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Risk-Benefit Assessment of Therapies for *Mycobacterium avium* Complex Infections

David E. Griffith

Center for Pulmonary Infectious Disease Control, The University of Texas Health Center at Tyler, Tyler, Texas, USA

Contents

Abstract . . . 137
1. Drug Toxicities and Drug-Drug Interactions . . . 139
   1.1 Cytochrome P450 Inducers . . . 139
   1.2 Cytochrome P450 Inhibitors . . . 141
2. Treatment of *Mycobacterium avium* Complex Lung Disease . . . 142
   2.1 Clarithromycin . . . 142
   2.2 Azithromycin . . . 144
   2.3 Rifabutin . . . 145
   2.4 Surgery . . . 146
   2.5 Risk-Benefit Considerations . . . 146
3. Treatment of Disseminated *Mycobacterium avium* Complex Disease . . . 147
   3.1 Clarithromycin . . . 147
   3.2 Azithromycin . . . 148
   3.3 Rifabutin . . . 148
   3.4 Combination Therapy . . . 148
   3.5 Risk-Benefit Considerations . . . 149
4. Conclusions . . . 150

Abstract

Mycobacterium avium complex (MAC) is an important pathogen that can cause chronic lung disease in immunocompetent patients and disseminated disease in patients with the acquired immunodeficiency syndrome (AIDS). Treatment of MAC with antituberculosis drugs was unsatisfactory, but the introduction of the newer macrolides, clarithromycin and azithromycin, and of rifabutin has greatly improved the outcome of treatment regimens for MAC. However, these agents are also associated with many new treatment-related adverse effects and potential drug-drug interactions.

Rifamycins [rifampicin (rifampin) more than rifabutin] induce cytochrome P450 enzymes and accelerate the metabolism of clarithromycin and HIV protease inhibitors. Conversely, clarithromycin inhibits these enzymes, resulting in increased rifabutin toxicity. The net results are treatment regimens that may be extremely difficult to tolerate, especially for elderly or debilitated patients. Clarithromycin and azithromycin must be administered in combination with other

agents such as ethambutol to prevent the emergence of macrolide resistance. Unfortunately, not all patients respond to the combination of a macrolide, rifabutin and ethambutol, and many have significant adverse effects (mostly gastrointestinal) with this regimen. For some patients the treatment is worse than the disease. The same 3-drug regimen is also effective therapy for disseminated MAC in AIDS patients, in whom the additional problem of a rifamycin/protease inhibitor interaction may be present. Fortunately, as opposed to pulmonary MAC disease in immunocompetent patients, disseminated MAC disease is a diminishing problem because of effective prophylactic regimens for MAC and improved antiretroviral therapy for HIV.

Significant progress has been made in the treatment of MAC disease with the introduction of the newer macrolides. It is to be hoped that even better drugs that are more active against MAC and are associated with less toxicity and drug-drug interactions will be introduced in the future.

Mycobacterium avium complex (MAC) emerged in the 1980s as an important pathogen in 2 settings. First, with the advent of the acquired immunodeficiency syndrome (AIDS) it was found that patients with far-advanced immunodeficiency developed disseminated MAC disease. Although other nontuberculous mycobacteria can also cause disseminated disease in patients with advanced AIDS, MAC was responsible for more than 90% of disseminated nontuberculous mycobacterial disease in these patients. There was debate initially about the significance of disseminated MAC infection and its impact on the prognosis of AIDS patients, because it occurred late in the course of AIDS and was frequently associated with other opportunistic infections. It has been shown subsequently, however, that disseminated MAC infection has a significant adverse effect on survival and that effective therapy of MAC improves survival.[1]

Secondly, MAC had long been recognised as a cause of cavitary mycobacterial lung disease, usually in men with pre-existing lung conditions such as chronic obstructive pulmonary disease. The prevalence of MAC lung disease was not known with certainty, but was thought to be relatively rare.[2] However, the spectrum of MAC lung disease was broader than had been appreciated.[3,4] Patients with MAC lung disease included an unlikely population, elderly nonsmoking women without underlying lung disease. These patients developed a noncavitary form of lung disease with mid and lower lung field nodular and reticular-nodular infiltrates associated with bronchiectasis.[3,4] The use of high resolution computed tomography scanning of the chest greatly facilitated the diagnosis of this form of MAC lung disease.[4] The recognition of MAC as a significant pathogen in this population also emerged slowly, since MAC was frequently considered a 'coloniser' of the tracheobronchial tree. With careful long-term clinical follow-up, it became clear that what was considered 'colonisation' was, in reality, a slowly progressive process characterised by chronic, progressive and unrelenting symptoms.[3,4] Although the exact incidence of MAC lung disease, both cavitary and noncavitary, remains unknown, it is probably much higher than previously estimated.

Prior to the AIDS epidemic, MAC disease (usually lung disease) was treated with 4 to 6 antituberculosis medications with variable success but predictable toxicity. The long-term results of treatment of MAC lung disease with antituberculosis drugs are difficult to assess, partly because these studies had high dropout rates associated with medication toxicity and high mortality, so that treatment results were frequently based on a small fraction of the patients initially evaluated. Overall, early sputum conversion rates ranged from 40 to 90%, but long-term sputum conversion rates were probably,

at best, 40 to 50%.[5-12] Early studies evaluating antituberculosis drug therapy for disseminated MAC in AIDS patients were also generally disappointing. The emergence and subsequent recognition of MAC as a frequent, significant pathogen did result in considerable pressure for the development of new MAC treatment strategies.

The introductions of the newer macrolide clarithromycin, the closely related azolid azithromycin, and rifabutin, a rifamycin closely related to rifampicin (rifampin), were the most important advances in the treatment of MAC disease since the introduction of rifampicin and ethambutol decades ago. Because of the close structural similarity of azithromycin to the macrolides, azithromycin will be considered here as a macrolide. The structural differences between clarithromycin and azithromycin versus the parent compound erythromycin result in major improvements in pharmacological behaviour and antimycobacterial activity, such as longer half-life, dramatically increased concentration in phagocytes and tissues and enhanced *in vitro* activity against MAC, which surpasses that of any previously available antimicrobial agent.[13-15] Rifabutin is also concentrated in tissues and is more active than rifampicin against MAC *in vitro*.[16]

Clofazimine and the newer fluoroquinolones ofloxacin and ciprofloxacin, are not included in the following discussion because, although these agents are sometimes used to treat MAC infections, they have no proven efficacy in either disseminated or pulmonary MAC disease.[17,18] These agents, especially clofazimine, have significant toxicities but no established role in the treatment of MAC infections.

