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Discontinuation of secondary prophylaxis in AIDS patients with disseminated non-tuberculous mycobacteria infection

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From June 1994 to June 2002, disseminated infections due to non-tuberculous mycobacteria (NTM) were diagnosed in 42 of 716 (5.9%) non-haemophiliac HIV-infected patients aged ≥15 years who were treated at National Taiwan University Hospital. The median age of these patients was 35 years (range, 27 to 60 years). The median CD4+ cell count and plasma viral load at the time of diagnosis of disseminated NTM infections were 8×10^6/L (range, 0 to 892×10^6/L) and 37,600 copies/mL (range, <400 to >750,000 copies/mL), respectively. The nadir CD4+ count during the observation period was 6×10^6/L (range, 0 to 30×10^6/L). The species of NTM isolated included *Mycobacterium avium* complex (MAC) [n = 35], *Mycobacterium kansasii* (4), *Mycobacterium chelonae* (1), *Mycobacterium abscessus* (1), and unidentified NTM (3). Co-infection with 2 species of NTM was diagnosed in 2 patients. NTMs were isolated from blood (n = 18), liver (18), lymph node (12), bone marrow (10), cerebral spinal fluid (1), ascites (1), and pericardial effusion (1). The median duration of antimycobacterial therapy of the 42 patients was 7 months (range, 0 to 24 months). Mortality during the study period was greater in the patients enrolled before highly active antiretroviral therapy (HAART) was introduced (14 of 15, 93%) than in those who received HAART (9 of 27, 33%). As of December 31, 2002, 15 patients (35.7%) had discontinued secondary prophylaxis against disseminated NTM infections when their median CD4+ count had increased to 119×10^6/L (range, 25 to 465×10^6/L), and 86.7% (13/15) of the patients had achieved an undetectable plasma viral load after HAART. During the median observation duration of 12 months (range, 2 to 57 months), none of the 15 patients had relapse of disseminated NTM infections. Our findings indicate that disseminated NTM infections without primary prophylaxis were associated with a high mortality rate, especially before HAART became available. In patients who received HAART and had a favorable response with viral suppression and immune restoration, discontinuation of secondary prophylaxis against disseminated NTM infections was safe.

Key words: AIDS, highly active antiretroviral therapy, *Mycobacterium avium* complex, *Mycobacterium kansasii*, non-tuberculous mycobacteria, prophylaxis

Non-tuberculous mycobacteria (NTM), especially *Mycobacterium avium* complex (MAC), are important etiologies of opportunistic infections among patients with advanced stage HIV infection, with a high morbidity and mortality rate [1]. During the natural course of HIV infection, up to 15% of patients will develop disseminated MAC (DMAC) infection within 12 months after their CD4+ count has fallen below 50×10^6/L [2]. Nightingale et al [3] found that the incidence of DMAC infection increased with the duration after diagnosis of AIDS (21% at 1 year and 43% at 2 years), and had an inverse relationship to CD4+ count: 39% in patients with a CD4+ count of $<10 \times 10^6$/L, 30% at 10 to 19×10^6/L, 20% at 20 to 39×10^6/L, 15% at 40 to 59×10^6/L, 8% at 60 to 99×10^6/L, and 3% at 100 to 199×10^6/L [3]. The median duration of survival of patients with HIV infection and DMAC infection was estimated to be 110, 185, and 339 days in 1991, 1994, and 1997, respectively [4].

Because of its associated high morbidity and mortality, the US Public Health Service and Infectious Diseases Society of America (USPHS/IDSA) recommend initiation of primary and secondary prophylaxis against MAC infection to prevent disseminated diseases among adults and adolescents with HIV infection [5]. With the introduction of highly active antiretroviral therapy (HAART), the incidence of MAC infection in patients with HIV infection decreased significantly from 3.7 to

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0.9 per 100 person-years [6,7], and such primary prophylaxis can be safely discontinued in patients with an increase of CD4+ count to 100×10^6/L or greater for at least 6 months after HAART [5].

As to secondary prophylaxis against DMAC infection, several studies [8-10] supported the safety of discontinuation in asymptomatic patients who had completed a 12-month course of anti-MAC therapy and had a CD4+ cell count increase to 100×10^6/L or greater for at least 6 months [5,8-10]. This study evaluated the clinical characteristics of disseminated infections due to NTM among HIV-infected patients treated at National Taiwan University Hospital (NTUH) from June 1994 to June 2002, and assessed the safety of discontinuation of secondary prophylaxis.

