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THERAPEUTIC GUIDELINES FOR OPPORTUNISTIC INFECTIONS MYCOBACTERIUM AVIUM COMPLEX (MAC)

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Abbreviations: ART, antiretroviral therapy; AZM, azithromycin; CLA, clarithromycin; EMB, ethambutol; MAC, *Mycobacterium avium* complex; MAC-IRIS, *Mycobacterium avium* complex immune reconstitution inflammatory syndrome; DMAC, disseminated *Mycobacterium avium* complex; HAART, highly active antiretroviral therapy; NSAID, non-steroidal anti-inflammatory drug; PLWH, persons living with HIV; RCT, randomized controlled trial; RFB, rifabutin

MYCOBACTERIUM AVIUM COMPLEX (MAC)

I) PROPHYLAXIS

a) Indication and recommended primary MAC prophylaxis:

Indication: Primary MAC prophylaxis is recommended for non-pregnant persons living with HIV (PLWH) with an absolute CD4 count of <50 cells/ml *plus* either not taking ART or on a failing ART regimen (AI). It is not indicated for those with a CD4 <50 cells/ml who immediately start what would be expected to be an effective ART regimen (AII)[1]. Despite this recommendation, for those either not taking ART or on a failing ART regimen, the clinical imperative is the initiation of an effective ART regimen rather than MAC prophylaxis.

Before starting prophylaxis, the possibility of disseminated MAC (DMAC) infection should be excluded by clinical evaluation, including a mycobacterial blood culture. Although rarely used, patients who may be starting rifabutin for MAC prophylaxis should also be screened in order to exclude active tuberculosis, since rifabutin monotherapy would be expected to result in the development of rifampin-resistant *M. tuberculosis*.

Recommended primary prophylaxis1:

- Azithromycin 1200 mg once weekly (AI)

Alternative prophylaxis options:

- Clarithromycin 500 mg twice daily (or 1000 mg XL once daily, slow-release formulation) (AI), OR
- Rifabutin 300 mg daily (BI)

Discussion

i) Evidence supporting the recommendation against the routine use of MAC prophylaxis in PLWH with severe CD4 lymphopenia (< 50 copies/mL).

The need for initiating MAC prophylaxis in PLWH who are about to begin an ART regimen to which they are expected to respond favourably was questioned within the first few years after the introduction of highly active antiretroviral therapy (HAART) regimens[2]; more recent studies provided additional evidence confirming the safety of this approach[3,4]. In 2018, this prompted both the IAS-USA Panel guidelines and also the US Department of Health and Human Services guidelines to drop the recommendation for primary MAC prophylaxis in all patients with a CD4 count of <50 cells/mL[1,5].

For PLWH with a CD4 <50 cells/mL who are starting ART, there is no clear evidence for additional benefit from MAC prophylaxis for preventing DMAC, based upon two cohort studies[3,4] and the evaluation of a provincial MAC prophylaxis program.[2] The HIV Outpatient Study (HOPS) was a retrospective analysis of 369 patients from 10 HIV clinics in the US who were prescribed ART

when the CD4 count was <50 cells/mL, of whom 175 (47%) were prescribed MAC prophylaxis[3]. Among 71 (19%) patients who were virologically suppressed, including 41 who were not taking MAC prophylaxis, there were no MAC infections documented. In a Korean study of 157 PLWH with CD4 <50 cells/mL who initiated or continued ART, the incidence of DMAC was low and not significantly different between those receiving (n=33) and not receiving (n=124) prophylaxis, with 3.4 and 0.8 episodes per 100 patient-years (p=0.368), respectively[4].