Although the macrolides and rifabutin have provided improved efficacy compared with antituberculosis drugs such as isoniazid, rifampicin, ethambutol, ethionamide, streptomycin and *p*-aminosalicylic acid for treatment of MAC disease, the range and severity of potential medication toxicity has also changed dramatically. Clarithromycin and azithromycin were approved for short-term use and initially there was little information about toxicity related to long term administration. All studies of macrolides administered over long periods of time for any form of MAC disease have demonstrated that these agents are associated with frequent, and sometimes intolerable, adverse effects. It also became clear that in addition to individual toxicities, combination drug regimens, especially those containing both clarithromycin and rifabutin, magnified toxicities because of drug-drug interactions that could result in unexpected, severe and limiting adverse effects.

The following discussion will summarise the efficacy of recent drug treatment trials for pulmonary and disseminated MAC infections with special emphasis on adverse events and toxicities. Recent studies evaluating macrolide-containing regimens for MAC lung disease involve nonrandomised noncomparative trials. The results of these studies should be assessed and compared carefully. These trials also include generally elderly, frail and chronically ill patients, which has an important impact on the number and severity of drug-related adverse events. The benefits of treatment for MAC infection are very clear for some patients, but frustratingly ambiguous in others. It is, therefore, entirely appropriate to discuss the treatment of MAC disease in the context of a risk-benefit analysis.

1. Drug Toxicities and Drug-Drug Interactions

All of the drugs currently used in the treatment of MAC disease have significant potential toxicities that are summarised in table I. Some of the toxicities were unanticipated but gained importance because of the long-term treatment strategies required. For instance, bitter taste (taste perversion, metallic taste) is reported as an uncommon adverse effect with short-term clarithromycin administration. With long-term administration at comparable dosages, however, bitter taste is a common complaint, although rarely dose limiting.

1.1 Cytochrome P450 Inducers

Pharmacokinetic drug interactions are an equally important management issue for patients

Table I. Adverse events associated with medications for *Mycobacterium avium* complex infections

Clarithromycin	Bitter taste, anorexia, nausea, vomiting, abnormal hepatic enzymes, decreased auditory acuity, hypersensitivity reactions
Azithromycin	Diarrhoea, nausea, vomiting, anorexia, abnormal liver enzymes, decreased auditory acuity, hypersensitivity reactions
Rifabutin	Nausea, vomiting, anorexia, abnormal hepatic enzymes, polyarthralgia, polymyalgia, hyperpigmentation, leucopenia, thrombocytopenia, anterior uveitis, hypersensitivity reactions
Rifampicin (rifampin)	Nausea, vomiting, anorexia, abnormal liver enzymes, hypersensitivity reactions, flu-like syndrome, thrombocytopenia, renal failure
Ethambutol	Optic neuritis with loss of red-green colour discrimination and/or loss of visual acuity

with MAC disease and are summarised in table II. The most important interactions are those that occur at the level of the cytochrome P450 (CYP) isoenzyme pathway of hepatic drug metabolism. Rifampicin and rifabutin are potent inducers of several CYP isoenzymes (rifampicin more than rifabutin) and may produce rapid elimination of drugs, resulting in subtherapeutic concentrations in plasma. For instance, in elderly patients with MAC lung disease receiving clarithromycin as monotherapy, serum clarithromycin concentrations averaged 5.4 ± 2.1 mg/L.[19] When clarithromycin was administered with rifampicin or rifabutin, mean serum concentrations of clarithromycin were markedly decreased to 0.7 ± 0.6 and 1.5 mg/L, respectively.[19] The clinical consequences of this reduction in plasma concentration of clarithromycin are uncertain. High tissue and intracellular concentrations of clarithromycin are achieved and measurement of the concentrations of the drug in peripheral blood may not adequately reflect its antimycobacterial efficacy. No study has yet demonstrated that either combination leads to increased treatment failure rates or that either rifamycin promotes the emergence of macrolide-resistant MAC isolates.

The HIV protease inhibitors are metabolised in the liver, primarily by the isoenzyme CYP3A4, and they are therefore also susceptible to significant drug interactions caused by CYP inducers (table II). Administration of saquinavir with the rifamycins, especially rifampicin, results in significant decreases in the area under the plasma concentration–time curve (AUC) of saquinavir, leading to lower serum concentrations that could reduce its antiretroviral effect.[20] Low protease inhibitor concentrations can lead to the development of HIV resistant to a specific protease inhibitor and, through cross-resistance, to the entire protease inhibitor class of drugs.[21]

Because of its profound effect on the protease inhibitor class of drugs, rifampicin is contraindicated for the treatment of tuberculosis in patients also receiving any of the protease inhibitors. For the same reason, rifampicin should not be used to treat MAC infection in AIDS patients receiving a protease inhibitor. Since rifabutin has a less profound effect on induction of hepatic enzymes, it can be administered at attenuated doses with selected protease inhibitors. Rifabutin does not appear to affect the AUC of ritonavir, and although the package insert for rotinavir states that the use of these 2 drugs together is contraindicated, the pharmacokinetic data suggest that they may be used together if the dosage of rifabutin is decreased to 150 mg/day.[22] Unfortunately, the effect of ritonavir on rifabutin metabolism also limits their coadministration (see section 1.2). Rifabutin at 300 mg/day when concomitantly administered with indinavir decreased the AUC of indinavir by 32%.[23,24] Based on the interaction, it has been recommended that the rifabutin dosage should be reduced to 150 mg/day for patients also receiving indinavir. Nelfinavir can also be used with rifabutin; however, the dosages of both indinavir and nelfinavir should be increased when these agents are used with rifabutin.[25,26]

