Prophylaxis against *Mycobacterium avium* complex infection in AIDS

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DW CAMERON. Prophylaxis against *Mycobacterium avium* complex in AIDS. Can J Infect Dis 1994;5(Suppl B):10B-13B. Disseminated *Mycobacterium avium* complex (MAC) infection in AIDS is increasing in frequency, although it remains under-recognized due to unlocalized clinical manifestations and subtle initial presentation, if not the need for specialized laboratory diagnostic methods. Ultimately, MAC accounts for much of the 'wasting syndrome' in the natural history of human immunodeficiency virus disease. Multidrug treatment of MAC in AIDS is problematic. That MAC is preventable has been demonstrated, and how much clinical benefit can be had from successful prophylaxis remains to be evaluated in the face of improved efficacy of both treatment and prophylaxis regimens under investigation.

Key Words: AIDS, Human immunodeficiency virus (HIV), *Mycobacterium avium* complex (MAC), Prophylaxis

DISSEMINATED INFECTION WITH *MYCOBACTERIUM AVIUM* complex (MAC) in human immunodeficiency virus (HIV) infection is a major cause of the wasting syndrome in AIDS. This opportunistic infection is diagnosed with increasing frequency, even as a first AIDS-defining illness, due to improved health maintenance in severe HIV-associated immunodeficiency through more effective prophylaxis of *Pneumocystis carinii* pneumonia (PCP). Primary MAC infection follows environmental ex-

posure and colonization. This is usually a subclinical focal enteric or pulmonic process, followed by metastatic and disseminated infection with eventual sustained mycobacteremia. The tempo of this sequence of events is felt to be many weeks to a few months.

In the presence of severe HIV-associated immunodeficiency, disseminated MAC infection may produce persistent fever and result in the familiar wasting syndrome of pernicious loss of energy, strength and body

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mass, with anemia and elevation of serum alkaline phosphatase activity. The 20% annual incidence of MAC bacteremia in advanced immunodeficiency, the severe morbidity and accelerated mortality of disseminated MAC infection, the poor tolerance and relative inefficacy of multidrug anti-MAC treatments make a strong rationale for MAC prophylaxis.

NATURAL HISTORY OF INFECTION

The natural history of infectious diseases has relevance to the design and evaluation of intervention studies. We are familiar with the temporal sequence of risk, infection, disease and outcome as serial clinical events. Intervention studies of treatments for disease observe a study population in which a pathogen has already established infection. The impact of treatment may be measured upon the clinical outcome of the disease, whether convalescence, equilibration or death of the human host as the next event in natural history.

Intervention studies of prophylaxis observe populations at risk, where the next measurable event in the above sequence is the infection. This may substantially precede the onset and the outcome of the disease, according to the tempo of the particular infection. In a population at risk for slowly developing disease due to disseminated MAC infection in AIDS, the impact of prophylaxis would naturally be easier to measure upon the infection itself than upon delayed clinical outcomes such as the wasting syndrome or death. Given the pathogenicity of MAC in AIDS, we may accept the ability of randomized clinical trials of prophylaxis to measure effectiveness against infection better than against delayed outcomes, due to the sequence and tempo of events. Therefore, in this setting we must be prepared to evaluate the evidence of benefit in prophylaxis studies with slightly different understanding than in more familiar treatment studies in infectious diseases.

CLINICAL TRIALS OF MAC PROPHYLAXIS

The published literature contains two prospective randomized clinical trials of MAC prophylaxis in AIDS. Abrams et al (1) described a small open trial of clofazimine 50 mg/day in persons with AIDS and CD4 T lymphocyte counts under 100 cells/ μ L. In observation under one year, 13% in each of treated and untreated patients developed disseminated MAC infection. Likewise, 17% of each group died. There was no evidence of efficacy, and the only significant predictor of disseminated MAC infection was progressive CD4 T lymphocytopenia to under 50 cells/ μ L.

Nightingale et al (2) reported on two large international multicentre, prospective, randomized double-blind placebo controlled clinical trials of MAC prophylaxis in AIDS. Rifabutin 300 mg daily was evaluated for prevention of MAC bacteremia. Patients with AIDS (1987 Centers for Disease Control and Prevention

definition) and CD4 T lymphocyte counts at or below 200 cells/ μ L were eligible for study. CD4 T lymphocyte counts were remeasured quarterly, and MAC bacteremia was the primary outcome parameter. MAC was to be detected in intensive surveillance by monthly, centralized blood cultures. Treatment upon detection with multidrug anti-MAC therapy, including rifabutin 600 mg daily, was encouraged by provision of the latter.

Rifabutin was well tolerated, with 47 (8%) placebo and 88 (16%) rifabutin randomized patients discontinuing study medication for minor adverse events ($P < 0.001$). Reasons for drug intolerance were rash (4%), gastrointestinal symptoms (3%) or neutropenia (2%).