The British Columbia azithromycin MAC prophylaxis program was evaluated over a two-year interval from 1996-1997, at which time the eligibility requirement was a CD4 <75 cells/mL.[2] An intent-to-treat analysis showed that the proportion of patients on triple-drug ART who developed DMAC after 12 months was not significantly different for those taking no prophylaxis (n=167) vs azithromycin (n=215) at 3.0% and 0.5% (p=.09), respectively[2]. In addition, at 12 months follow-up the mortality rates for the two groups were also not significantly different at 15.5% and 12.3% (p=0.127), respectively[2]. In contrast, in a pre-HAART era randomized controlled trial (RCT) (eligible for enrollment if CD4 <100 cells/mL), Oldfield et al[6] observed rates of DMAC among patients taking placebo vs azithromycin of 24.7% and 10.6% (hazard ratio 0.34; p=0.004), respectively. Although MAC-related mortality was reduced with MAC prophylaxis in the latter study, neither study showed an overall survival benefit with azithromycin prophylaxis.[2,6]

Among patients with a baseline CD4 count of <50 cells/mL who start and remain adherent to ART, a significant proportion of MAC events occurring within the first few months are localized disease, consistent with a diagnosis of MAC immune reconstitution inflammatory syndrome (IRIS), for which azithromycin and other MAC antimicrobials do not appear to be protective[2,7]. In a series of 51 patients with non-tuberculous IRIS (at least 84% of which were due to MAC), 21 (43%) were taking primary or secondary MAC prophylaxis at the time of MAC-IRIS diagnosis[7].

ii) Azithromycin prevents DMAC in patients with CD4 <50 cells/mL as demonstrated in two RCTs conducted in the pre-HAART era[6,8]. The incidence of DMAC in patients randomized to rifabutin or azithromycin or both drugs was 15.3, 7.6, and 2.8%, respectively[8]. In the same study, bacterial respiratory tract infections were also reduced with azithromycin[8]. However, combination prophylaxis (rifabutin plus azithromycin) is not recommended due to the lack of a survival benefit over monotherapy, cost, increased drug interactions and toxicity (AI)[9].

iii) Clarithromycin. The main disadvantages of clarithromycin prophylaxis include the greater pill burden and the finding that macrolide (clarithromycin and azithromycin) resistance is more likely to be present in cases of breakthrough MAC bacteremia compared to azithromycin prophylaxis (~29-58%[10,11] vs. 0-11%,[6,8] respectively). As for azithromycin, bacterial respiratory tract infections are also reduced with clarithromycin.[12]

iv) Rifabutin was the first drug demonstrated to have prophylactic efficacy for HIV-related DMAC.[13] However, rifabutin's disadvantages compared to the macrolides include reduced efficacy,[8] numerous drug interactions, and adverse effects (see IIId).

b) Secondary MAC prophylaxis (chronic maintenance therapy)

Due to a substantial risk of relapse, all PLWH with DMAC infection should continue to receive combination MAC therapy indefinitely (AII), unless all of the criteria listed below for discontinuing therapy are met (see Ic).

c) Discontinuing MAC prophylaxis

i) **Discontinuing primary MAC prophylaxis.** For PLWH who had previously started MAC prophylaxis at a CD4 count of <50 cells/mL, it can be safely discontinued at the time of starting an ART regimen which is expected to be effective, regardless of CD4 cell count (AI). However, primary MAC prophylaxis is not recommended for those who immediately begin ART (see Ia).

Discussion

The evidence supporting the recommendation not to use MAC prophylaxis for PLWH who have a CD4 <50 cells/mL and immediately begin ART is outlined above (Ia-i). Prior to 2018, the recommendation for discontinuing primary MAC prophylaxis applied to those who had started it when the CD4 count was <50 cells/mL, but then increased to >100 cells/mL for at least 3 months after initiating ART. This recommendation had been supported by the findings of two RCTs and observational studies involving national cohorts.[14,15,16,17] The combined data from the 2 RCTs showed that the MAC infection rate was very low at 0.16 event per 100 person-years of follow-up in those discontinuing prophylaxis.[14,15] Furthermore, the only 2 MAC infections identified in the prophylaxis discontinuation groups of these 2 trials were both atypical in that they were localized, involved the vertebral spine, and occurred late after ART initiation (43-65 weeks). These characteristics are most consistent with MAC-IRIS[7]. The benefits of stopping MAC prophylaxis include a reduction in pill burden, drug interactions, adverse effects, costs, and risk of developing bacterial resistance.[15]

ii) **Discontinuing secondary MAC prophylaxis.** PLWH may be considered for stopping chronic suppressive therapy for MAC if they meet all of the following criteria: sustained increase in CD4 to >100 cells/mL for at least 6 months with ART; completed ≥ 12 months of combination therapy for MAC; and remained free of signs or symptoms of MAC disease.

