In-vitro sensitivities and treatment of less common mycobacteria

Brian Watt*

Scottish Mycobacteria Reference Laboratory, City Hospital, Greenbank Drive, Edinburgh EH10 5SB, UK

There are very few new agents available for the treatment of infections due to the less common mycobacteria. There have been very few systematic studies of in-vitro activity and fewer clinical trials. Yet such mycobacteria are an important cause of serious disease and often conventional antimycobacterial agents are unsuitable either because of in-vitro resistance of the pathogen concerned, or toxicity of one of the components of drug regimens. At present, newer macrolides and quinolones offer promise, but there is a need to extend the in-vitro studies already under way of newer agents against Mycobacterium avium and/or Mycobacterium tuberculosis, to the other, less common mycobacteria. The benzoxazinorifampicins, the oxazolidinones and the acridinones may prove to be of clinical value. In addition to more information on the in-vitro activity of newer agents, alone and in combination, based on systematic studies involving larger numbers of mycobacterial strains, we need clearer clinical information to enable therapeutic regimens to be formulated and validated. The British Thoracic Society study is but a first step. There need to be more.

Introduction

There is an increasing interest in the pathogenic potential of non-tuberculous mycobacteria. The importance of infection due to Mycobacterium avium complex in AIDS is probably the best known example, but other less common mycobacteria such as Mycobacterium malmoense may also pose challenges both in immunocompromised and immunocompetent patients. A recent study of therapeutic outcomes highlights the difficulties in treating non-tuberculous mycobacterial infections.

The purpose of this review is to consider the potential of newer antimycobacterial agents for the treatment of these infections due to such less common mycobacteria. The treatment of M. avium complex infections is a large topic in its own right and merits consideration separately. This review will not discuss the many older agents such as doxycycline, cefoxitin or sulphonamides which have been used to treat such infections. These have been reviewed elsewhere.

Although a wide variety of agents have some antimycobacterial activity in vitro, relatively few compounds have been developed recently for this purpose. Compounds that may be considered ‘new’ include rifamycins, benzoxazinorifampicins, certain macrolides, quinolones, oxazolidinones, acridinones and gangamicin. These are considered separately. Their potential use in the treatment of tuberculosis has recently been reviewed but many have not yet been tested in any systematic way against lesser known mycobacteria.

In-vitro studies

Rifamycins

Rifabutin. Rifabutin, previously known as ansamycin (LM 427), is a semi-synthetic spiroperyridyl derivative of rifampicin; it is more active than rifampicin against Mycobacterium tuberculosis and M. avium and has important pharmacokinetic differences from rifampicin, notably lower oral bioavailability and lower mean plasma concentrations even after repeated administration, possibly due to a large volume of distribution. It has a longer half-life than rifampicin, thus allowing it to be given less frequently.

The antimycobacterial activity of rifabutin has been extensively reviewed. The compound is more active than
rifampicin against Mycobacterium kansasi and Mycobacterium fortuitum, although the MIC \(_{90}\) for M. fortuitum is as high as 8 mg/L. Other susceptible mycobacteria include Mycobacterium scrofulaceum, Mycobacterium haemophilum, Mycobacterium marinum and M. malmoense, whereas M. ycobacterium chelonei and Mycobacterium simiae are less susceptible (Table I).

Thus, rifabutin has appreciable activity against many mycobacteria, although the number of strains tested has often been small (\(<20\)). Although toxic effects such as acute uveitis with hypopyon have been reported when rifabutin is used in HIV-positive patients,\(^8\) the syndrome responds well to topical corticosteroids. There is no satisfactory explanation why such a fulminant inflammatory response should occur: it appears to be a ‘unique mechanism of ocular inflammation’\(^8\) that warrants further investigation.

One problem in assessing the potential use of rifabutin is the choice of breakpoint concentrations to define resistance. Values used range considerably and are often based on serum concentrations, which fail to take account of factors such as the high intracellular concentrations of the compound, often ten-fold greater than extracellular concentrations. Della Bruna & Ollivaro,\(^9\) in reviewing this problem have, as a consequence, suggested breakpoint concentrations that differ for different test systems (\(>2\) mg/L for liquid medium, \(>40\) mg/L for egg media). It is not clear how these relate to Bacteriologically radiometric technology.