Coadministration of rifamycins and the HIV non-nucleoside reverse transcriptase inhibitors (NNRTIs) also results in decreased AUC values for the NNRTIs.[27-29] As with the HIV protease inhibitors, rifampicin is also contraindicated for use in patients who are receiving NNRTIs.[20] Rifabutin, however, can be administered with nevirapine or

efavirenz.[28,29] Neither rifampicin nor rifabutin is recommended for coadministration with delavirdine.[26,30] It is unclear if dosage adjustments for rifabutin or the NNRTIs are routinely necessary when these drugs are used concomitantly.[26]

1.2 Cytochrome P450 Inhibitors

Competitive inhibition of CYP3A4 by clarithromycin results in an increase in rifabutin plasma concentrations by approximately 77% when the 2 drugs are administered concomitantly.[31] The principal clinical effect of the increased rifabutin concentrations is an increase in rifabutin toxicity, including severe toxicity such as uveitis. Azithromycin is not known to affect CYP enzyme activity and, therefore, a similar effect of azithromycin on rifabutin metabolism and toxicity has not been described.[32]

The protease inhibitors as a class are also CYP inhibitors. Ritonavir is the most potent inhibitor of CYP3A4 isoenzymes available. When combined with clarithromycin, ritonavir results in an increase in clarithromycin AUC of about 77%.[33] Although no dosage adjustment for clarithromycin is currently recommended for patients with normal renal function, the use of clarithromycin with ritonavir may be associated with an increase in adverse effects related to clarithromycin. Data regarding interactions with azithromycin and protease inhibitors are limited; however, since azithromycin is not principally metabolised via the CYP3A4 isoform, it is probably not significantly affected by the protease inhibitors.[32]

Table II. Major drug interactions with medications for *Mycobacterium avium* complex infections

Primary drug	Interacting drug	Effect	Recommended option
Cytochrome P450 inducers (increase hepatic metabolism)			
Rifampicin (rifampin)	Clarithromycin	Markedly reduced serum clarithromycin concentrations	Effect on treatment outcome unknown
Rifampicin	HIV protease inhibitors and NNRTIs	Reduced serum concentrations of protease inhibitors and NNRTIs	Rifampicin contraindicated with protease inhibitors and NNRTIs
Rifabutin	Clarithromycin	Reduced serum clarithromycin concentrations (less profound effect than rifampicin)	Effect on treatment outcome unknown
Rifabutin	HIV protease inhibitors and NNRTIs	Reduced serum concentrations of protease inhibitors and NNRTIs (less profound effect than rifampicin)	Rifabutin 150 mg/day indicated with indinavir and nelfinavir, contraindicated with ritonavir. Saquinavir soft gel capsule formulation and amprenavir probably not contraindicated with rifabutin. Rifabutin indicated with nevirapine and efavirenz but not delavirdine
Cytochrome P450 inhibitors (decrease hepatic metabolism)			
Clarithromycin	Rifabutin	Enhancement of rifabutin toxicity including uveitis	In combination with clarithromycin, rifabutin dosage not to exceed 150-300 mg/day with careful clinical monitoring
Clarithromycin	Rifampicin	No described enhancement of toxicity	No dosage adjustment required
Ritonavir	Clarithromycin	Variable	With normal renal function, dosage adjustment usually not necessary
Ritonavir	Rifabutin	Enhancement of rifabutin toxicity including uveitis	Concomitant use contraindicated
Indinavir	Rifabutin	Variable	Dosage adjustment
Indinavir	Rifabutin	Less profound effect than ritonavir	Rifabutin 150 mg/day with indinavir
Azithromycin			Not known to affect drug metabolism via this mechanism

NNRTIs = non-nucleoside reverse transcriptase inhibitors.

Administration of ritonavir with rifabutin resulted in a 4-fold increase in the AUC of rifabutin.[34,35] These increases were associated with an attendant increase in the occurrence of uveitis and other rifabutin-associated adverse events. Although it is probably reasonable to administer rifabutin with ritonavir from the perspective of the effect of rifabutin on protease inhibitor concentrations, it is not a good combination because of potential severe rifabutin toxicity. Indinavir is a reversible and less potent inhibitor of CYP3A4 than ritonavir, and the pharmacokinetic interaction of indinavir with rifabutin is less profound than that seen between ritonavir and rifabutin.[24] As previously noted, an adjustment in the dosage of rifabutin to one-half the standard dosage is necessary for patients receiving this combination. No dosage adjustment is currently recommended for patients taking indinavir and clarithromycin.

2. Treatment of *Mycobacterium avium* Complex Lung Disease

MAC lung disease has been and continues to be difficult to treat, for a number of reasons. Most importantly, effective drugs with significant *in vitro* activity against MAC have only recently been available. Because MAC was frequently viewed in the past as nonpathogenic and a 'colonising' organism, patients were (and regrettably still are) frequently diagnosed after long periods of disease progression, resulting in far advanced radiographic abnormalities. Medication regimens must be given for prolonged periods of time (18 to 24 months), which exaggerates toxicity and promotes noncompliance. Frequent adverse events and toxicity limit the ability of elderly patients to tolerate extended multidrug treatment regimens.

2.1 Clarithromycin

In an initial study of clarithromycin-containing regimens for treatment of MAC lung disease, Dautzenberg et al.[36] reported results from 45 patients treated with a mean of 1600 mg/day of clarithromycin for an average of 10 months. Clarithromycin was generally well tolerated at this relatively high dosage. Patients received either clarithromycin monotherapy or combination therapy that included clofazimine, a quinolone, ethambutol and/or rifampicin. At 3 months, 36 out of 39 patients (92%) were sputum culture–negative. At 12 months, 32 out of 38 (81%) remained culture-negative. The investigators in this study concluded that the companion drugs appeared to offer no advantage over clarithromycin alone. It is difficult to explain the lack of emergence of clarithromycin-resistant MAC isolates in this study when it is compared with subsequent experience.