Discussion

A number of small observational studies have evaluated the risk of recurrent MAC disease among PLWH who have discontinued secondary MAC prophylaxis following a favourable response to the initiation of ART. A European study included 103 such patients, 2 of whom had documented recurrent MAC infection for an incidence of 0.9 per 100 person-years of follow-up (95% CI, 0.11 to 3.25 per 100 person-years)[18]. Other studies have reported similar low relapse rates following the discontinuation of secondary MAC prophylaxis[19,20,21]; and as for the discontinuation of primary MAC prophylaxis, the few relapses were often atypical, with localized disease consistent with MAC-IRIS.

d) **Restarting MAC Prophylaxis**

i) **Primary MAC Prophylaxis** should be restarted if the CD4 count is <50 cells/mL and the person is not pregnant and is not taking a fully suppressive ART regimen (AIII)[1].

ii) **Secondary MAC Prophylaxis** should be restarted if the CD4 count is <100 cells/mL and the person is not taking a fully suppressive ART regimen (AIII)[1].

II) DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Disseminated MAC (DMAC) is the most common form of HIV-related MAC disease. It should be suspected in the setting of CD4 lymphopenia (usually <50 cell/mL) in a patient presenting with symptoms which may include fevers, night sweats, fatigue, abdominal pain, diarrhea, and/or weight loss.[22,23] This is in contrast with MAC disease in various other patient populations in whom the disease location and symptoms most often involve the respiratory tract. Occasionally DMAC is detected in PLWH who have minimal or no symptoms. This became evident in the rifabutin prophylaxis RCTs (including PLWH with baseline CD4 of <200 cells/mL) in which 2.3% of PLWH who were enrolled already had unsuspected DMAC indicated by baseline blood cultures which were positive for MAC[13]. The percentage would have been higher if limited to those with CD4 counts <50 cells/mL. Associated laboratory abnormalities in DMAC may include anemia, hypoalbuminemia, and elevated alkaline phosphatase[23]. Hepatosplenomegaly or lymphadenopathy may be evident on physical examination or by abdominal imaging[24].

The diagnosis is usually confirmed by collecting 2 mycobacterial blood cultures which usually become positive within 1-2 weeks using currently available microbiology methodology. Less often is there a need for tissue biopsy (e.g., bone marrow, lymph node, small bowel); however, such specimens often become culture positive before the development of persistent mycobacteremia[25]. The detection of MAC in sputum or stool specimens may reflect colonization or invasive disease, has low sensitivity for disseminated disease, and has low utility in the diagnosis of AIDS-related DMAC[26].

Sometimes there may be delays in species identification for mycobacteria, making it difficult to determine the appropriate choice of initial treatment. However, among 357 PLWH in British Columbia with positive mycobacterial cultures from various clinical specimens, almost all were identified as MAC, including 298 with mycobacteremia (98% MAC), 82 bone marrow biopsies (99% MAC), and 19 intestinal biopsies (100% MAC)[27]. In contrast, this was not the case with 25 lymph node biopsies (72% MAC, 24% *M. tuberculosis*) and 96 sputum cultures (63% MAC, 18% *M. tuberculosis*, and 17% *M. kansasii*)[27], in which other species accounted for a substantial proportion of infections. These data guide the initiation of therapy according to the source of the positive culture when species identification is delayed.

