The Canadian Multicentre MAC Treatment Study

STEPHEN D SHAFRAN MD FRCPC AND THE MAC STUDY GROUP OF THE CANADIAN HIV TRIALS NETWORK

SD SHAFRAN AND THE MAC STUDY GROUP OF THE CANADIAN HIV TRIALS NETWORK. The Canadian Multicentre MAC Treatment Study. Can J Infect Dis 1994;5(Suppl B):21B-23B. Mycobacterium avium complex (MAC) infection is a common complication of the advanced stages of human immunodeficiency virus (HIV) infection causing both morbidity and premature mortality. While it is acknowledged that MAC infection requires treatment with a combination of antimycobacterial drugs, the optimal regimen has not been defined. A Canadian Multicentre MAC Treatment Trial was proposed in 1990 and finally implemented in late 1992 via the Canadian HIV Trials Network with the assistance of 6 pharmaceutical companies. The specific drug regimens and study design are outlined and the timetable for analysis and completion are also indicated. Collaborative, Canadian, multicentre clinical trials in HIV disease can be successfully implemented.

Key Words: AIDS, Canadian trials, Human immunodeficiency virus (HIV), Mycobacterium avium complex (MAC)

MYCOBACTERIUM AVIUM COMPLEX (MAC) IS THE MOST frequent bacterial pathogen in adults with AIDS. MAC infection has been reported in 15 to 53% of AIDS patients (1-4). In a prospective study, Nightingale et al (5) demonstrated that MAC bacteremia occurred at a rate of 20% per year following a diagnosis of AIDS, reaching 50% 30 months after an AIDS diagnosis. MAC infection is a late complication of HIV disease, occurring at CD4 lymphocyte counts below 50x10^6 cells/L in the vast majority of subjects (1-5).

Because of the late occurrence of MAC infection in AIDS patients, the contribution of MAC infection to mortality in these patients was formerly questioned (6). However, several studies have demonstrated that MAC infection is an independent risk factor for premature mortality in AIDS, even adjusting for CD4 lymphocyte count (7,8). There are considerable data from uncontrolled studies showing that antimycobacterial drugs can result in both bacteriological improvement (either sterilization or reduction in bacterial load), as well as MAC-related symptoms of fever, night sweats and weight loss (9-13). In addition, three retrospective case-control studies have demonstrated a survival advantage for MAC-infected AIDS patients who receive antimycobacterial therapy, compared with MAC-infected AIDS patients who do not receive antimycobacterial therapy (14-16).

In response to the recognition of the importance of MAC infections in AIDS patients and the recent data suggesting that therapy is beneficial, the United States Public Health Service convened a Task Force on MAC...
vitro activity against 
"ber of advances in the treatment of 
 responded that it was very interested in supporting a study in this area, but wished to convene a workshop for the further development of this protocol. The workshop was held in September 1990, and participants included potential investigators, primary care physicians with experience in HIV medicine and representatives from the medical departments of several pharmaceutical companies. A study protocol was further developed and resubmitted to the CTN for the January 1991 competition, and this protocol was subsequently approved by both the Scientific Review Committee and the Steering Committee. 

Subsequent to the approval of the protocol, a number of advances in the treatment of MAC infection occurred. First, two comparative studies evaluating the efficacy of rifabutin monotherapy for the prevention of MAC bacteremia were completed and showed clear efficacy of rifabutin for this indication (18). Therefore, there was clear evidence for an in vivo beneficial effect of rifabutin on MAC. Second, the new macrolide, clarithromycin, which was known to possess good in vitro activity against MAC, was shown to possess potent in vivo activity as well (12). Third, the California Collaborative Treatment Group (CCTG) demonstrated that a four-drug oral regimen consisting of rifampin, ethambutol, clofazimine and ciprofloxacin resulted in both clinical and bacteriological improvement in a substantial proportion of patients (11). As a result, two major review papers on MAC infection, published in 1991, recommended the use of the CCTG regimen (1,2).

A logistical problem that needed to be overcome was the general reluctance of both the Health Protection Branch of Health and Welfare Canada and individual pharmaceutical companies to permit the use of more than one investigational drug in the same research study.