Materials and Methods

Patients

A total of 716 consecutive non-hemophiliac HIV-infected patients treated at NTUH from June 1994 through June 2002 were included in this study. More than 65% (467) and 50% (389) of the 716 patients had baseline CD4+ count of $\leq 200 \times 10^6$/L and $\leq 100 \times 10^6$/L, respectively, and nearly 75% had a diagnosis of AIDS. Patients were eligible for inclusion in the study if they had disseminated infections due to NTM during the study period. All patients were followed up until December 31, 2002.

A standardized case record form was used to retrieve data on age; gender; risk of HIV transmission; CD4+ cell count at diagnosis of disseminated NTM infection, at nadir, and at discontinuation of secondary prophylaxis; plasma viral load (pVL) at diagnosis of disseminated NTM infection and at discontinuation of secondary prophylaxis; antiretroviral therapy; antimycobacterial therapy; and outcome.

The HIV infection and AIDS Registry of the Center for Communicable Disease Control and Vital Statistics of the Department of Health, Taiwan, were searched to identify outcomes of the patients who might also have been followed up at other designated hospitals. The survival duration of patients with disseminated NTM infection was estimated from the date of diagnosis, and loss to follow-up at this hospital or other designated hospitals till the end of the study period on December 31, 2002.

Antimycobacterial and antiretroviral therapy

During the 8-year study period, patients followed at this hospital did not receive primary prophylaxis against MAC and patients with positive skin test to PPD did not receive rifampin plus pyrazinamide against tuberculosis. For patients with a diagnosis of disseminated NTM infection, antimycobacterial therapy was initiated with ciprofloxacin, clarithromycin or azithromycin, and ethambutol.

Antiretroviral therapy provided to the patients consisted of 2 nucleoside reverse transcriptase inhibitors (NRTIs) before April 1997 and of HAART consisting of 2 NRTIs plus 1 to 2 protease inhibitors (PIs), which were introduced into Taiwan in April 1997, or 2 NRTIs plus non-nucleoside reverse transcriptase inhibitor (nNRTI) treatment, which was introduced into Taiwan in July 1999. Because discontinuation of secondary prophylaxis against relapse of disseminated NTM infections was not recommended before 2000, decisions to discontinue secondary prophylaxis were made at the discretion of treating physicians.

Laboratory studies

The stepwise diagnostic investigations for NTM infections used in this study were described in a previous report [11]. For patients presenting with palpable lymphadenopathy, lymph node biopsy was also performed. Bronchoscopy was performed in patients presenting with pulmonary infiltrates who had negative acid-fast staining of at least 3 sputum specimens. Bone marrow and liver biopsy and culture were performed when blood cultures were negative for other bacteria or fungi but patients remained febrile. All clinical specimens were cultured for mycobacteria using standard procedures. Blood cultures for mycobacteria were performed using the BACTEC 960 MGIT (Mycobacteria Growth Indicator Tube) System (Becton-Dickinson Diagnostic Systems, Sparks, MD, USA). The medium for primary isolation was Lowenstein-Jensen slant (BBL, Becton Dickinson) from 1994 through 1995. From 1996, in addition to previous methods, Middlebrook 7H10 agar (BBL, Becton Dickinson) was added and blood and bone marrow aspirates were cultured using the Isolator lysis-centrifugation system (Dupont, Wilmington, DE, USA).

pVL was quantified using reverse transcriptase polymerase chain reaction (Roche Amplicor, version 1.5) with a detection limit of 400 (2.60 $\log_{10}$) copies/mL, which was introduced into clinical use in late 1998. CD4+ count was determined using FACFlow (Becton Dickinson).

Definitions

Disseminated NTM infection was defined as NTM isolated from blood or other sterile sites, such as bone

marrow, liver, spleen, lymph node, ascites, pleural effusion, pericardial effusion, joint fluid, and cerebral spinal fluid (CSF). Patients with NTM isolated from specimens of respiratory tract (sputum, bronchioalveolar lavage, sinus), gastrointestinal tract (gastric lavage, colon biopsy, stool), or wound were not considered to be disseminated NTM infection when cultures of sterile sites yielded negative results.