Rifapentine. Rifapentine, a cyclopentyl derivative of rifampicin, is in clinical trials in various countries for the treatment of M. avium infections. Its MICs are substantially lower than those of rifampicin,\(^4\) and it has a longer half-life,\(^10\) which makes it more suitable for intermittent therapy. There are, however, no published data about its activity against less common mycobacteria.

Benzoaxazino-rifampicins. These are a group of new rifampicin derivatives, the first of which, KRM-1648, has recently been synthesized and is in early development. Saito et al.\(^13\) studied the activity of several such compounds, including KRM-1648, against a range of mycobacteria. KRM-1648 had good activity against M. kansasi and M. marinum (MIC \(<0.25\) mg/L), but poor activity against M. fortuitum or M. chelonei. KRM-1648 has a long half-life and very good tissue distribution,\(^12\) but there are no available data as yet on its in-vivo activity against less common mycobacteria.

Macrolides

Clarithromycin, azithromycin and roxithromycin are three macrolides that have antimycobacterial activity. The subject has been studied by a number of authors, chiefly in the context of M. avium complex infections but useful reports on other atypical mycobacteria include those by Yew et al\(^13\) and Rapp et al.\(^14\)

Both clarithromycin and azithromycin are much more active than erythromycin against mycobacteria.\(^14\) In general, MICs of clarithromycin are lower than those of azithromycin, but it is clear that, on the basis of MICs, some species of mycobacteria are more resistant than others to both agents (Table II). However, these have to be related to achievable intracellular concentrations; Kirst & Sides\(^15\) showed that both agents had high tissue: plasma concentration ratios, implying greater concentration at the site of infection (e.g. for azithromycin, 0.4 mg/L maximum serum concentration and concentrations of 3.2 mg/kg within tonsillar tissue).

Bernard et al.\(^16\) showed that clarithromycin (MIC \(_{90}<0.25\) mg/L) was more active than azithromycin (MIC \(_{90}\) 8 mg/L) against isolates of M. haemophilum. Wallace et al.\(^17\) tested 180 clinical isolates of M. chelonei and found that for all, MICs were \(<1\) mg/L. Brown et al.\(^18\) showed that clarithromycin, azithromycin and roxithromycin had good activity against M. chelonei but less consistent activity against the M. fortuitum group. Clarithromycin was not active in vitro against M. simiae\(^19\) (the organism most closely resembling M. ycobacterium genavense), thus casting doubt on its potential use in the treatment of M. genavense infections.

Roxithromycin, the 9-(O-(2-methoxyethoxy) methyl)oxime of erythromycin A, is another macrolide derivative that has antimycobacterial activity in vitro. Rastogi et al.\(^20\) studied its activity against 28 different strains of mycobacteria in the Bactec system and showed that MICs \(<10\) mg/L (its peak serum level) were found for all of the test species except M. simiae and M. fortuitum. The authors drew attention to the influence of pH on the results of susceptibility testing, with MICs two- to four-fold higher at pH 6.8 (the routine pH for Bactec radiometric testing) than at pH 7.4 (a more physiological value). It may be that adjustment of the pH to the higher value should be considered for sensitivity testing. These authors concluded that the antimycobac-

| Table I. In-vitro activity (mg/L) of rifabutin against mycobacteria\(^a\) |
|---------------------|-------|-------|
| Test species        | No. of strains | MIC\(_{50}\) | MIC\(_{90}\) |
| M. fortuitum        | 30    | \(>2\) | \(>2\) |
| M. marinum          | 12    | \(<0.5\) | \(<0.5\) |
| M. gordonae         | 32    | \(<0.5\) | \(<0.5\) |
| M. haemophilum      | 17    | \(\leq 0.03\) | \(\leq 0.03\) |
| M. malmoense        | 22    | 0.25  | \(>0.25\) |
| M. simiae           | 3     | \(>2\) | \(>2\) |
| M. kansasii         | 32    | \(<0.5\) | \(<0.5\) |
| M. xenopi           | 3     | \(<0.5\) | \(<0.5\) |
| M. chelonei         | 60    | \(>2\) | \(>2\) |

\(^a\) Based on data from Heifets & Iseman,\(^3\) Bernard et al.\(^16\) and Hoffner et al.\(^34\)
The activity of the quinolones against mycobacteria has been well reviewed by other authors. They tested eight quinolones (ciprofloxacin, clinafloxacin, levofloxacin, ofloxacin, A-80556, sparfloxacin, temafloxacin and tosunofloxacin) against various mycobacteria (Table III). Of the test compounds, sparfloxacin was the most active, except in the case of M. chelonei. All the test compounds were inactive (MIC₉₀ > 8 mg/L) against this organism, an observation also made earlier.

