damage classification by examining the agreement between the two classification systems among patients with both sets of data. Because the QIs that target treatment choice focused on patients with class A liver damage, we calculated the sensitivity and specificity of the Child–Pugh class A in predicting liver damage class A. All of the statistical analyses were performed using STATA 11.1 (College Station, TX, USA). The study protocol was approved by the institutional review board of the National Cancer Center of Japan.

RESULTS

Sample characteristics

IN TOTAL, 16 187 patients were included. Table 2 presents the sample characteristics. The mean age of patients was 67 years (71.6% male). Approximately 50% of patients had liver damage of class A and 50% had solitary tumors. Similar numbers of patients underwent surgery, percutaneous local ablation, and transcatheter arterial chemoembolization (TACE).

Table 2 Sample characteristics

	n (%)
Age, mean (SD)	67 (SD = 9.4)
Male *n* (%)	11 592 (71.6%)
Liver damage class	
A	8089 (50.0%)
B	4439 (27.4%)
C	1058 (6.5%)
Unknown/No response	2601 (16.1%)
Child–Pugh class	
A	10 585 (65.4%)
B	3444 (21.3%)
C	867 (5.4%)
Unknown/No response	1291 (8.0%)
Number of tumors	
1	8970 (55.4%)
2	2727 (16.9%)
3	1198 (7.4%)
>3	3733 (15.7%)
Unknown/No response	757 (4.9%)
Tumor diameter (cm), mean (SD)	4.1 (4.0)
Primary treatment modality	
No treatment	1238 (7.7%)
Surgical resection, transplantation	4895 (30.2%)
Percutaneous local ablation	4733 (29.2%)
TACE	4423 (27.3%)
Systemic chemotherapy	718 (4.4%)
Other treatment	110 (0.7%)
No answer	70 (0.4%)

SD, standard deviation; TACE, transarterial chemoembolization.

Table 3 Cross-tabulation of Child–Pugh and Liver damage classes

CP	LD				
	A	B	C	Unknown	Total
A	7729	1813	35	1008	10 585
B	131	2445	290	578	3 444
C	6	56	693	112	867
Unknown	223	125	40	903	1 291
Total	8089	4439	1058	2601	16 187

CP, Child–Pugh classification; LD, liver damage.

Quality scores

On average, quality indicators had 5767 patients applicable, and overall the indicated care processes were provided 83.9% of the time. Table 1 presents quality scores and data completeness for each QI. The score was lowest for the QI "Surgical therapy in patients with HCC 3–5 cm in diameter" (64.4%) and highest for the QI "Indocyanine green (ICG) checkup before surgical resection" (91.1%). Although the availability of data for denominators ranged from 78.3% to 100%, information for numerators was available for more than 90% of patients for all QIs. QIs that use liver damage classification, tumor number, and tumor size were least commonly available for the denominator (78.3%). Liver damage classification, tumor number, and tumor size were missing or unknown for 2601 (16%), 757 (4.7%), and 1134 patients (7.0%), respectively.

Distribution of liver damage and the Child–Pugh classification

Table 3 presents the analysis of the concordance between Child–Pugh and liver damage classifications. These two classification systems agreed in 82.3% of patients for whom sufficient data were available. Child–Pugh A could predict liver damage class A with 98.3% sensitivity and 65.3% specificity.

DISCUSSION

WE HAVE DEMONSTRATED that certain aspects of the quality of care for patients with liver cancer can be measured using the liver cancer registry operated by the Liver Cancer Study Group of Japan. To our

knowledge, this was the first study to measure the quality of care for HCC. Standardizing the care process is challenging given the complexity of HCC care, as a range of treatment modalities from surgical resection to percutaneous and transcatheter therapy exists. The choice of treatment is influenced not only by the cancer stage but also by the baseline liver function. The QIs in this study, developed by the consensus of clinical experts, examined the actual care provided against the standards of pretherapeutic evaluation, the collection of pertinent tumor information, and treatment choice. The quality scores were high for most of the QIs, but there was also room for improvement. Although not all of the QIs developed were used for this analysis, we believe that the identification of a focus for improvement is an important initial step.