Results

Over the 8-year study period, 72 cases of NTM infection were diagnosed and 42 of these cases fulfilled the criteria for disseminated NTM infection. The clinical characteristics of these patients are shown in Table 1. Most of the patients with disseminated NTM infection were in the advanced stage of HIV infection, with a median nadir CD4+ cell count of 6×10^6/L (range, 0 to 30×10^6/L) and a CD4+ cell count of 8×10^6/L (range, 0 to 892×10^6/L) at the diagnosis of disseminated NTM infection. The incidence of NTM was 8.8% (41/467) and 10.3% (40/387) among patients with a baseline CD4+ count of $\leq 200 \times 10^6$/L and $\leq 100 \times 10^6$/L, respectively. The median pVL at initial diagnosis of disseminated NTM infection was 37,600 (range, <400 to >750,000 copies/mL).

The majority of NTM were isolated from blood (n = 18), liver (18), lymph node (12), and bone marrow (10) [Table 1]. MAC was the most common isolate causing disseminated infection (n = 35), followed by *Mycobacterium kansasii* (4), *Mycobacterium chelonae* (1), and *Mycobacterium abscessus* (1). Three isolates remained unidentified.

At the time of diagnosis of NTM infection, concurrent opportunistic infections included oroesophageal candidiasis (30), *Pneumocystis carinii* pneumonia (PCP) [18], cytomegalovirus disease (16), herpes simplex virus infection (10), non-typhoidal salmonellosis (6), penicillosis marneffei (2), rhodococcal pneumonia (1), parvovirus B19 infection (1), and bacteremia (2).

Anti-NTM therapy consisted of ethambutol, clarithromycin plus ciprofloxacin in 37 patients and of ethambutol, clarithromycin plus rifabutin or rifampin in 2 patients. Three patients did not receive anti-NTM therapy because they were lost to follow-up, or died before therapy could be initiated. Twelve patients were taking 1 or 2 NRTI agents at the time of diagnosis of NTM infection, which was during the pre-HAART period in 10 of them. Two patients did not receive HAART during the study period.

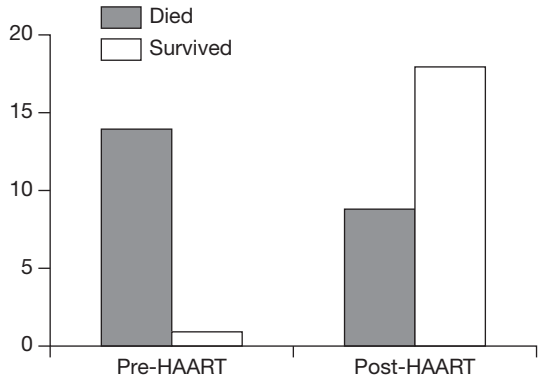

Fig. 1. Case number of disseminated infection due to non-tuberculous mycobacteria and deaths in the pre-HAART and post-HAART period.

As of December 31, 2002, 23 patients (54.8%) had died and 1 was loss to follow up. Fourteen of the 15 patients (93.3%) treated before HAART was introduced in April 1997 died, while 9 of 27 patients (33.3%) who received HAART died (Fig. 1). The causes of death in patients with disseminated NTM were septic shock (11) and advanced/terminal stage of AIDS (7). The cause of death in the other 5 patients remained unknown.

Of the 18 patients who survived, 15 had discontinued secondary prophylaxis, and 3 continued secondary prophylaxis. The median duration of anti-NTM therapy before discontinuation of secondary prophylaxis in the 15 patients was 11 months (range, 2 to 20 months), and their median CD4+ count was 119×10^6/L (range, 25 to 465×10^6/L). The CD4+ count at the discontinuation of secondary prophylaxis was 50 to 99×10^6/L in 4 (26.7%) of the 15 patients, 100 to 199×10^6/L in 7 (46.7%), and $\geq 200 \times 10^6$/L in 4 (26.7%). The median pVL at discontinuation was <400 copies/mL (range, <50 to >750,000 copies/mL), and 13 patients (86.7%) had an undetectable pVL. There was no relapse during the total of 251 person-months of observation after discontinuation of secondary prophylaxis for disseminated NTM infection.