MAC isolates should undergo susceptibility testing when first identified and in the presence of persistent or recurrent disease. Macrolide resistance is seldom encountered prior to initiation of treatment.[28] In a series of 98 isolates from patients with diverse underlying diseases including HIV, 98.8% were clarithromycin susceptible.[29]

Differential diagnosis. The clinical presentation of DMAC may resemble that of a wide range of other

opportunistic diseases in PLWH. Constitutional symptoms (e.g., fevers, night sweats, weight loss) and cytopenias may also be seen with other infections (e.g., tuberculosis, disseminated histoplasmosis, cryptococcosis, and bartonellosis) and neoplastic disorders (e.g., non-Hodgkin's lymphoma and multicentric Castleman disease). Gastrointestinal symptoms and signs should prompt consideration of other infections including cryptosporidiosis, isosporiasis, *Salmonella* spp. infection, and cytomegalovirus colitis.

III) TREATMENT

a) Indication and recommended treatment

Indication

Patients in whom MAC is recovered from normally sterile body fluids (e.g., blood) or tissue biopsy (e.g., bone marrow) have invasive MAC disease and require therapy.

Recommended treatment:

Combination therapy using a 2- or 3-drug regimen (AI):

- Clarithromycin 500 mg twice daily or 1000 mg XL once daily (slow-release formulation) (AI)

PLUS

- Ethambutol 15 mg/kg once daily

PLUS/MINUS

- Rifabutin 300 mg once daily

Alternative treatment:

- Azithromycin 500-600 mg once daily (AII)

PLUS

- Ethambutol 15 mg/kg once daily

PLUS/MINUS

- Rifabutin 300 mg once daily

Discussion

The first RCT including a macrolide-containing regimen (clarithromycin, ethambutol, and rifabutin) compared to the previous standard of care combination therapy (ciprofloxacin, ethambutol, rifampin, and clofazimine) demonstrated improved clinical outcomes with respect to survival (median 8.6 months vs 5.2 months) and clearance of MAC bacteremia in PLWH after 4 weeks of treatment (78% vs 40%, respectively, p<0.001).[30]

A randomized, placebo-controlled study of MAC bacteremia conducted in the pre-HAART era demonstrated that the addition of rifabutin (RFB) versus placebo to the combination of clarithromycin (CLA) and ethambutol (EMB) was associated with similar bacteriologic response at 16 weeks follow-up (63% vs 61%, p=0.81) and no survival benefit.[31] However, among patients who had a bacteriologic response at week 16, 1 of 44 (2%) in the rifabutin (3-drug) group demonstrated clarithromycin resistance compared to 6 of 42 (14%) in the placebo (2-drug) group (p=0.055). The conclusion from this study was that the addition of rifabutin may protect against the development of macrolide resistance

in those who respond to therapy[31]. The significance of this finding in the current era of ART is uncertain.

A smaller, open-label RCT of MAC bacteremia compared clarithromycin in combination with ethambutol, rifabutin, or both.[32] The 12-week microbiologic response rates were not significantly different among treatment groups; however, the relapse rates following a response to treatment with CLA + RFB, CLA + EMB, and CLA + EMB + RFB were 24%, 7%, and 6%, respectively ([CLA + RFB] vs [CLA + EMB + RFB], p=0.027)[32]. Between the 2-drug regimens evaluated in this study, CLA + RFB was shown to be less effective than CLA + EMB. There was also improved survival in the 3-drug arm of this study (vs both 2-drug arms), in contrast to the above-mentioned, larger, placebo-controlled RCT reported by Gordin et al.[31] The 3-drug regimen (CLA + EMB + RFB) is preferred for patients with more profound CD4 lymphopenia, advanced MAC disease, higher mycobacterial load (>2 $\log_{10}$ colony forming units/mL of blood), or in the absence of optimal ART (CIII).[1]

A double-blind RCT comparing azithromycin (AZM) + EMB versus CLA + EMB for treatment of MAC bacteremia included 125 PLWH enrolled between 1994-1998, most of whom did not receive HAART.[33] There was no significant difference in the proportion of patients who had a negative blood culture by week 24 (59% vs 61%, respectively, p=0.80) or in the mortality rate (69% vs 63%, p=0.73) between the two treatment arms. This study supports the rationale for the use of azithromycin as an alternative to clarithromycin in patients who have drug interactions or intolerance which may be more problematic with the use of CLA compared to AZM. In contrast, an earlier open-label RCT comparing the same two treatment combinations showed a lower rate of clearance of MAC bacteremia with AZM + EMB compared to CLA + EMB (37.5% vs 85.7%, p=.007).[34] However, this was a much smaller study, including only 37 evaluable patients.