Other workers have confirmed that sparfloxacin has good activity, both in terms of bactericidal activity and in terms of intracellular killing, against mycobacteria in vitro, is more active than ofloxacin and ciprofloxacin, and appears to act synergically in combination with ethambutol in vitro. However, it is only moderately active against M. haemophilum. Bernard et al. tested 17 isolates and found the MIC₉₀ of sparfloxacin to be 4 mg/L. A nether new quinolone, A M 1155, is more active than sparfloxacin or ofloxacin against many atypical mycobacteria (Table IV).

Saito et al. evaluated the activity of another new
B. Watt

Table III. Comparative activity (mg/L) of quinolones against atypical mycobacteria (based on data from Yew et al.13)

<table>
<thead>
<tr>
<th>Test species (n)</th>
<th>CIP</th>
<th>CLIN</th>
<th>LEV</th>
<th>OFX</th>
<th>A-80556</th>
<th>SPAR</th>
<th>TEM</th>
<th>TOS</th>
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</thead>
<tbody>
<tr>
<td>M. chelonei (25)</td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>&gt;8</td>
<td>&gt;8</td>
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<td>MIC&lt;sub&gt;90&lt;/sub&gt;</td>
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</tr>
<tr>
<td></td>
<td>MIC range</td>
<td>4–8</td>
<td>0.25–&gt;8</td>
<td>4–&gt;8</td>
<td>4–&gt;8</td>
<td>1–&gt;8</td>
<td>8–&gt;8</td>
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<td>MBC&lt;sub&gt;90&lt;/sub&gt;</td>
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<tr>
<td>M. fortuitum (25)</td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>1</td>
<td>0.5</td>
<td>2</td>
<td>2</td>
<td>8</td>
<td>0.5</td>
<td>2</td>
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<tr>
<td></td>
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</tr>
<tr>
<td></td>
<td>MIC range</td>
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<td>0.03–2</td>
<td>0.25–&gt;4</td>
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<td>0.03–2</td>
<td>0.5–8</td>
</tr>
<tr>
<td></td>
<td>MBC&lt;sub&gt;90&lt;/sub&gt;</td>
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<td>2</td>
<td>4</td>
<td>&gt;4</td>
<td>&gt;8</td>
<td>2</td>
<td>8</td>
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<tr>
<td>M. kansasii (20)</td>
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<td>8</td>
<td>2</td>
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<td>MIC range</td>
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<td>0.5–&gt;8</td>
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<td>&gt;8</td>
<td>4</td>
<td>8</td>
<td>&gt;8</td>
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<tr>
<td>M. scrofulaceum (25)</td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
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<td>2</td>
<td>1</td>
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<td>8</td>
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</tr>
<tr>
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<td>MIC range</td>
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<td>0.5–&gt;8</td>
<td>0.5–4</td>
<td>1–&gt;4</td>
<td>2–&gt;8</td>
<td>0.125–&gt;8</td>
<td>0.5–4</td>
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<td>&gt;8</td>
<td>&gt;4</td>
<td>&gt;4</td>
<td>&gt;8</td>
<td>4</td>
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</tbody>
</table>

Abbreviations: CIP, ciprofloxacin; CLIN, clinafloxacin; LEV, levofloxacin; OFX, ofloxacin; SPAR, sparfloxacin; TEM, temafloxacin; TOS, tosufloxacin.