In the two trials, incident MAC bacteremia analyzed on intention to treat occurred in 51 of 298 (17%) placebo versus 24 of 292 (8%) rifabutin randomized patients (study A, $P < 0.001$), and in 51 of 282 (18%) placebo versus 24 of 274 (9%) rifabutin randomized patients (study B, $P = 0.002$). Survivorship analysis on intention to treat for time to MAC bacteremia revealed over twofold reduction of cumulative risk due to rifabutin (study A, proportional hazard ratio 2.33, 95% confidence interval 1.43 to 3.78; study B, proportional hazard ratio 2.11, 95% confidence interval 1.30 to 3.45). Adjustment of this for potentially confounding baseline parameters, in particular baseline CD4 T cell counts, did not influence the protective effect of rifabutin prophylaxis.

Associated clinical outcomes were compared for the two studies combined, for patients receiving double-blinded medication on study. There was significantly reduced incidence or delay in onset of fatigue (risk ratio [rr] 0.74, $P = 0.003$), fever (rr 0.76, $P = 0.006$), decline in Karnofsky performance status (rr 0.79, $P = 0.026$), decline in hemoglobin (rr 0.80, $P = 0.008$), and elevation of serum alkaline phosphatase activity (rr 0.68, $P = 0.002$). Hospitalizations (rr 0.81, $P = 0.035$) and days spent hospitalized were fewer in the rifabutin patients.

During the double-blind period of study, 47 placebo and 33 rifabutin randomized patients died (proportional hazard ratio 0.68, 95% confidence interval 0.43 to 1.06, Logrank $P = 0.086$). Including unblinded follow-up observation, 200 placebo and 226 rifabutin randomized patients died (Logrank $P = 0.14$).

The development of drug-resistant MAC infection, or drug-resistant tuberculosis, would be a concern in long term use of a rifamycin class antimycobacterial drug in a population at risk. These studies excluded persons with latent or active tuberculosis; thus, little information was provided on the development of reactivation or resistant tuberculosis. Eighty-eight of 150 first blood isolates of MAC were evaluated for the minimum inhibitory concentration of rifabutin. No significant association of randomization to rifabutin or to placebo with minimum inhibitory concentration of rifabutin was present. Conversely, if the failures of prophylaxis are related to breakthrough bacteremia with susceptible

organisms, then a higher dose of rifabutin, or addition of a second antimycobacterial drug, may improve prophylactic efficacy.

These clinical trials demonstrate the safety and protective effectiveness of rifabutin against MAC bacteremia in AIDS. The greater effect observed against the infection than against attributable morbidity and mortality is to be expected considering the limitations of any prophylactic intervention study design in this setting, as discussed above. This prophylaxis targeted to the appropriate population represents an advance in the tactics of medical health maintenance available to persons living with HIV. Although these studies prove effective in person with AIDS and CD4 T cells less than 200/ μ L, several epidemiological studies suggest that substantial risk for disseminated MAC infection begins at very low CD4 T cell counts, and that prophylaxis may rationally be targeted to persons with fewer than 100 CD4 T cells/ μ L.

CLINICAL IMPACT

Prospective clinical trials identify relatively long term population risk, and population risk reduction on prophylaxis, rather than the shorter term and more individualized risks and benefits relevant to clinical decisions of a physician and a patient. The severity and the progression of CD4 T lymphopenia is the major determinant of risk for MAC infection, and life expectancy in persons with severe, advanced immunodeficiency is estimated in months. Survivorship analysis upon time may be adjusted for, or even conducted on CD4 T cell count decline, provided similar assumptions in analytical methodology. If the passage of time is less important to the changing risk for MAC infection than the progression of immunodeficiency, this may provide more precise measurement and resolution of risk and risk reduction in such studies.

Using serial CD4 T cell counts at baseline, remeasured quarterly, and the individual results of three corresponding monthly MAC blood cultures, we estimated the 90-day risk for MAC bacteremia and for death across strata of 20 CD4 T cells/ μ L, and estimated risk reduction on rifabutin. Stratified for progression of CD4 T cell count decline, the 90-day risk of MAC bacteremia was significantly reduced on rifabutin (maximal likelihood rr 0.4, 95% confidence interval 0.3 to 0.7, $P < 0.001$). The 90-day risk of death was also significantly reduced on rifabutin (maximal likelihood rr 0.7, 95% confidence interval 0.5 to 1, $P = 0.03$). Similar analytical methods may provide short term information more relevant to individual clinical decision making, and may also permit improved measurement of risk and risk reduction

in randomized clinical trials of prophylaxis of opportunistic infections in AIDS.

