J. D. McKinney, P. Brodin, T. Christophe, S. Waddell, P. Butcher, J. Albrethsen, I. Rosenkrands, R. Brosch, V. Nandi, S. Bharath, S. Gaonkar, R. K. Shandil, V. Balasubramanian, T. Balganesh, S. Tyagi, J. Grosset, G. Riccardi, and S. T. Cole.** 2009. Benzothiazinones kill *Mycobacterium tuberculosis* by blocking arabinan synthesis. Science **324:**801–804.
12. **Nannini, E. C., M. Keating, P. Binstock, G. Samonis, and D. P. Kontoyiannis.** 2002. Successful treatment of refractory disseminated Mycobacterium avium complex infection with the addition of linezolid and mefloquine. J. Infect. **44:**201–203.
13. **Nikonenko, B. V., V. M. Reddy, M. Protopopova, E. Bogatcheva, L. Einck, and C. A. Nacy.** 2009. Activity of SQ641, a capuramycin analog, in a murine model of tuberculosis. Antimicrob. Agents Chemother. **53:**3138–3139.
14. **Rosowsky, A., R. A. Forsch., C. H. Sibley, C. B. Inderlied, and S. F. Queener.** 2004. New 2,4-diamino-5-(2′,5′-substituted benzyl)pyrimidines as potential drugs against opportunistic infections of AIDS and other immune disorders. Synthesis and species-dependent antifolate activity. J. Med. Chem. **47:**1475–1486.
15. **van den Boogaard, J., G. S. Kibiki, E. R. Kisanga, M. J. Boeree, and R. E. Aarnoutse.** 2009. New drugs against tuberculosis: problems, progress, and evaluation of agents in clinical development. Antimicrob. Agents Chemother. **53:**849–862.
16. **Wayne, L. G., and L. G. Hayes.** 1996. An in vitro model for sequential study of shiftdown of *Mycobacterium tuberculosis* through two stages of nonreplicating persistence. Infect. Immun. **64:**2062–2069.

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