Table IV. Comparative activity (mg/L) of AM 1155, a new quinolone, against mycobacteria (data from Tomioka et al.30)

<table>
<thead>
<tr>
<th>Test species</th>
<th>No. of strains</th>
<th>Test agent</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;</th>
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</thead>
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<tr>
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<tr>
<td></td>
<td></td>
<td>sparflaxacin</td>
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<td></td>
<td></td>
<td>ofloxacin</td>
<td>0.78</td>
<td>3.13</td>
</tr>
<tr>
<td>M. marinum</td>
<td>10</td>
<td>A M 1155</td>
<td>1.56</td>
<td>1.56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sparflaxacin</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>ofloxacin</td>
<td>12.5</td>
<td>25</td>
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<tr>
<td>M. scrofulaceum</td>
<td>19</td>
<td>A M 1155</td>
<td>3.13</td>
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<td>12.5</td>
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<td></td>
<td></td>
<td>ofloxacin</td>
<td>12.5</td>
<td>25</td>
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<tr>
<td>M. fortuitum</td>
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<td>0.2</td>
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<td>ofloxacin</td>
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<td>3.13</td>
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<td>M. abscessus</td>
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<td>&gt;100</td>
<td>&gt;100</td>
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<td></td>
<td></td>
<td>ofloxacin</td>
<td>&gt;100</td>
<td>&gt;100</td>
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<td>sparflaxacin</td>
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<td></td>
<td></td>
<td>ofloxacin</td>
<td>12.5</td>
<td>50</td>
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</table>

quinolone derivative, DU -6859a, against several species of pathogenic mycobacteria, by an agar dilution method (7H 11 medium). Although the MIC for M. avium strains was 12.5 mg/L, those for other species, including M. marinum and M. fortuitum were <1.56 mg/L. The MIC for M. chelonei was 6.25 mg/L. The authors also recorded some modest activity of the compound in mice infected with Mycobacterium intracellulare.

Bauernfeind,32 in a comparative study of the new quinolone, BAY y3118, tested a number of quinolones against single strains of several mycobacterial species, including M. kansasii, M. scrofulaceum, M. gordonae, M. xenopi, Mycobacterium flavescens, Mycobacterium terrae, M. avium, M. fortuitum and Mycobacterium nonchro -
mogenicum and found that against those species sensitive to quinolones, BAY y3118 was the most active agent with MICs of <1 mg/L. Ciprofloxacin, sparflaxacin and CI-960 were also highly active. These findings were confirmed by R avizzola et al., who showed that BAY y3118 had good activity against M. tuberculosis (82 strains), M. avium (51 strains) and five strains of other mycobacteria.

A new quinolone to show antitubercular activity is irloxicin (E-3432), a new quinolone derivative in which a pyrrol group is substituted for the piperazine group in position 7. This compound showed in-vitro activity comparable to that of ciprofloxacin against M. tuberculosis but was less active against M. chelonei.

New quinolone derivatives will undoubtedly appear as structure–activity relationships become more clearly understood. At present, of the newer derivatives, only sparflaxacin has been used in clinical practice. So far, acquired resistance, although described for ofloxacin in the case of M. tuberculosis, has not been noted for other mycobacteria.