The information available in the registry was sufficiently complete for quality measurements to be made. Although information required to determine eligibility for QIs was occasionally missing, the information required to assign each QI a "pass" or "fail" status was generally available, which indicated little ambiguity in the scoring of the eligible patients. Among the missing information, the liver damage classification was the most frequently missing, presumably due to the lack of the ICG test. Although the liver damage classification was used for the QIs that focused on treatment choice in accordance with the Japanese Clinical Practice Guidelines, alternative criteria would be necessary to review actual practices. The comparison of the Child–Pugh class and liver damage class, however, revealed that the former underestimated the liver damage. For example, the Child–Pugh class A includes patients with more severe disease and is broader than liver damage class A. This result was expected, as the prothrombin criteria threshold is lower for the Child–Pugh classification.[16] Furthermore, this is consistent with a previous report that reviewed the medical records of the HCC patients.[17] If the Child–Pugh classification is used in place of the liver damage classification for the patients whose liver damage classification data are missing, the QIs targeting patients with liver damage class A would also include a broader group of the patients with liver damage class B or C. Thus, caution should be exercised when using these liver function classifications interchangeably.

For other types of cancer, we have a predecessor on using the national database for quality measurements and feedback. In the National Cancer Database, the Commission on Cancer of the American College of Surgeons measured six QIs (three for breast cancer and three for colorectal cancer) and provided feedback regarding the scores of the individual participating facilities and the distribution of these scores among other facilities.[18] This program is now developing the Rapid Quality Reporting System, in which the facilities submit and update the information continuously and the quality of care is monitored in real time. Our study indicates that the same service is theoretically possible in Japan using the liver cancer registry.

Some limitations must be considered when interpreting the results of the current study. First, the QIs that examined the appropriate documentation of vascular invasion and tumor differentiation were scored based on the availability of data in the dataset rather than on the actual medical records. This may underestimate or overestimate the quality scores for these QIs. Underestimation occurs when physicians keep appropriate documentation but fail to enter that information into the dataset, and overestimation occurs when physicians enter the information into the dataset but fail to document it in the medical record. Accordingly, caution must be exercised while interpreting these scores. Second, quality assessment requires the consideration of exceptional cases. For example, in some cases where a QI indicated surgery, surgery may not be appropriate due to compromised cardiac or respiratory functions. As the database does not contain information on the reasons why surgery was not performed, it is possible that patients who were appropriately excluded from surgery may be labeled as having received poor quality care. Hence, the results of the measurements of quality from the database should be regarded as starting points for discussions of quality and not as the final conclusions about quality. Third, the fact that the facilities participated in the registry voluntarily must be taken into account, as they are motivated and likely to be more specialized than the average Japanese hospitals. Therefore, the quality scores from these facilities may be higher than those provided by typical hospitals in Japan. Fourth, the QIs were based on the clinical practice guidelines issued in 2005, [6] but our study was comprised of patients diagnosed in 2002 and 2003. Thus, the guidelines used may have already improved some of the aspects of care scored in this analysis, but our study has demonstrated that the Liver Cancer Registry Database can be a useful data source for analyzing quality of care. Finally, the timing of the evaluation and the start of treatment for each patient was uncertain. Although the QIs targeting pretherapeutic laboratory tests (tumor markers and ICG retention) require knowledge of whether these tests were performed before the treatment was initiated, the test dates were not available in the

registry. Thus, we assumed that the tests were performed before the start of the therapy and we therefore overestimated the quality scores.

Despite these limitations, we have demonstrated that the Liver Cancer Registry Database can be a tool for quality measurement. To date, cancer registries have primarily focused on clinical and epidemiological research, and the examination of the quality of care is a new area of research. Professional societies, however, have the responsibility to promote improved quality of patient care. Because the ultimate goal is to improve patient outcome, the role of these societies should not be limited to the discovery of new knowledge but should also include the monitoring of the extent to which the new knowledge is applied to patient care nationwide. This study serves as an initial step for the future growth of such activities.

