IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME IN ADULT HUMAN IMMUNODEFICIENCY VIRUS-INFECTED PATIENTS IN THAILAND

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Abstract. Immune reconstitution inflammatory syndrome (IRIS) is an important adverse event among human immunodeficiency virus (HIV)-infected patients taking highly active antiretroviral therapy (HAART). The epidemiology of IRIS in Thailand has not been well examined, especially among adult HIV-infected patients. In the present study, we reviewed the medical records of 174 HIV-infected, antiretroviral therapy-naïve patients older than 15 years (the median CD4 count at commencement of HAART was 37 cells/mm^3) and compared characteristics of patients with and without IRIS. During a 12-month follow-up period after commencement of HAART, 11 cases (6.3%) of IRIS were identified (4.2 /100 patient-years HAART). The cases included nine cases with mycobacterial infection, one with cytomegalovirus retinitis and one with cryptococcal meningitis. The patients with IRIS were significantly younger than those without IRIS (29 *vs* 36 on medians, p=0.022). The median interval between commencement of HAART and the onset of IRIS was 22 days. Although all patients with IRIS improved with or without corticosteroids, they were more frequently hospitalized during a 12-month follow-up period while taking HAART (1 *vs* 0 on medians, p<0.001). The incidence of IRIS in advanced adult HIV-infected patients in Thailand was lower than that reported from Europe and the United States, which may be attributable to deferment of HAART after diagnosing opportunistic infections.

Key words: IRIS, HIV-infected patients, HAART, Thailand

INTRODUCTION

Recent advances in highly active antiretroviral therapy (HAART) against human immunodeficiency virus (HIV) infection have contributed greatly to restoration of host immune systems in HIV-infected patients and decreased the mortality associated with acquired immunodeficiency syndrome (AIDS) (Mocroft *et al*, 2003). In HIV-infected patients with advanced disease, restoration of the immune system with HAART may result in an inflammatory reaction against underlying pathogens causing clinical deterioration

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despite favorable immunological and virological responses. This syndrome called immune reconstitution inflammatory syndrome (IRIS) (Lipman and Breen, 2006; Shelburne *et al*, 2006) sometimes results in serious or even fatal reactions. IRIS is usually associated with infective agents, such as *Mycobacterium tuberculosis*, non-tuberculous mycobacteria (NTM), *Pneumocystis jiroveci*, cytomegalovirus, *Cryptococcus neoformans* and is rarely associated with non-infectious diseases, including autoimmune diseases and sarcoidosis (French *et al*, 2004). To date, the risk factors for and preventive measures against IRIS have not been fully clarified.

In Thailand, IRIS is one of the biggest concerns physicians have in treating HIV-infected patients because many patients do not visit healthcare facilities until the disease advances to AIDS (Manosuthi *et al*, 2006). There have been a few reports regarding IRIS in the literature due to specific pathogens or in pediatric HIV-infected patients (Manosuthi *et al*, 2006; Puthanakit *et al*, 2006; Sungkanuparph *et al*, 2003, 2006). However, the epidemiology of IRIS has not been well studied. In the present study, we investigated the incidence and clinical features of IRIS in adult HIV-infected patients.

MATERIALS AND METHODS

Patients

We retrospectively reviewed the medical records of HIV-infected patients that began to receive HAART between December 2004 and November 2005 at the Anonymous Clinic, Chon Buri Regional Hospital, located in eastern Thailand. Inclusion criteria were: 1. inexperience to antiretroviral therapy; 2. age ≥15 years old at commencement of HAART; 3. patients in whom CD4 cell counts at baseline and follow-up for 12 months while taking HAART were known. At the end of the follow-up period, treatment success (defined by an increase in the CD4 cell count of >50 cells/mm^3 over baseline or a reduction in HIV plasma viral load to <50 copies/ml), frequency of hospitalization and change in body weight were evaluated.

Diagnosis of IRIS

Following five criteria (Shelburne *et al*, 2002) to diagnose IRIS were used with some modifications: 1. an increase in the CD4 cell counts; 2. a reduction in HIV plasma viral load; 3. improvement in clinical signs and symptoms; 4. emergence or re-emergence of inflammatory responses, including high fever, lymphadenitis, and abscess formation; 5. exclusion of alternative causes, including newly acquired infection or side effects of therapy. Reliability of diagnosis was defined as "definite" if it fulfilled criteria 1 or 2 and all criteria from 3 to 5, as "probable" if it fulfilled three or four of the five criteria and "possible" if it fulfilled one or two of the five criteria of IRIS). Two of the authors evaluated the clinical conditions potentially related to IRIS and they agreed on the diagnosis.