Other agents

There is a range of other agents that have been described as having antitubercular activity (usually on the basis of activity against M. tuberculosis and/or M. avium only) but most have not been tested against less common mycobacteria. Such agents may well have significant clinical potential. They include: (i) oxazolidinones, a new class of antimicrobial compounds acting as specific inhibitors of bacterial protein synthesis. Kilburn and co-workers synthesized a series of multi-cyclic fused ring oxazolidinones and showed that many of them had potent activity against M. tuberculosis, including multi-drug resistant strains (MICs ≤1 mg/L); (ii) gangamicin, also called azaquinone, is recently synthesized analogue of the ubiquinone (coenzyme Q10) that acts as an inhibitor of cell wall synthesis. It has good in-vitro activity against M. tuberculosis (MIC = 0.12 mg/L) and M. avium strains (MICs 2–8 mg/L), as well as useful activity against these organisms in mouse and human macrophages; (iii) rimenophenazine compounds, such as clofazimine, are the focus of renewed interest for the treatment of multi-drug resistant tuberculosis. Reddy et al. investigated the activities of clofazimine and two analogues (B 4154 and B 4157) against 20 strains of M. tuberculosis including 16 drug-resistant strains. All strains were susceptible to both analogues (MIC $90 = 0.5$ and 0.12 mg/L respectively), but one strain was moderately resistant to clofazimine. Of the two analogues, B 4154 showed better intracellular activity and performed as well as clofazimine in mice at doses of 20 mg/kg. None of the compounds were tested against lesser known mycobacteria although, in the author’s experience, clofazimine is active against some strains and such compounds may well be useful for the treatment of other mycobacterial infections; (iv) M-fluorophenylalanine (an inhibitor of mycoside-c biosynthesis) functions, like ethambutol, as an enhancer of the susceptibility of M. avium to other antimycobacterial agents. It may have a potential role in the treatment of other mycobacterial infections; (v) phenothiazines: trifluoroperazine, a calmodulin antagonist, has been shown to be active against M. bovis and M. avium, while chlorpromazine has been shown to inhibit the replication of M. tuberculosis and M. avium at concentrations of 0.23–3.6 mg/L in a human macrophage cell system and to interact synergically with several antimycobacterial agents, but not with ethambutol. The mechanism of action of these compounds is not known, but both may have potential against mycobacteria; (vi) acridinones have shown in-vitro activity against a variety of microorganisms, including Mycobacterium smegmatis, and may prove to be of value as antimycobacterial agents.

Animal models

There are no established animal models for infections caused by many of the less common mycobacteria. Some workers have tested a few compounds in macrophage cell systems, but in-vitro activities of new compounds (in cell-free systems) may not correlate well with results in cell cultures or in animal models. Shiratsuchi et al. have recently shown, in a study of the activity of 47 quinolones against M. avium strains, that there was poor correlation between MICs in the cell free system and inhibitory activity within monocytes.

Helm et al. compared topical ciprofloxacin, clarithromycin and amikacin with vancomycin in the treatment of M. fortuitum keratitis in an animal model. All three regimens significantly reduced the numbers of organisms in the eye compared with untreated controls.

Treatment of infections due to less common mycobacteria

Clinical experience

There are few data available on clinical trials of these newer agents. The British Thoracic Society is at present organizing a trial of the treatment of pulmonary infection with opportunist mycobacteria (M. xenopi, M. malmoense and M. avium complex) in which four regimens will be compared: rifampicin + ethambutol + ciprofloxacin, rifampicin + ethambutol + clarithromycin, and either regimen with intradermal injections of M. vaccae four times in the first six months (I. A. Campbell, personal communication). Guidelines for clinical trials of new antimycobacterial agents were laid down by a joint Federal Drugs Agency/Infectious Diseases Society of America Working Group in the USA and give valuable help for other future studies.

Patel et al. reviewed a total of 82 cases, including four of their own, of infections caused by nontuberculous myco-
bacteria in solid organ transplant recipients. Of the patients, 67% presented with involvement of skin, soft tissue, bone and/or joints and 28% had pulmonary infections. Of patients with M. kansasii infection, those treated with three drugs (usually rifampicin, isoniazid and ethambutol, sometimes with the addition of ciprofloxacin or pyrazinamide) did better than those given only two agents. In the case of patients with M. haemophilum infection, treatment regimens varied widely from minocycline and ethambutol to rifampicin + isoniazid + ethambutol + minocycline. A II patients were eventually cured. Twenty-one cases of M. fortuitum/M. chelonei infections in renal transplant patients were reviewed. Some had a combination of surgical excision with antimicrobial therapy, others had antimicrobial therapy alone. Regimens included co-trimoxazole + minocycline + ethambutol; rifampicin with cefoxitin, ciprofloxacin, sulphisoxazole, kanamycin or co-trimoxazole; and isoniazid + ethionamide. Virtually every patient had a different regimen. Not all of the clinical outcomes were documented; it appeared that there was no clear correlation with individual agents but that patients did best if treatment was given for more than a year. Earlier discontinuation led to reactivation of disease.