b) Macrolide–resistant MAC and treatment failure

Clarithromycin, azithromycin, ethambutol, and rifabutin are the most effective and well- tolerated antimicrobials available for the treatment of DMAC. Results of in vitro susceptibility testing are predictive of therapeutic outcome with clarithromycin and azithromycin.[35] Some evidence supports a correlation between in vitro susceptibility testing of amikacin and clinical treatment outcome in HIV-negative patients.[36] However, such clinical outcome correlation studies are lacking for other drugs in the treatment of MAC, which makes interpretation of such results problematic. There are only tentative MAC susceptibility breakpoints for moxifloxacin and linezolid.[35] Susceptibility testing with respect to the macrolide class of drugs should be limited to clarithromycin.[35]

In general, all wild type (untreated) strains of MAC are macrolide-susceptible.[28] Consideration of second line drugs in a combination regimen is usually limited to patients with documented macrolide-resistant MAC (clarithromycin minimum inhibitory concentration [MIC] ≤8 mg/mL [susceptible], 16 mg/mL [intermediate], and ≥32 mg/mL [resistant])[35].

Constructing an alternate treatment regimen for documented macrolide-resistant MAC should ideally include 2 new drugs which the patient has not previously received. Options are limited but include: a quinolone (e.g., moxifloxacin, ciprofloxacin, or levofloxacin), rifabutin, ethambutol, and amikacin

(CII). Although unrelated to macrolide-resistant MAC, studies in HIV-related DMAC relevant to the choice of alternative treatment regimens include the following findings: a) no benefit with the addition of intravenous amikacin to a 4-drug oral regimen[37]; b) increased mortality with the addition of clofazimine to the combination of CLA plus EMB,[38] and c) increased mortality with the use of daily clarithromycin dosage of greater than 500 mg twice daily.[39] Other agents for which there is scant evidence for a role in macrolide-resistant DMAC include: ethionamide, cycloserine, linezolid, mefloquine,[40] and interferon-g.[41] Clofazimine should be avoided[38] (AI). Immune reconstitution with a fully suppressive ART regimen is the priority in macrolide-resistant DMAC, as for most other drug-resistant or untreatable opportunistic infections (AIII).

Patients who have persistent symptoms (e.g., fevers, fatigue, night sweats, weight loss) despite combination antimycobacterial therapy may benefit from a trial of corticosteroids (e.g., dexamethasone 2-4 mg daily).[42,43] However, the significance of these findings in the current era of ART is uncertain.

Lack of clinical response to combination MAC therapy in localized MAC infection (e.g., regional lymphadenitis) in the setting of MAC-IRIS is not uncommon with macrolide-susceptible MAC[7]. The role of antimycobacterial therapy in MAC-IRIS remains unclear; a tapering course of corticosteroids for inflammatory lesions may be more helpful than the addition of second line antimycobacterials.[7]

c) Monitoring response to therapy

Although not endorsed in other guidelines[1], consideration should be given to repeating a mycobacterial blood culture monthly until it becomes negative, given that symptoms may not reliably predict resolution of MAC bacteremia. Patients who are intolerant of or not responding to the standard treatment after a 4-week trial should have a repeat MAC blood culture and be considered for the addition of drugs not included in the initial regimen, particularly if a 2-drug regimen is being used. If a blood culture remains positive at this point, then clarithromycin susceptibility testing should be considered. However, if macrolide resistance develops, it typically occurs after the first couple of months of therapy[44]. If blood cultures have become negative but fevers continue, then other causes of fever should be considered, including other opportunistic infections and MAC-IRIS, assuming that ART had recently been started or revised.