Therefore, MAC is an important opportunistic infection in severe HIV immunodeficiency, which is amenable to prevention through prophylaxis with rifabutin 300 mg per day. Persons with HIV and CD4 T cell counts under 100 cells/ μ L can expect at least a twofold reduced risk for disseminated MAC infection, improved health maintenance through its prevention, and reduced likelihood of need for multidrug therapy of MAC.

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The wasting syndrome in AIDS – clinical scenario

Mr X, a 38-year-old professional man, has a medical history of atopy and irritable airways disease. He was referred for HIV seropositivity and possible lingual hairy leucoplakia in mid-1989. He reported over 100 lifetime sexual partners during the previous 10 years, knowledge of HIV exposure, and ongoing unprotected receptive anorectal penetrative intercourse.

Systems review revealed persistent, familiar mild cough attributed to asthma, exacerbated with exercise or cold. Physical examination revealed obesity (90 kg), generalized mild lymphadenopathy, oral-lingual aphthous ulcers, external haemorrhoids and monilial intertrigo. Laboratory evaluation revealed CD4 T lymphocyte counts at 600, 350 and 470 cells/ μ L, and mild absolute lymphocytosis.

By 1992, investigations revealed CD4 T cells in the hundreds, and stool culture positive for cytomegalovirus. Colonoscopy with biopsies was unhelpful, and stains of stool revealed the presence of *Entamoeba coli*, *Iodamoeba butschlii* and *Blastocystis hominis*. With persistent diarrhea and progressive weight loss, he was further treated with metronidazole, iodoquinol and ketoconazole. There was fair response of diarrhea and abdominal symptoms. For suspected recurrent PCP, he was treated subsequently with dapsone-trimethoprim, with little clinical improvement. During this episode of polypharmacy, including drug eruption due to dapsone, his weight dropped further to 70 kg and he began to complain of impaired memory and concentration. Computerized cranial tomography revealed no specific abnormality except sphenoid sinusitis, which was treated with amoxicillin-clavulanic acid. Laboratory investigation revealed slight elevation of serum alkaline phosphatase activity, mild macrocytic anemia, low erythrocyte folate levels and low serum vitamin B₁₂ levels. This was managed with vitamin replacement and supplement therapy.

Over the first six months of 1992, he lost a further 13 kg, and had recurrent and persistent diarrhea and abdominal discomfort. Although there was fatigue, there was no fever or night sweats, anemia remained mild, and serum alkaline phosphatase gradually rose two- and threefold. Despite suggestions for empirical antimycobacterial combination therapy, he declined for fear of drug reaction. CD4 T cells were now below 50, and monthly blood cultures for MAC were negative until June, when a positive culture was reported. He then accepted empirical MAC therapy. His constitutional symptoms remitted, although diarrhea has persisted, requiring antimotility drugs for its control.

Since beginning anti-MAC therapy, he has suffered

SUMMARY

38-year-old HIV+ male, sexually active. Asthmatic, atopic, weight 90 kg

1989/90:

Asymptomatic. Moderate CD4 T lymphopenia, immune activation and inflammation. Antiretroviral therapy. Anemia. Thrush.

1991:

Weight loss 13 kg. Cough, Sinusitis. Drug eruption. Exertional dyspnea. Anti-PCP therapy. Drug eruption.

1991/92:

Weight loss 7 kg. Diarrhea. Hypovitaminosis (B₁₂ and folate) therapy. Antiparasitic therapy. Anti-PCP therapy. Drug eruption.

1992:

Weight loss 13 kg. Intermittent diarrhea. Abdominal discomfort, early satiety, Fatigue. Persistent mild anemia, elevated serum alkaline phosphatase activity. Delayed empiric antimycobacterial therapy. Weight gain 3 kg. MAC bacteremia reported. CD4 T cells fewer than 50/ μ L.

1992/93:

Stable constitutional condition, weight 60 kg. Persistent diarrhea, ketoconazole refractory thrush. Localized cutaneous Kaposi's sarcoma. Severe facial *Molluscum contagiosum*.

Current medications:

- zidovudine, didanosine
- trimethoprim-sulfamethoxazole
- clarithromycin, rifabutin and ethambutol
- fluconazole
- loperamide; vitamin B₁₂ and folate.

next: ganciclovir $\pm$ foscarnet?

recurrent oral candidiasis refractory to ketoconazole treatment, but responding to fluconazole. He has developed severe facial *Molluscum contagiosum*, and Kaposi's sarcoma of the lower legs managed with local radiotherapy. PCP prophylaxis was resumed with daily oral cotrimoxazole, which has been well tolerated, and anti-retroviral therapy has been maintained with zidovudine and didanosine. Body weight increased about 4 kg on several months of anti-MAC therapy, and has stabilized since at 60 kg, 30 kg less than his stable weight before illness. No evidence of cytomegalovirus disease has been found despite surveillance.