Patel et al. also reviewed 14 renal transplant patients with assorted other mycobacterial infections (including those caused by M. avium complex, M. xenopi, M. marinum, M. scrofulaceum, and M. gastri). Virtually all received isoniazid and ethambutol, often with rifampicin. Most patients recovered; two died. There was no correlation between outcome and regimen. In the case of 22 heart transplant patients with infections caused by a variety of mycobacteria (including M. kansasii, M. avium complex, M. fortuitum and M. scrofulaceum), almost all received rifampicin + isoniazid, sometimes with other agents including co-amoxiclav. The outcome was not documented in all patients but some deaths occurred in patients on multiple agents, although details of duration of therapy were not given. The only ‘new’ agent that was used as part of the treatment regimen was clarithromycin (in one patient, who responded).

Bernard et al. studied the activity of a variety of agents against 17 isolates of M. haemophilum from 12 patients and discussed the clinical course of two patients. One responded to 12 months’ treatment with multiple agents including ethambutol, isoniazid, rifampicin, doxycycline, ciprofloxacin and amikacin but relapsed when treatment was stopped because of abnormal liver function tests. The other patient was initially treated with isoniazid, ethambutol and rifampicin, followed by several months of treatment with rifabutin, clofazimine, ciprofloxacin and amikacin, together with clarithromycin for a brief (unspecified) period. Later isolates from this patient were resistant to rifampicin and rifabutin (MICs both > 16 mg/L) but sensitive to clarithromycin (MIC = 1 mg/L). The authors stress the need for prolonged therapy and for follow-up cultures in patients who relapse. Kiehn & White, reviewing the world literature on M. haemophilum infections, give details of a total of 40 patients. In general, isolates were sensitive to amikacin, ciprofloxacin, clarithromycin, rifabutin and rifampicin, and resistant to ethambutol, ethionamide, isoniazid and streptomycin. Of the 40 patients, five with adenitis were treated by excision of the affected gland(s) and all resolved. The remaining patients were treated by a variety of regimens which included the following: ethambutol + isoniazid + streptomycin (or rifampicin), sometimes with a tetracycline; isoniazid + rifampicin; co-trimoxazole + doxycycline + sulphamethoxazole; ciprofloxacin + doxycycline + minocycline; PAS + rifampicin; erythromycin + minocycline + rifampicin; amikacin + ciprofloxacin + clarithromycin + ethambutol + isoniazid + minocycline + rifampicin. Most patients responded. Six patients responded then relapsed; one patient died and the infection persisted in a further six patients. There was no obvious correlation between treatment regimen and clinical outcome. The authors cite a further two patients in whom resistance to the rifamycins developed while on multiple therapy. In general they advise that therapy should be with at least two agents (they suggest ciprofloxacin with rifampicin) and that it should be continued for at least a year.

There have been no trials of prophylaxis for infections due to these organisms but O pravil et al. suggested that, on the basis of retrospective analysis of a trial of 501 HIV-positive patients, the use of a dapsone/pyrimethamine regimen for prophylaxis against Pneumocystis carinii pneumonia and toxoplasmosis also reduced infection with mycobacteria (including M. genavense). They suggested that this regimen merited further trials in HIV-positive patients.

Drug combinations
Most patients with mycobacterial infection are treated with combinations of drugs, but there are very few in-vitro studies of combinations involving newer agents. A review of the interaction of quinolones with other antimicrobial agents merely noted that pefloxacin, ofloxacin and ciprofloxacin showed synergy with standard antimycobacterial agents against M. fortuitum and M. chelonei.

Fitzgerald et al. noted that a combination of clarithromycin and ciprofloxacin was effective in a case of cutaneous infection due to M. abscessus and, in a review of infections due to ‘mycobacteria other than tuberculosis’, Wolinsky advocated combinations of clarithromycin and ciprofloxacin as part of treatment regimens in a wide range of mycobacterial infections. There are no clinical trials.

Adjuncts to therapy
Broadley et al. have recently shown that ethambutol potentiates the effects of two antiseptics (chlorhexidine...
Treatment of less common mycobacteria

diacetate and cetylpyridinium chloride) on mycobacteria. The mechanism of this effect is not clear, but it is analogous to the enhancement of M. avium drug susceptibility by ethambutol and by the compound m-fluorophenylalanine (an inhibitor of mycoside-c biosynthesis). Further studies are needed to investigate the mechanisms and therapeutic potential of such 'enhancers' of antimycobacterial drugs.

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References


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B. Watt