In an early trial, we studied high dose clarithromycin (1000mg twice daily) as monotherapy for patients with either MAC lung disease or *M. abscessus* lung disease.[37] All of the patients in this study were over 55 years of age and 85% weighed less than 70kg. Adverse events were noted in all (100%) patients with this dosage of clarithromycin. The majority of adverse events were gastrointestinal, including bitter taste (92%), nausea (92%) and other symptoms such as vomiting, anorexia, bloating and/or diarrhoea (92%). 10 patients with intolerable gastrointestinal adverse effects who had a reduction in dosage to 500mg twice daily had resolution of their dose-limiting gastrointestinal adverse effects. 5 patients (38%) developed abnormal liver enzymes, including elevated hepatic transaminases and alkaline phosphatase levels. In all patients with abnormal liver enzymes, discontinuation of the high dosage of clarithromycin with subsequent decrease in the dosage to 500mg twice daily was associated with a significant fall in the liver enzyme measurements. Other adverse events included tinnitus and dizziness, light-headiness, confusion or insomnia. It was our conclusion that elderly patients with MAC lung disease could not tolerate clarithromycin at 1000mg twice daily even as monotherapy.

Clarithromycin serum concentrations were obtained from 8 patients in this study.[37] At 1000mg twice daily, the mean value was 12.9 ± 3.6 mg/L with several samples exceeding 15 mg/L. Of the patients who discontinued the high-dosage therapy,

all had serum concentrations consistently above 12 mg/L. Only 2 patients were able to tolerate the high dose clarithromycin for a prolonged period and in neither of the 2 patients was a value above 12 mg/L documented. The high incidence of adverse events appear to have been dose- and serum concentration–related. In contrast, in 12 healthy elderly patients who received 5 doses of clarithromycin 500mg twice daily, peak clarithromycin concentrations averaged 3.3 mg/L.

We next evaluated an initial period of clarithromycin monotherapy at 500mg twice daily for 4 months with additional medications (rifabutin or rifampicin, ethambutol and streptomycin) added either at sputum conversion (if it occurred prior to 4 months) or after 4 months of clarithromycin monotherapy.[38] Of 19 patients with pretreatment clarithromycin-susceptible isolates, 58% became sputum-negative and 21% showed significant reductions in sputum positivity after 6 months of therapy. Overall, 18 of 19 patients (95%) showed an improvement in sputum cultures, chest radiographs or both. Of 19 isolates, 3 (16%) developed clarithromycin resistance, (minimum inhibitory concentration >32 mg/L) following the period of clarithromycin monotherapy. Adverse effects potentially related to clarithromycin were relatively common and included bitter taste (85%) and gastrointestinal adverse effects (70%). The gastrointestinal symptoms were generally mild, intermittent and of short duration. No patient interrupted or discontinued therapy because of these adverse events. Other adverse effects included tinnitus, a subjective change in auditory acuity and a general sense of malaise. No patient had a rise in liver enzymes on clarithromycin therapy. Serum concentrations of clarithromycin were obtained from 19 of the 20 patients who completed the study. 43 of 47 concentrations (92%) determined in patients receiving 500mg twice daily were between 3.4 and 11.5 mg/L.

From this study it was evident that clarithromycin 500mg twice daily as monotherapy, in contrast with 1000mg twice daily, was well tolerated and effective in MAC lung disease. However, when clarithromycin was administered as monotherapy, there was a significant risk of development of clarithromycin-resistant MAC isolates.

We next evaluated our first 50 patients treated with clarithromycin-containing regimens for MAC lung disease.[39] Most patients received clarithromycin 500mg twice daily with ethambutol, rifabutin or rifampicin and initial streptomycin. 39 patients received a minimum of 5 months of drug therapy. Of those 39 patients, 36 (92%) converted their sputum to negative and 32 (82%) remained culture-negative long term. Despite reduced clarithromycin serum concentrations in patients also receiving rifampicin, 10 out of 13 patients (77%) receiving this regimen were successfully treated. Although not directly compared with previous regimens containing antituberculosis drugs, the success of this regimen strongly suggested that it was more effective than previous non–clarithromycin-containing regimens. An editorial that accompanied publication of this study suggested that the results of this study represented '. . .the most important progress made in more than 20 years in treating MAC pulmonary disease'.[40]

Of these 50 patients, 11 (22%) failed to complete more than 3 months of clarithromycin therapy. 6 discontinued drugs because of suspected adverse drug reactions, including subjective hearing loss, hepatitis and severe fatigue. One or more companion drugs were discontinued in 16 of 39 (41%) of patients because of adverse events. 2 patients developed intolerance to both major companion drugs (rifabutin and ethambutol) and relapsed with clarithromycin-susceptible organisms after many months of negative cultures. Isolates from 6 out of 39 patients (15%) became clarithromycin-resistant. All of these patients had received an initial period of clarithromycin monotherapy.

In an effort to minimise cost and adverse effects of clarithromycin and companion drugs, we have studied intermittent (Monday-Wednesday-Friday; 'MWF') clarithromycin-containing regimens for MAC lung disease.[41] We enrolled 55 patients to receive clarithromycin 1000mg MWF with rifabutin or rifampicin and ethambutol. 16 patients

did not receive at least 6 months of therapy, 4 because of clarithromycin-related gastrointestinal adverse effects. Of the remaining 39 patients, 29 (73%) converted their sputum to negative within 6 months, results that are almost identical to previous results at 6 months with daily clarithromycin-containing regimens.[38] No MAC isolate from the 39 patients who completed 6 months of intermittent therapy developed clarithromycin resistance. Clarithromycin given 1000mg MWF was generally well tolerated. Severe toxicity requiring dosage adjustment was essentially limited to companion drugs, usually rifabutin.

2.2 Azithromycin

In our first study, 39 patients, of whom 87% were older than 55 years and 82% weighed less than 70kg, with MAC or *M. abscessus* lung disease received azithromycin 600 mg/day as initial monotherapy.[42] Adverse events occurred in 33 of 39 patients (85%), most commonly gastrointestinal symptoms (82%) and hearing impairment (26%). The majority of the gastrointestinal symptoms included diarrhoea or loose stools (62%), abdominal cramping (41%), anorexia (33%), unusual taste sensation (33%), nausea (28%), vomiting (18%) and abdominal bloating, gas and constipation (10%). 24 of 39 patients (62%) required a lower dosage or withdrawal of the drug. Decreasing the daily dosage to 300mg resulted in resolution of most adverse events.