Diagnosis of opportunistic infections

Tuberculosis was diagnosed by positive culture for *Mycobacterium tuberculosis*, a positive acid-fast smear with compatible clinical symptoms or an apparent improvement in clinical symptoms with antituberculous treatment. Infection with nontuberculous mycobacteria (NTM) was diagnosed when the patient had a CD4 cell count of ≤100/mm^3 and demonstrated clinical manifestations such as prolonged fever, weight loss, chronic diarrhea, hepatosplenomegaly and a favorable improvement with administration of anti-NTM drugs. Pneumocystis pneumonia

(PCP) was diagnosed when the chest x-ray showed compatible findings and there were a good response to PCP-specific treatment. A diagnosis of cryptococcosis was made by a positive blood culture or a positive result on either a *C. neoformans* antigen test or an India ink test of the cerebrospinal fluid. Cytomegalovirus retinitis was diagnosed by funduscopic examination by an ophthalmologist.

Statistical analyses

Epi Info version 3.3.2 (Centers for Disease Control and Prevention, USA) was used for data analysis. categorical data were analyzed by chi-square test or Fisher's exact test as appropriate. The Mann-Whitney *U* test was used for analyzing numerical data. A $p < 0.05$ was considered significant.

Ethical approval

The present study was approved by the ethics committee of the Chon Buri Regional Hospital.

RESULTS

Demographic characteristics of patients

A total of 174 patients (99 males, median age 35.5 years) were included in the present study. The median CD4 cell count at baseline was 37cells/mm^3 (range: 0-360 cells/mm^3, Table 1). On commencement of HAART, 159 patients (91.4%) were diagnosed as having AIDS using CDC criteria (Centers for Disease Control and Prevention, 1992); 155 patients (89.1%) had a CD4 cell count less than 200 cells/mm^3.

Characteristics of cases with IRIS

There were 11 cases (6.3%) of IRIS in our study, 7 with tuberculosis, 2 with NTM or *M. tuberculosis* (NTM/TB) infection, one with cytomegalovirus retinitis and one with cryptococcal meningitis (Table 2). In the two cases with NTM/TB infection, acid-fast bacilli were detected on biopsy but the organisms could not be cultured. The overall incidence of IRIS was estimated to be 4.21/100 patient-years of HAART. The reliability of the diagnosis of IRIS was "definite" in one case of tuberculosis, "probable" in two cases of tuberculosis and one cases of cytomegalovirus infection, and "possible" in four cases of tuberculosis, two of NTM/TB infection, and one of cryptococcosis. The median interval between commencement of HAART and the onset of IRIS was 22 days (range: 14-231 days). Patients with IRIS were significantly younger than those without IRIS (29 *vs* 39 on medians, $p=0.022$), and the rate of patients younger than 30 years was higher in those with IRIS ($p=0.013$). There were no significant differences in patients with IRIS and without IRIS by gender, CD4 cell count, body weight, or body mass index (Table 1).

Clinical course under HAART

The increase in CD4 cell count was significantly less in patients with IRIS at month 3 of HAART ($p=0.027$) but not at months 6 and 12 (Table 3). Among 162 patients (93.1%) completing 12-month follow-up, hospitalizations were significantly more frequent in patients with IRIS than those without IRIS (1 *vs* 0 on medians, $p<0.001$). There were no significant differences in patients with and without IRIS the rates of patients with treatment success or increases in body weight. No deaths were seen during the follow-up period.

All patients with IRIS improved with specific treatment without interruption of HAART. Corticosteroids were given to one patient with cervical tuberculous lymphadenitis, one with cytomegalovirus retinitis, and one with cryptococcal meningitis. A patient with a cerebral tuberculoma had a craniotomy for removal of the abscess. Fluid was aspirated for palliation of

Table 1
Demographic characteristics of the 174 studied patients.

Variable	Total (n=174)	With IRIS (n=11)	Without IRIS (n=163)	*p*-value
Age (years) [a]	35.5 (18, 68)	29 (23, 68)	36 (1, 65)	0.022
Age<30 years [b]	37 (21.3)	6 (54.5)	31 (19.0)	0.013
Gender: male [b]	99 (56.9)	6 (54.5)	93 (57.1)	1.000
Baseline status [a]				
CD4 count (cells/mm^3)	37 (0, 360)	37 (2, 209)	36 (0, 360)	0.621
Body weight (kg)	52.6 (30, 76)	51 (36, 60)	52 (30, 76)	0.498
Body mass index [c]	19.7 (12.3, 29.1)	18.3 (14.4, 25.5)	19.2 (12.3, 29.1)	0.121
OIs prior to HAART [b]	136 (78.2)	9 (81.8)	127 (77.9)	1.000
Tuberculosis	61(35.1)	5 (45.5)	56 (34.4)	0.455
CMV infection	8 (4.6)	1 (9.1)	7 (4.3)	0.414
Cryptococcosis	16 (9.2)	1 (9.1)	15 (9.2)	1.000
PCP	40 (23.1)	1 (9.1)	39 (23.9)	0.460
Herpes zoster	32 (18.4)	1 (9.1)	31 (19.0)	0.692
Others [d]	88 (50.6)	6 (54.5)	82 (50.3)	1.000