d) Drug toxicity

Ethambutol ocular toxicity. Optic or retrobulbar neuritis may complicate the course of daily ethambutol therapy for MAC in up to 6% of patients[45], and it may not be reversible. Baseline visual acuity (Snellen chart) and colour vision testing should be done for PLWH who will be receiving ethambutol. They should also have monthly visual acuity and colour vision testing (red-green colour discrimination), periodic ophthalmology assessments including visual fields, be questioned regarding visual symptoms at monthly follow-up visits, and asked to report promptly any new ocular symptoms between visits.[46]

Rifabutin has been associated with uveitis,[30,47] particularly when used in treatment regimens which include clarithromycin. The uveitis is dose-related and the estimates of cumulative risk of it developing by 7 months of treatment were 48% with rifabutin 600 mg/day and 13% with rifabutin 300 mg/

day (p<0.001).[30,47] Rifabutin dosages above 300 mg/day are not recommended based upon these findings. Patients with ocular symptoms should be evaluated promptly by an ophthalmologist. If uveitis is suspected, then rifabutin should be stopped immediately. Rifabutin may also cause drug interactions, hepatotoxicity, neutropenia, pseudojaundice (normal bilirubin), a polyarthralgia syndrome, and red-orange discolouration of various body fluids (e.g., tears, saliva, sweat, and urine).

Clarithromycin and azithromycin adverse effects may include drug interactions, reduced hearing (usually reversible), and rarely QTc-prolongation with cardiac arrhythmia.

e) Treatment in pregnancy

Birth defects have been observed in some animal studies with clarithromycin, but not azithromycin. Multiple studies in humans have shown no association between the use of azithromycin in the first trimester and major congenital malformations;[48,49] however, one study found it to be associated with spontaneous abortion (adjusted odds ratio 1.65, 95% confidence interval 1.34-2.02).[50] Primary MAC prophylaxis is not recommended during pregnancy.[1] For both the initial treatment and chronic maintenance therapy (secondary prophylaxis) of DMAC in pregnancy, the 2-drug regimen of azithromycin and ethambutol is recommended (BIII).[1]

IV) MAC IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME AND TIMING OF ART.

Among patients with disseminated MAC, the initiation of ART was associated with the development of MAC-IRIS in approximately 31% of cases.[51] In a series of 51 patients with non-tuberculous mycobacterial IRIS (84% due to MAC), 75% had no history of mycobacterial infection prior to initiating ART, consistent with an unmasking of subclinical disease.[7] The clinical features of MAC-IRIS most often include peripheral lymphadenitis, or pulmonary-thoracic or intraabdominal findings; however, any organ system may be involved.[7] Clinical manifestations are often atypical and may not be encountered in AIDS-related MAC prior to initiating ART. This may include lesions involving the spine, central nervous system[52], prostate, or chylous ascites[53]. The median survival in disseminated MAC treated with clarithromycin plus ethambutol plus rifabutin in the era before combination ART was only 8.7 months,[30] underlining the importance of prompt initiation of ART, which should occur around the same time as starting MAC therapy and take into account possible drug interactions (CIII).[1]

Although there have been no controlled trials, the benefit of antimycobacterial therapy in MAC-IRIS appears to be modest, and the addition of second line antimycobacterial drugs for patients with persistent symptoms is not recommended.[7] For patients with moderate to severe symptoms related to MAC-IRIS, consideration should be given to a trial of a nonsteroidal anti-inflammatory drug (NSAID) or a corticosteroid[1,7,54] (e.g., prednisone 20-40 mg/day for 4-8 weeks). If ART had already been initiated before the MAC diagnosis, then it should not be interrupted (CIII).

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Rating System for Prevention and Treatment Recommendations

Strength of Recommendation	Quality of Evidence for the Recommendation
A. Strong recommendation for the statement B. Moderate recommendation for the statement C. Optional recommendation for the statement	I. One or more randomized trials with clinical outcomes and/or validated endpoints II. One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes III. Expert opinion