Of the 39 patients, 10 (26%) complained of hearing impairment during therapy. Of these 10 patients, 9 underwent paired hearing tests showing a significant objective change in hearing. The mean serum concentration in patients who required a dosage reduction because of hearing impairment was 0.8 ± 0.4 mg/L, and that in patients whose reduction was necessitated by gastrointestinal symptoms was 0.7 ± 0.4 mg/L. In comparison, the mean serum concentration was 0.3 ± 0.16 mg/L in patients with no adverse events. Serum concentrations with monotherapy were comparable to concentrations after the addition of other antituberculosis drugs, including rifamycins (rifampicin or rifabutin).

In a study similar to our previous clarithromycin study, we evaluated an initial period of azithromycin monotherapy at 600 mg/day for 4 months with additional medications (rifabutin or rifampicin, ethambutol and streptomycin) added either with sputum conversion (if it occurred prior to 4 months) or after 4 months of azithromycin monotherapy.[38,43] Of 29 patients, 23 completed at least 6 months of therapy. Only 2 of 6 patients did not complete 6 months of therapy because of adverse events. Cultures of sputum converted to negative in 67% of patients after 6 months, which was comparable to the previous clarithromycin study.[38] Macrolide resistance did not develop in any MAC isolates during this study.

Adverse effects related to azithromycin were common. For patients who completed 6 months of therapy, 95% had at least 1 adverse event. Gastrointestinal complications (most commonly loose stools and/or diarrhoea) occurred in 87%, and subjective decreases in hearing occurred in 52%, of patients who completed the study. The high incidence of adverse events suggested that azithromycin should be given at lower dosages or less frequently.

We have also studied two intermittent (MWF) azithromycin-containing regimens for MAC lung disease.[44] We enrolled 21 patients to receive azithromycin 600mg MWF with daily companion drugs (ethambutol, rifabutin or rifampicin) or 47 patients who received azithromycin 600mg MWF with companion drugs also administered MWF. Only 1 patient (5%) receiving the first regimen and 4 patients (9%) receiving the second regimen dropped out because of adverse events before completing at least 6 months of therapy. Sputum conversion rates were comparable to previous studies using daily azithromycin or clarithromycin.[38,43] No MAC isolate developed clarithromycin resistance (the standard macrolide for *in vitro* testing) with these intermittent regimens. 6 patients (total from both regimens) required a decrease in azithromycin dosage to 300mg MWF because of

gastrointestinal or auditory symptoms. As with the intermittent clarithromycin regimens, the most severe toxicity requiring dosage adjustment was usually due to rifabutin.

We have completed or are in the process of completing five studies utilising daily or intermittent clarithromycin- or azithromycin-containing regimens.[38,39,41,43-45] Although we have not directly compared the 2 macrolides in a head-to-head study and have not completed all the studies, so far daily clarithromycin administration in a multidrug regimen appears to be associated with the best overall treatment response.[39,45] Important questions remain, especially how best to minimise adverse events and maximise patient compliance.

2.3 Rifabutin

O'Brien et al.[46] evaluated rifabutin at dosages of 150, 300 and 450 mg/day in multidrug treatment regimens not containing a macrolide for patients with pulmonary MAC disease. They did not report uveitis or polyarthralgia in this population, even though 16% of these patients received 450 mg/day. The most important adverse events in their patients included hepatotoxicity (1.5%), haematological abnormalities (1.5%) and gastrointestinal symptoms (2.5%), all occurring at incidence rates well below those we subsequently found.

We evaluated high-dosage rifabutin (600 mg/day) in multidrug regimens for pulmonary MAC disease.[47] 26 patients received regimens that included rifabutin and either clarithromycin (15 patients) or azithromycin (11 patients). 77% of patients receiving rifabutin 600 mg/day experienced some adverse event and 54% experienced multiple adverse events. 58% of all patients receiving 600 mg/day required adjustment of therapy as a result of an adverse event. Essentially all patients experienced a fall in white blood cell and platelet counts. In spite of the frequent occurrence of leucopenia, only 3 patients (12%) required adjustment of therapy on this basis and only 1 (4%) required an adjustment because of thrombocytopenia. There were no episodes of opportunistic infection or bleeding complications. Discontinuation of rifabutin therapy predictably resulted in a rebound in the white blood cell or platelet count.

11 patients (42%) had gastrointestinal symptoms and 8 required a decrease in dosage or withdrawal of the drug. Adjustment in the dosage was associated with abatement of symptoms. 3 patients (12%) had abnormal liver enzyme measurements, of whom 1 (4%) required dosage adjustment. In 5 patients (19%) a diffuse polyarthralgia syndrome (without frank arthritis) developed and all 5 required at least temporary withdrawal of the drug because of this adverse event. Uveitis developed in 2 patients (8%), which resulted in discontinuation of therapy for both. Both of these patients were also receiving clarithromycin. The polyarthralgia syndrome and uveitis resolved within several weeks of discontinuation of rifabutin. Hyperpigmentation was noted in 4 patients (15%) and all 4 of the patients subsequently developed either diffuse polyarthralgia syndrome or uveitis.

Surprisingly, the type of adverse event requiring adjustment of therapy did not differ between patients who received clarithromycin or azithromycin with the exception of uveitis, which occurred only in patients receiving clarithromycin. On the basis of its lack of effect on hepatic enzymes, azithromycin would not be expected to augment rifabutin toxicity. These findings suggest that most rifabutin toxicity is not dependent on drug interactions. It was clear from this study that patients, especially those receiving clarithromycin, should not receive more than 300mg of rifabutin per day.

