Strategies to Improve Outcome of Drug Treatment for Mycobacterium abscessus Pulmonary Disease

To the Editor—In the May 2011 issue of Clinical Infectious Diseases, Jarand et al [1] reported on the outcome of treatment in their cohort of patients with Mycobacterium abscessus pulmonary disease. Despite optimal regimens, only 33 (48%) of 69 patients experienced conversion to negative culture results. Outcome was significantly worse in patients who received drug treatment only, without adjunctive surgical treatment (28% vs 57%). In his editorial, Griffith [2] placed these findings in a historical context, one that leaves little room for optimism. Simply put, antibiotic treatment alone has little to offer; this leaves one to wonder why it has little to offer. Study of the M. abscessus genome offers some interesting insights. As Jarand et al [1] note, the existence of an erythromycin resistance methylase (erm) gene implies that M. abscessus bacteria can induce macrolide resistance [1]. The genome, however, has additional disconcerting features: an additional erm-like gene, multiple efflux pumps, an aminoglycoside 2'-N-acetyltransferase, and 12 homologs of aminoglycoside phosphotransferases [3]. What do these aminoglycoside-converting enzymes mean for the efficacy of amikacin, the second most important drug after the macrolides in
M. abscessus treatment regimens? One possible reason for the frequent failure of antibiotic treatment for M. abscessus disease is that M. abscessus has acquired erm genes, aminoglycoside converting enzymes, and other armaments, not because of antibiotics, but as protective mechanisms against the antimicrobial molecules secreted by the micro-organisms with which M. abscessus shares its environmental habitats. It shares these habitats, soil and water, with microorganisms including Streptomyces and closely related genera, the producers of aminoglycoside and macrolide antibiotics. The close contact is illustrated by the large number of genes that M. abscessus has acquired from Streptomyces and related genera by lateral gene transfer [3]. Therefore, Griffith’s [2] remarks about the potential of TMC207 [2] are of interest: TMC207 is not a microbe-derived molecule. TMC207 is the lead molecule for the class of diarylquinoline antimicrobials, a class selected after screening of large libraries of molecules for in vitro activity against mycobacteria [4]. Owing to its nature, the defense mechanism against this type of molecule or protective mechanisms covering the drug target, ATP synthase [4], is not likely to be present in mycobacteria. This renders TMC207 as an appealing compound for treatment regimens for M. abscessus pulmonary disease. Synthetic compounds that disturb generic defense mechanisms, such as efflux pumps and cell wall permeability, may be interesting adjunctives to novel regimens; the phenothiazines (eg, thioridazine) and clofazimine affect these mechanisms [5, 6]. Clofazimine has the advantage that it has intrinsic activity in vitro against M. abscessus [5], and thioridazine probably does not have this activity [6]. Both show promising synergistic activity with other antimycobacterial compounds [5, 7]. Treatment regimens for M. abscessus disease need to be optimized, preferably by introduction of compounds not derived from microbes, such as TMC207; adjunctive agents that affect cell wall permeability and efflux pumps may also prove to be helpful. Hopefully, their use will finally increase the long-term culture conversion rates in M. abscessus pulmonary disease.

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