Discussion

In this study, we found that disseminated NTM infections, mostly DMAC infection, were not uncommon in patients in the advanced stage of HIV infection in our hospital, and occurred in 10.3% of patients with a CD4+ count of 100×10^6/L or less. Similar to findings from western countries [1,3], the majority of disseminated NTM infections occurred in patients with a depleted CD4+

Table 1. Clinical characteristics of 42 HIV-infected patients with disseminated infection due to non-tuberculous mycobacteria (NTM)

Characteristic	
Age [median (range); years]	35 (27-60)
Gender (male/female)	37/5
Route of transmission [n (%)]	
Homosexual/bisexual	23 (55)
Heterosexual	17 (40)
Intravenous drug use	2 (5)
CD4+ count, median (range; $\times 10^6$/L) or [n (%)]	
Nadir	6 (0-30)
At diagnosis of NTM infection	8 (0-892)
<50	37 (88.1)
51-100	3 (7.1)
101-200	1 (2.4)
>200	1 (2.4)
At discontinuation of NTM therapy	119 (25-465)
<100	4 (26.7)
101-200	7 (46.6)
>200	4 (26.7)
Date diagnosis [n (%)]	
Pre-HAART	15 (35.7)
Post-HAART	27 (64.3)
Symptom/sign of NTM [n (%)]	
Fever	16 (38.1)
Hepatosplenomegaly	17 (40.4)
Lymphadenopathy	12 (28.6)
ALP [median (range); IU/L]	303 (81-3069)
Species of NTM [n (%)]	
MAC	35 (83.3)
Mycobacterium kansasii	4 (9.5)
Other NTMs	5 (11.9)
Positive cultures for NTM [n (%)]	
Blood	18 (42.9)
Liver	18 (42.9)
Lymph node	12 (28.6)
Bone marrow	10 (23.8)
Cerebrospinal fluid	1 (2.4)
Ascites	1 (2.4)
Pericardial effusion	1 (2.4)
Outcome [n (%)]	
Survived	18 (42.9)
Discontinuation of secondary prophylaxis	15 (35.7)
Died	23 (54.8)
Pre-HAART	14 (93.3)
Post-HAART	9 (33.3)
Loss to follow-up	1 (2.4)
Time from diagnosis to death [mean (range)]	4 months (2 days to 19 months)
Pre-HAART	7 months (2 to 19 months)
Post-HAART	3 months (2 days to 18 months)
Cause of death [n (%)]	
Terminal stage, AIDS	7 (30.4)
Septic shock	11 (47.8)
Unknown	5 (21.7)

Abbreviations: ALP = alkaline phosphatase; HAART = highly active antiretroviral therapy; MAC = *M. avium* complex

count (median, 8×10^6/L) who did not receive primary prophylaxis with new macrolides or rifabutin [12]. In Taiwan, *Mycobacterium tuberculosis* infection is much more prevalent than NTM infection and drug-resistant *M. tuberculosis* infection may have a greater prevalence in this island. Therefore, clinicians caring for HIV-infected patients may hesitate to initiate primary prophylaxis for NTM infection because of the lack of epidemiologic studies and concern about the emergence of *M. tuberculosis* resistant to rifamycins [13].

The case-fatality rate of disseminated NTM infection was especially high in the pre-HAART period [1]. More than 90% of our patients enrolled before HAART was introduced died within a median interval of 7 months after diagnosis. In the post-HAART period, the fatality rate was 33.3%, with deaths occurring within a median interval of 3 months after diagnosis. The overall high fatality rate has been related to the severity of immunosuppression and concurrent opportunistic illness. Clinical signs and symptoms suggestive of DMAC or disseminated NTM infection include fever, night sweats, weight loss, diarrhea, abdominal pain, lymphadenopathy, anemia, leukopenia, thrombocytopenia, hepatomegaly, splenomegaly, and elevated alkaline phosphatase [14,15]. Such findings should alert clinicians in Taiwan caring for HIV-infected patients to the possibility of disseminated NTM infection in patients with a CD4+ count of 50×10^6/L or less who present with prolonged fever, hepatosplenomegaly, and elevated alkaline phosphatase. Although the incidence of DMAC infection has declined in the era of HAART in this hospital [16], initiation of primary prophylaxis with new macrolides, clarithromycin or azithromycin, should be considered in patients who present with a CD4+ count of $\leq 50 \times 10^6$/L by following the USPHS/IDSA guidelines [5].