In a follow-up study, we treated 53 patients with lower dosages of rifabutin, either 300 mg/day, 600mg MWF or 300mg MWF as part of multidrug regimens containing either azithromycin or clarithromycin.[48] Statistically significant reductions in white blood cell counts and platelet counts occurred in patients who received rifabutin 300 mg/day and 600mg MWF, but not in patients who received rifabutin 300mg MWF. The severity and frequency of leucopenia also appeared to be related to the total dose of rifabutin administered. Again, rifabutin affected white blood cell and platelet

counts for patients taking azithromycin as well as clarithromycin. Therefore, the haematological abnormalities are not merely the result of a drug interaction.

2.4 Surgery

Surgical resection of limited (usually) cavitary MAC lung disease remains an important therapeutic option despite the availability of the macrolides and rifabutin.[49,50] The exact indications for surgery in MAC lung disease are not well defined, but include medication treatment failures (including the emergence of macrolide-resistant MAC isolates), destroyed (nonfunctional) lung, massive haemoptysis and adequate respiratory reserve to tolerate surgery. In our experience, surgery (usually upper lobe lobectomy) is highly effective with more than 90% of patients converting sputum to negative with continued post-operative administration of medication. It is also associated with frequent complications, including persistent air leak requiring surgical correction, bronchopleural fistulae and, on rare occasions, postoperative death (7%).[49]

Surgery is very effective for a small number of carefully selected patients. Morbidity is relatively high, even with experienced surgeons, but postoperative complications are generally manageable. Because of the frequent difficult complications, this type of surgery should be done only in centres with extensive experience of surgical treatment of mycobacterial lung disease.

2.5 Risk-Benefit Considerations

Table III outlines risk-benefit considerations for treatment of MAC lung disease.

Because therapy of MAC lung disease is frequently toxic and not always effective, there will be patients who have MAC isolated from a respiratory specimen, but who might not benefit from medical therapy. Patients who have transient or self-limited respiratory symptoms with a single smear-negative, MAC culture-positive sputum specimen, but who are otherwise asymptomatic with a normal chest radiograph and who subsequently have multiple other specimens that are acid-fast bacilli smear and culture-negative, do not require therapy. These patients probably do not have significant MAC lung disease. Certainly, these patients should have some clinical follow-up, including further sputum acid-fast bacilli analysis and chest radiographs, to confirm the lack of significant MAC lung disease.

Others, even with established MAC lung disease, might not benefit from MAC medications. These include patients who have severe co-existing medical problems that will limit life expectancy, or patients with severe or complicated medical problems where MAC medications might adversely affect other treatment regimens and, ultimately, the quality of a patient's life. A few patients who have significant hypersensitivity responses to either macrolides or rifamycins would not be candidates for the most aggressive and potentially toxic multidrug approach.

Some elderly patients with noncavitary MAC lung disease will have very slowly progressive disease that is not especially bothersome from a symptomatic standpoint and is not likely to affect life

Table III. Risk-benefit considerations for treatment of *Mycobacterium avium* complex (MAC) lung disease

- Macrolides (clarithromycin, azithromycin) should not be used as monotherapy because of the risk of developing macrolide-resistant MAC isolates
- The toxicity of clarithromycin and azithromycin is related to dosage and serum concentration. Dosages greater than clarithromycin 1000 mg/day and azithromycin 300 mg/day are poorly tolerated
- Rifabutin at dosages >300 mg/day is associated with frequent limiting adverse events. Elderly patients frequently require dosages of 150 mg/day or cannot tolerate rifabutin at all
- The effect of rifampicin (rifampin) to decrease serum clarithromycin concentrations is worrisome because of questions about efficacy and the possible emergence of macrolide-resistant MAC isolates
- The regimen with the highest sputum conversion rates includes daily clarithromycin, rifabutin and ethambutol
- In multidrug regimens for MAC lung disease, dosage adjustments are frequently necessary because of adverse events
- Close toxicity monitoring is required for all patients receiving treatment for MAC lung disease

expectancy. These patients also might not benefit from an aggressive medication approach. Selection of these patients requires clinical familiarity over a long period of time, in order to be sure that they have indolent disease and that they have few and relatively stable symptoms due to MAC disease. It would be impossible, for instance, to make a determination about whether or not a patient with MAC lung disease should have treatment withheld on the basis of 1 or 2 physician-patient interactions. Ideally, these patients should be identified after extensive follow-up, so that the physician is familiar with the pattern and severity of the patient's symptoms and has radiographic and microbiological documentation of the slow progression of their MAC disease. Certainly, if there is acceleration of the patient's MAC lung disease, either on a symptomatic, microbiological or radiographic basis, then the decision to treat the patient could and should be revisited. Overall, the worst mistake a clinician can make in a patient with MAC lung disease is not a delay in starting therapy. Rather, it is a lack of appropriate clinical and laboratory follow-up for a patient found to have a respiratory MAC isolate who then has significant progression of MAC lung disease without appropriate follow-up.

Finally, there will be patients, especially elderly patients, who regardless of the symptoms associated with MAC disease, the rate of progression of the disease or the extent of the disease on chest radiograph, will simply decide that the adverse effects of the medication are less tolerable than the symptoms associated with the MAC lung disease. An alternative approach for these patients might be a relatively nontoxic regimen for 'suppression' of the MAC lung disease; such a regimen might include 'low dosage' clarithromycin (≤500 mg/day) or azithromycin (≤300 mg/day) plus ethambutol (15 mg/kg/day). Although the efficacy of this approach is unproven so far in MAC lung disease, clarithromycin and ethambutol may be an effective regimen in disseminated MAC disease (see section 3.4).