OIs indicates opportunistic infections; CMV, Cytomegalovirus; PCP, Pneumocystis pneumonia.
[a]Median (range)
[b]No. of cases (%)
[c]Data from one patient without IRIS were missed.
[d]Others include oral or esophageal candidiasis, nontuberculous mycobacteria infection, toxoplasmosis, histoplasmosis etc.

symptoms in one patient with tuberculous lymphadenitis and one with pleuritis.

Opportunistic infections prior to HAART

Before commencement of HAART, 136 of the 174 patients had a history of an opportunistic infection: 61 had tuberculosis, 8 had cytomegalovirus retinitis, 16 had cryptococcosis and 40 had pneumocystis pneumonia (Table 1). The median number of days from beginning treatment for opportunistic infection and commencement of HAART were 174.5 days with tuberculosis, 30.5 days with cytomegalovirus infection, 89 days with cryptococcosis (Table 4) and 113 days with pneumocystis pneumonia. Seven of the 11 cases of IRIS had a deterioration or relapse of a preceding opportunistic infection. The length of time between onset of treatment for an opportunistic infection and commencement of HAART was not significantly associated with the occurrence of IRIS.

DISCUSSION

In the present study of adult HIV-infected patients in Thailand, 6.3% of patients experienced IRIS during the first year following commencement of HAART and the estimated incidence of IRIS was 4.2/100 patient-years of HAART. This finding is lower than those reported from Europe or the United States (15-25%) (French *et al*, 2000; Jevtovic *et al*, 2005; Shelburne *et al*, 2005; Ratnam *et al*, 2006). One reason for the lower prevalence of IRIS may be a difference in definition of IRIS. For

Table 2
Characteristics of 11 patients with IRIS.

No	Age, gender	Disease[a]	Preceding opportunistic infection	Interval (days)		CD4 count (cell/mm^3)		Viral loads [c] (copies/ml)		Clinical manifestation	Reliability of diagnosis
				OI-ART[b]	ART-IRIS	Baseline	Nearest to IRIS	Baseline	Nearest to IRIS		
1	25, M	TB	Yes	164	231	7	91	ND	<50	Skin abscess, pneumonia brain tuberculoma	Definite
2	26, M	TB	Yes	364	154	53	76	ND	ND	Skin abscess, pneumonia	Probable
3	28, F	TB	Yes	27	18	43	101	ND	ND	Intra-abdominal lymphadenitis spleen microabscess	Probable
4	31, F	TB	No	-	14	9	129	ND	ND	Pneumonia	Possible
5	23, F	TB	Yes	166	171	2	431	ND	ND	Cervical lymphadenitis	Possible
6	42, F	TB	No	-	73	209	331	ND	ND	Left pleulitis	Possible
7	35, M	TB	Yes	49	22	53	131	ND	ND	Left calf abscess	Possible
8	68, M	NTM/TB	No	-	19	82	141	ND	ND	Erythema nodosum,pneumonia	Possible
9	34, M	NTM/TB	No	-	19	37	74	ND	ND	Cervical lymphadenitis	Possible
10	29, M	CMV retinitis	Yes	7	62	10	85	ND	ND	Retinitis, uveitis	Probable
11	25, M	CM	Yes	77	14	37	100	ND	ND	Fever, headache	Possible

[a] TB indicates tuberculosis; NTM, nontuberculous mycobacterium; CMV, cytomegalovirus; CM, cryptococcal maningitis

[b] OI-ART, interval between beginning treatment for opportunistic infection and initiating HAART; ART-IRIS, interval between commencement of HAART and onset of IRIS

[c] Viral loads were not tested except in case No.1 at the onset of IRIS. ND indicates no data. Case numbers 8,9, and 10 achieved viral suppression to less than 50 copies/ml several months or year after the onset of IRIS.

Table 3
Clinical courses under HAART.