Finally, funding of the study presented significant challenges since, unlike the AIDS Clinical Trial Group (ACTG) in the United States, which is fully funded by the United States government to conduct AIDS-related clinical trials, the CTN is funded only as an infrastructure and is unable to provide complete funding for clinical trials. Ultimately, the cooperation of six member companies of the Pharmaceutical Manufacturers’ Association of Canada was obtained, and these companies provided all six study medications. Pharmacia, the manufacturer of rifabutin, provided a major grant towards the study as well as providing their clinical research associates to help in the monitoring of the study. Abbott Laboratories, the manufacturer of clarithromycin, also provided financial support for the study. A key principle of this study is that it is open to all Canadian centres affiliated with the CTN.

THE FINAL PROTOCOL

The protocol was finalized in September 1992 after a meeting of site investigators. The study design is prospective, randomized, multicentre and comparative. There are two treatment arms, each receiving equal allocation, and the randomization is blocked by centre. Twenty-four centres in 15 cities in nine provinces agreed to participate.

The major inclusion criteria are age 16 years or older, HIV-seropositivity and MAC bacteremia. Patients are excluded if they have an enrollment Karnofsky score below 20, a serum creatinine level greater than 250 μmol/L, a serum aspartate aminotransferase level greater than five times the upper limit of normal (unless due to MAC infection), have undergone previous treatment for MAC infection or have received drugs with antimycobacterial activity in the four weeks preceding randomization. Pregnant and lactating women are also excluded.

The two drug regimens under study are the CCTG regimen: rifampin 600 mg daily, ethambutol 15 mg/kg daily, clofazimine 100 mg daily, and ciprofloxacin 750 mg bid; and the ‘experimental’ arm consisting of clarithromycin 1000 mg bid, ethambutol 15 mg/kg daily, and rifabutin 600 mg daily. The study could not be blinded for practical reasons. Although open-label ethambutol could be given, it would be necessary to provide placebo controls for the five other study drugs in a group of patients with advanced HIV disease who are generally receiving multiple other medications. In addition, the central reference mycobacteriology laboratory staff are blinded to patient assignment and since the primary efficacy parameter is bacteriological (see later), the assessment of the bacteriological response is unlikely to be affected by blinding.

The study consists of an intense phase of 16 weeks duration with the option for life-time continuation of study medications. During the intense phase, patients are assessed at baseline, and at weeks 2, 4, 8, 12 and 16. At each study visit, a medical history is taken, a physical examination is performed and the patient completes the 30 question medical outcome survey adapted for HIV (MOS-HIV); in addition, the investigator calculates the MAC symptom score, which was created expressly for this study. A mycobacterial blood culture
is collected and processed centrally and quantitatively by the mycobacteriology section at the Provincial Laboratory of Public Health for Northern Alberta, Edmonton.

After the 16-week intense phase, patients are followed every four weeks until death. Mycobacterial blood cultures (nonquantitative) are performed in local laboratories and the MAC treatment record is monitored.

The primary analysis will be bacteriological. Specifically, this will involve the comparison of the proportion of patients in each of the two treatment arms who achieve blood culture sterilization, defined as two consecutive negative blood cultures after a positive baseline blood culture. In addition, the clinical response will be measured in several ways. The principal clinical outcome will be the MOS-HIV scale. As well, the MAC symptom score and individual MAC symptoms will be assessed and compared between the two groups. Additional analyses will include survival, tolerance of each of the regimens, tolerance of individual drugs, drug toxicities and in vitro susceptibility studies. The intended sample size is 200 patients, and one interim analysis will be performed.

REFERENCES

TIMETABLE
The first patient was enrolled on November 23, 1992. At the time of the MAC symposium in September 1993, 102 patients had been randomized in the study. An interim analysis will be done early in 1994 and if the study continues after the interim analysis, the final analysis will likely be performed in either late 1994 or early 1995.

ADDENDUM
The interim analysis was reviewed by the Safety and Efficacy Review Committee of the Canadian HIV Trials Network in March 1994; the committee recommended that this study be continued. As of March 22, 1994, 147 patients had been enrolled.

Submit your manuscripts at
http://www.hindawi.com