3. Treatment of Disseminated *Mycobacterium avium* Complex Disease

3.1 Clarithromycin

Chaisson et al.[51] evaluated the efficacy of clarithromycin as monotherapy for disseminated MAC disease in 154 patients with AIDS. Patients were randomly assigned to 1 of 3 clarithromycin dosages: 500, 1000 or 2000mg, all given twice daily. At dosages of 1000 or 2000mg twice daily, patients had more rapid decline in bacteraemia than at 500mg twice daily. However, these higher dosages offered no advantage in clinical response or long-term outcome and were, in fact, associated with a higher incidence of unacceptable gastrointestinal adverse effects. For instance, 40% of the patients on the 2000mg twice daily dosage discontinued clarithromycin because of adverse events. Additionally, and surprisingly, mortality was greater at the 2 higher clarithromycin dosages, in spite of the faster clearance of MAC bacteraemia. The overall proportion of patients who failed to complete 12 weeks of therapy because of adverse events, death or withdrawal from the study was 58% for patients assigned to 2000mg twice daily, 43% for patients assigned to 1000mg twice daily and 28% for patients assigned to 500mg twice daily. The survival advantage of the 500mg twice daily dosage could not easily be explained, even accounting for differences in patient tolerance. Monotherapy with clarithromycin at any of the dosages tested was also frequently followed by clinical relapse with a clarithromycin-resistant MAC isolate. Although clarithromycin monotherapy was effective, the risk of developing macrolide-resistant MAC isolates precludes this approach.

Clarithromycin monotherapy has been utilised for prophylaxis against disseminated MAC infection in AIDS patients. Pierce et al.[52] studied 667 patients with AIDS assigned to receive either placebo or clarithromycin 500mg twice daily. The group receiving clarithromycin had a significantly lower incidence of MAC bacteraemia, as well as a significant improvement in survival, compared

with the placebo group. Clarithromycin was tolerated well at 500mg twice daily. An almost equal number of patients withdrew from the study because of adverse events from the placebo group as from the clarithromycin group, although the clarithromycin group did have a significantly higher incidence of gastrointestinal disturbances and taste perversion. For patients in the clarithromycin group who subsequently developed MAC bacteraemia, 11 of 19 had MAC isolates that were resistant to clarithromycin.

3.2 Azithromycin

Havlir et al.[53] studied azithromycin 1200mg once weekly versus rifabutin 300 mg/day or a combination of daily rifabutin and weekly azithromycin for prophylaxis against disseminated MAC in AIDS patients. The once-weekly azithromycin administration was associated with a significant decline in MAC bacteraemia compared with daily rifabutin. More patients assigned to once-weekly azithromycin or to the azithromycin/ rifabutin combination had adverse events than did those assigned to rifabutin monotherapy, primarily because of gastrointestinal adverse effects. Most gastrointestinal problems in the azithromycin-containing regimens did not result in discontinuation of the medication. The permanent discontinuation of study medications due to gastrointestinal problems was similar in all 3 medication groups. Dose-limiting toxic effects, in general, were most common in the patients receiving both azithromycin and rifabutin. Uveitis was a dose-limiting toxic event in 5 patients in the 2 rifabutin-containing regimens. Of 18 patients who developed MAC bacteraemia in spite of azithromycin prophylaxis, 2 had isolates resistant to azithromycin. None of the MAC isolates from patients who received the azithromycin/ rifabutin combination and who later developed disseminated MAC were macrolide-resistant. Although the 2-drug regimen was extremely effective for preventing disseminated MAC and preventing the emergence of macrolide-resistant MAC isolates, there were more dose-limiting toxic effects (primarily related to rifabutin) with the combination regimen than with either single-drug regimen.

3.3 Rifabutin

Rifabutin monotherapy has been tolerated well in HIV-infected patients even at high dosages. In a trial to investigate the possible antiretroviral activity of rifabutin, 16 HIV-infected patients received high dosage rifabutin monotherapy for up to 66 weeks.[54] Significant adverse events, such as arthritis/ arthralgia and uveitis, occurred only when the dosage of rifabutin was more than 1000 mg/day. Haematological abnormalities were also unusual. Hyperpigmentation (pseudojaundice) was almost universal at these high dosages but was not dose-limiting. Parenthetically, rifabutin had no antiretroviral activity.

Rifabutin is, however, effective as prophylaxis against disseminated MAC in HIV-infected patients. In 2 studies involving 566 AIDS patients who received rifabutin 300 mg/day as MAC prophylaxis, the incidence of MAC bacteraemia was decreased approximately 50% compared with placebo.[55] In a follow-up evaluation, it was also shown that rifabutin prophylaxis improved survival in those patients.[56] Rifabutin 300 mg/day was generally well tolerated. Therapy was discontinued because of adverse events in 16% of the rifabutin group and 8% of the placebo group.[55] Reasons for discontinuation of rifabutin were rash, gastrointestinal symptoms and neutropenia. No cases of uveitis were reported in this study. Havlir et al.,[57] however, did report uveitis as a rare occurrence in a similar population treated with rifabutin for prophylaxis against disseminated MAC.

3.4 Combination Therapy

Although rifabutin monotherapy is well tolerated by AIDS patients, combination regimens, including clarithromycin, produce therapy-limiting adverse events, especially uveitis, much more commonly. In a group of 59 HIV-infected patients receiving clarithromycin and rifabutin 600 mg/day

for disseminated MAC disease, 23 patients (40%) were reported by Shafran et al.[58] to have developed uveitis.

Shafran et al.[17] also compared 2 multidrug treatment regimens for MAC bacteraemia in AIDS patients. 229 patients with AIDS and MAC bacteraemia were assigned to receive either a 4-drug regimen of rifampicin 600 mg/day, ethambutol 15 mg/kg/day, clofazimine 100 mg/day and ciprofloxacin 750mg twice daily or a 3-drug regimen of rifabutin 600 mg/day, ethambutol 15 mg/kg/day and clarithromycin 1000 mg/day. The 3-drug regimen was clearly superior to the 4-drug regimen, with more rapid and frequent resolution of bacteraemia and improved survival. Unfortunately, 24 of the first 63 patients (38%) who received rifabutin 600 mg/day developed uveitis. The dosage of rifabutin was subsequently reduced to 300 mg/day and only 3 of 53 (6%) patients developed uveitis. This study demonstrated the efficacy of regimens also containing clarithromycin, as well as the increased incidence of rifabutin toxicity in such regimens.