	Total	Patients with IRIS	Patients without IRIS	*p*-value
CD4 count increase [a]				
At month 3	93 (-192,457) [*n*=91]	47.5 (23,78) [*n*=6]	95 (-192,457) [*n*=85]	0.027
At month 6	101 (-188,433) [*n*=109]	73.5 (55,122) [*n*=6]	101 (-188,433) [*n*=103]	0.212
At month 12	158.5 (7,604) [*n*=80]	141 (104,429) [*n*=5]	162 (7,604) [*n*=75]	0.835
0-12 months				
Hospital admission [a]	0 (0-5) [*n*=162]	1 (0-2) [*n*=10]	0 (0-5) [*n*=152]	<0.001
At month 12				
Treatment success	159/174 [b]	10/11	149/163	1.000
Body weight: BW (kg)	57 (38,81) [*n*=162]	61 (42,68) [*n*=10]	57 (38,81) [*n*=152]	0.376
BW increase rate (%)	8.4 (-15.8,62.9)	14.8 (6.7,31)	8.0 (-15.8,62.9)	0.064

[a]Median (range); [ ]: number of analyzable cases; [b]yes/total sample

Table 4
Interval between beginning treatment for a major opportunistic infection and initiating HAART.

Preceding infection	Interval in days, median (range)			*p*-value
	Total	With IRIS	Without IRIS	
Tuberculosis	174.5 (27,737) [*n*=54] [a]	164 (27,491) [*n*=5]	175 (44,737) [*n*=49]	0.731
CMV retinitis	30.5 (0,78) [*n*=8]	7 [*n*=1]	32 (0,78) [*n*=7]	-
Cryptococcosis	89 (37,472) [*n*=13]	77 [*n*=1]	91 (37,472) [*n*=12]	-
Total	115 (0,491) [*n*=69]	77 (7,491) [*n*=7]	120.5 (0,472) [*n*=62]	0.585

[a] [ ]: number of analyzable cases

example, herpes zoster appearing during HAART was considered as IRIS in some previous studies; whereas five cases of uncomplicated herpes zoster were excluded from the present study, because we considered the presentation of herpes zoster occurred due to low immune status and was indistinguishable from IRIS. Another reason could be the longer interval between outset of treatment for opportunistic infection and commencement of HAART in our study (Table 4). A previous study found HAART was started within two months of the beginning of treatment for a major opportunistic infection (tuberculosis, cytomegalovirus retinitis or cryptococcal meningitis) (Shelburne *et al*, 2005). In contrast, the median interval in the present study was 115 days (range: 0-491 days). The majority of cases of IRIS (72.7%) occurred within the first 90 days of initiating HAART as described previously (French *et al*, 2004; Lipman and Breen, 2006; Shelburne *et al*, 2006).

Previously, low baseline CD4 counts and close intervals between the commencement of treatment for opportunistic infections and HAART were indicated

as risk factors for developing IRIS (French *et al*, 2000; Navas *et al*, 2002; Shelburne *et al*, 2005). These factors, however, were not related to developing IRIS in the present study. We speculate the reasons for discrepancies were the low CD4 cell counts at baseline in all examined patients and a delay in the commencement of HAART in patients with active opportunistic infections. Younger ages in our study were associated with developing IRIS, similor to the findings of another recent study (Ratnam *et al*, 2006). Immune systems in younger ages may be restored more promptly than older ages, which may increase the risk of developing IRIS.

A previous study described that significantly greater increases in CD4 cell counts after 3 months of HAART and more rapid decreases in plasma viral loads were related to the development of IRIS (Shelburne *et al*, 2005). In the present study, increases in CD4 cell counts in the patients with IRIS was significantly less than in patients without IRIS at month 3 after commencing HAART, but there was no difference after 3 months of HAART. Although reasons for the discrepancy remain unknown, we consider an initial rapid increase in CD4 cell count with HAART does not necessarily predict occurrence of IRIS.

All patients with IRIS in the present study were successfully managed without discontinuing HAART. There were no differences found between outcomes in patients with and without IRIS, including treatment success, body weight and body mass indexes at 12 months of HAART. However, patients with IRIS were hospitalized more frequently than those without IRIS. It is likely the occurrence of IRIS increased the need of hospitalization and invasive procedures that resulted in physical and financial burdens for the patients.

The retrospective study and the subjective diagnosis of IRIS were major limitations of the present study. We attempted to minimize this issue by requiring 2 physicians to agree on a diagnosis of IRIS before being classified. Insufficient medical resources were another factor affecting the results of the present study. CD4 cell counts and plasma viral loads were unavailable in a number of patients because they could not afford to have frequent blood tests. The lack of these data may have influenced the diagnosis of IRIS. Fewer chances for microbiological examination may have been related to an imprecise diagnosis of opportunistic infection. As a result, 7 of the 11 IRIS cases were diagnosed as "probable". A well designed prospective study is required to resolve these problems.

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