With the introduction of HAART, morbidity and mortality rate have declined dramatically following immune restoration [7], and discontinuation of primary prophylaxis against opportunistic infection, such as PCP and DMAC infection, has become possible and safe [17]. Discontinuation of secondary prophylaxis against PCP relapse has also been shown to be safe in patients responding to HAART [17,18]. According to the USPHS/IDSA guidelines [5], the criteria for discontinuation of secondary prophylaxis of DMAC

Table 2. Summary of reported studies of discontinuation of secondary prophylaxis against disseminated infections due to *Mycobacterium avium* complex (MAC) or other non-tuberculous mycobacteria (NTM)

Characteristic	Kirk et al [8]	Zeller et al [9]	Shafran et al [10]	Others [22-26]	Present report
Case number (n)	103	26	52	16	15[a]
CD4+ count ($\times 10^6$/L) [mean (range)]:					
at diagnosis of NTM infection	16 (7-50)	10 (1-17)	16 (9-30)	8 (4-23)	13 (0-892)
at discontinuation of secondary prophylaxis	190 (129-290)	105 (1-254)	230 (130-312)	193 (88-321)	119 (25-465)
Percent of undetectable pVL at discontinuation of secondary prophylaxis	66.3	31.0	NA	87.5	86.7
pVL at discontinuation [mean (range); copies/mL]	<50-1183	NA	<50-4800	NA	<400->750,000
Duration of anti-NTM therapy [mean (range); months]	26 (15-36)	23 (6-48)	32 (4-87)	17 (7-23)	11 (2-20)
Duration of HAART before anti-NTM therapy [mean (range); months]	19 (11-26)	13 (1-39)	NA	NA	14 (0-65)
Observation duration after discontinuation of anti-NTM therapy [mean (range); months]	26 (NA)	35 (15-57)	20 (4-52)	13 (4-57)	12 (2-57)
Relapse (n)	2	3	1	4	0
Incidence per 1000 person-years	0.9	4.0	1.2	NA	0
OI during observation periods	2 toxoplasmosis; 1 CMV retinitis + Kaposi's sarcoma; 1 candidiasis + CMV retinitis	11 viral infection; 9 bacterial infection; 3 PCP; 3 malignancies	NA	NA	0

Abbreviations: CMV = cytomegalovirus; HAART = highly active antiretroviral therapy; NA = not available; OI = opportunistic infection; PCP = *Pneumocystis carinii* pneumonia; pVL = plasma viral load

[a]Eleven disseminated MAC infection, 4 disseminated *M. kansasii* infection, 1 disseminated *M. abscessus* infection, 1 disseminated infection due to unidentified NTM; 3 patients presenting with disseminated infection due to 2 species of NTM.

infection is a sustained increase of CD4+ count to >100 $\times 10^6$/L for more than 6 months in patients who had completed a 12-month course of anti-MAC therapy and remain asymptomatic. However, such recommendations have not been validated through clinical studies.

Recently, studies investigating the safety of discontinuation of secondary prophylaxis against disseminated MAC infection have been reported (Table 2) [8-10,19-26]. Although the studies' designs may be different, and criteria for discontinuation varied, the rate of relapse was low in patients who responded to HAART with an increase of CD4+ count to 100 $\times 10^6$/L or greater. Studies by Kirk et al [8], Zeller et al [9], and Shafran et al [10] showed only 2, 3, and 1 case of relapses during total observation periods of 222, 75.8, and 86.7 person-years, with an incidence rate of 0.9, 4.0, and 1.2 relapses per 100 person-years, respectively. In this study, relapse of disseminated NTM infection did not occur after discontinuation of secondary prophylaxis in patients whose median CD4+ count was 119 $\times 10^6$/L. Review of the reported studies [8-10] and our data indicates that complete viral suppression is not a prerequisite for discontinuation of secondary prophylaxis, although more studies are needed to confirm this finding. Detectable viral load should not preclude discontinuation of secondary prophylaxis as long as the CD4+ count continues to increase with HAART.

In conclusion, disseminated NTM infection is associated with a high mortality rate in patients with advanced stage HIV infection in our hospital and this association was especially strong in the pre-HAART era. Discontinuation of secondary prophylaxis is safe in patients responding to HAART, as evidenced by increase of CD4+ count to 100 $\times 10^6$/L or greater.

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