The use of protease inhibitors in aggressive multidrug AIDS regimens could potentially affect this treatment approach. The 3-drug regimen outlined above (rifabutin, clarithromycin and ethambutol) is a regimen that could be administered in a slightly modified form with decrease in the rifabutin dosage to 150 mg/day and inclusion of the appropriate protease inhibitor. The efficacy of this approach has not been documented, however. Additionally, improvements in immune function produced by the newer potent antiretroviral regimens may eliminate the need for lifelong MAC therapy in some patients.

Elimination of the rifamycin component from MAC treatment regimens would significantly simplify the treatment of MAC in AIDS patients. Gordin[59] recently published results of a trial involving 198 AIDS patients comparing clarithromycin and ethambutol versus rifabutin, clarithromycin and ethambutol for treatment of disseminated MAC infection. There were no differences in bacteriological response or survival between patients receiving a regimen with or without rifabutin. Ward et al.[60] evaluated 37 AIDS patients with MAC bacteraemia who received either clarithromycin plus ethambutol or azithromycin plus ethambutol. Clearance of bacteraemia occurred in 85.7% of the clarithromycin-treated patients but in only 37.5% of azithromycin-treated patients.[60] Although the regimen of clarithromycin, rifabutin and ethambutol is effective for treating disseminated MAC in AIDS patients, the 2-drug combination of clarithromycin and ethambutol may be as effective with less potential drug-related toxicity.

3.5 Risk-Benefit Considerations

Table IV outlines risk-benefit considerations for the prophylaxis and treatment of disseminated MAC disease in patients with AIDS.

Because of improved survival in AIDS patients with disseminated MAC who receive appropriate therapy, the risk-benefit analysis for treatment of MAC disease in AIDS patients is less complicated than for patients with chronic MAC lung disease. Although adverse effects are relatively common, they may be better tolerated in AIDS patients because of the severe consequences of discontinuing

Table IV. Risk-benefit considerations for prophylaxis and treatment of disseminated *Mycobacterium avium* complex (MAC) disease

- Weekly azithromycin, daily clarithromycin and daily rifabutin are all effective as prophylaxis of disseminated MAC. Azithromycin may be the preferred agent because of no significant drug interactions and relatively low cost
- Macrolides (clarithromycin, azithromycin) should not be used as monotherapy for disseminated MAC disease because of the risk of developing macrolide-resistant MAC isolates
- Clarithromycin is not tolerated well and is not associated with improved outcome at dosages >1000 mg/day
- Rifabutin is not tolerated well at dosages >300 mg/day, especially if combined with clarithromycin
- The best current treatment regimen for disseminated MAC disease is clarithromycin, rifabutin and ethambutol. Clarithromycin and ethambutol without a rifamycin may also be effective
- Some HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can be given to patients receiving rifabutin. Dosage adjustment may be necessary for rifabutin and the antiretroviral drugs
- Close toxicity monitoring is required for all patients receiving treatment or prophylaxis of disseminated MAC disease

Table V. Monitoring of treatment and prophylaxis regimens for *Mycobacterium avium* complex disease

Drug	Monitoring required
Clarithromycin	Monthly[a] clinical status and hepatic enzymes
Azithromycin	Monthly[a] clinical status and hepatic enzymes
	Baseline auditory acuity, repeat as indicated
Rifabutin	Monthly[a] clinical status, hepatic enzymes, complete blood count
	Eye examinations as indicated
	Appropriate companion drug serum concentrations as indicated
Rifampicin	Monthly[a] clinical status, hepatic enzymes, complete blood count
	Blood urea nitrogen and serum creatinine as indicated
	Appropriate companion drug serum concentrations as indicated
Ethambutol	Monthly[a] red-green colour discrimination and visual acuity

a Monthly evaluation may not be necessary for the entire duration of therapy, depending on drug dosages, companion drugs and duration of clinical stability on a drug.

therapy. It is also unfortunately possible that some of these patients do not survive long enough to experience as many or as severe drug reactions as patients with chronic lung disease.

There are additionally at least 2 factors favourably affecting the incidence and treatment of disseminated MAC in AIDS patients. First, the introduction of new multidrug therapeutic regimens for AIDS, including protease inhibitors and NNRTIs, has reduced the number of patients with severe immunosuppression and very low CD4+ counts. The incidence of disseminated MAC in the AIDS population, therefore, is falling and will probably continue to decline, which will make toxic multidrug therapy for disseminated MAC less necessary. Secondly, for those patients who have advanced AIDS and very low CD4+ counts, effective prophylaxis against disseminated MAC is already available with the choice of at least 3 drugs with demonstrated activity in this setting: clarithromycin 500mg twice daily, azithromycin 1200mg weekly and rifabutin 300 mg/day.[52,53,55] Although data are still being accumulated, azithromycin appears to be associated with substantially fewer interactions than clarithromycin or rifabutin and, under some circumstances, these interactions may favour the use of azithromycin for long-term prophylaxis of MAC over the other 2 drugs. Unfortunately, disseminated MAC cannot be completely eliminated since some patients will fail even aggressive multidrug AIDS regimens with the development of progressive immunosuppression. In these patients, prompt institution of MAC chemoprophylaxis and when necessary, treatment of disseminated MAC will remain necessary.

4. Conclusions

The inclusion of the newer macrolides in multidrug regimens for treatment of MAC disease unquestionably improved treatment outcome for AIDS patients with disseminated MAC disease. These regimens also appear to improve outcome for patients with pulmonary MAC disease. The price for improved efficacy has been frequent and significant drug-related adverse events as a result of drug toxicities that are magnified by drug-drug interactions. All patients receiving therapy for MAC disease require close toxicity monitoring (table V). For some patients, especially frail elderly patients with MAC lung disease, the effectiveness of the drug regimen is moot because the treatment may be associated with worse symptoms than the disease, and therefore, be intolerable. Although the treatment of MAC disease has improved significantly in the last 10 years, for further improvement we must develop even better drugs with greater activity against MAC, less toxicity and fewer drug interactions.

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Correspondence and reprints: Dr *David E. Griffith,* Center for Pulmonary Infectious Disease Control, University of Texas Health Center at Tyler, 11937 US Highway 271, Tyler, TX 75708, USA.
E-mail address: griffith@uthct.edu