ACKNOWLEDGMENT

THE STUDY WAS funded by a grant in aid from the Ministry of Health, Labor, and Welfare of Japan. The authors thank Kenji Ikeda, MD, PhD (Toranomon Hospital), Takao Iwasaki, MD (Tohoku University Hospital), Yoshiaki Kajiyama, MD, PhD (Juntendo University), Shoji Kubo, MD, PhD (Osaka City University Hospital), Kiyoshi Matsueda, MD (Cancer Institute Hospital), Kyoji Moriya, MD, PhD (University of Tokyo Hospital), Yo Sasaki, MD PhD (Yao Hospital), Yoshito Takeuchi, MD, PhD (National Cancer Center Hospital), and Kaoru Yamada, MD (Sanraku Hospital) for their service in the expert panel to review candidate quality indicators.

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APPENDIX

The list of the quality indicators (QIs) approved by the expert panel

	Denominator (target patients)	Numerator (standard care processes)
Pre-treatment work-up		
1	Patients who were diagnosed with hepatocellular carcinoma (HCC)	AFP and PIVKA-2 levels were measured before treatment
2	HCC patients who underwent surgical resection, percutaneous local ablation therapy and transarterial chemoembolization (TACE) therapy	Dynamic CT/MRI study was performed before treatment
3	Patients who were diagnosed with HCC and received treatment	The medical records documented the clinical stage (TNM or TNM factors) and liver function level (the Child–Pugh class or the liver damage class)
4	Patients who underwent surgical resection of HCC for the first time	15-min ICG retention rate was measured before treatment
Treatment choice of local therapy		
5	HCC patients with liver damage class A, having three or less tumors of 3 cm or smaller in diameter	Surgical resection or percutaneous local ablation therapy (PEI, MCT, or RFA) was performed.
6	HCC patients with liver damage class A having a solitary tumor of 3–5 cm in diameter	Surgical resection was performed.
7	HCC patients with liver damage class A or B and three or fewer tumors smaller than 3 cm who had surgical resection or percutaneous local ablation therapy	The advantages and disadvantages of each therapy were explained and documented in the medical records
8	HCC patients with liver damage class C who underwent surgical resection, percutaneous local ablation therapy or TACE	The risks and benefits of the treatments received were explained and documented in the medical records
9	HCC patients receiving percutaneous ethanol injection (PEI) as the initial treatment	Medical records documented the reasons why RFA was not performed
10	HCC patients with Stage IVa or earlier, Vp 0–2 and Child–Pugh class A or B, in whom surgery and percutaneous local ablation therapy were not possible (patients who did not receive surgery or percutaneous local ablation therapy within 3 months after diagnosis)	TACE was performed.
11	Recurrent HCC patients with liver damage class A and a solitary tumor of 3–5 cm in diameter	Surgical resection was performed, or the medical record documented the reasons for not performing surgery
12	Recurrent HCC patients with liver damage class A and solitary tumor of 3 cm or smaller in diameter	Surgical resection or percutaneous local ablation therapy (PEI, MCT or RFA) is performed or the medical record documents the reasons for not performing these therapy
13	Recurrent HCC patients with liver damage class A and two or three tumors of 3 cm or smaller in diameter	Surgical resection, percutaneous local ablation therapy (PEI, MCT or RFA), or TACE was performed, or the medical record documented the reason for not performing these therapies.
14	HCC patients who received TACE	Lipiodol was used in the procedure
15	HCC patients with liver damage class C who satisfied Milan criteria	The option of liver transplantation was explained and documented
Documentation and explanation		
16	HCC patients who underwent surgical resection	Medical record (including pathological report) documented the degrees of vascular invasion and tumor differentiation was postoperatively determined.
17	HCC patients who underwent surgical resection	The medical record documented the physician's judgment on the postoperative risk of recurrence
18	HCC patients who underwent surgical resection	The pathological findings after surgery were explained to patients and were documented in the medical record

	Denominator (target patients)	Numerator (standard care processes)
Systemic therapy		
19	HCC patients who received systemic chemotherapy	Medical records documented the explanation to patients that surgical resection, percutaneous local ablation therapy or TACE could not be performed and that evidence for the efficacy of chemotherapy was lacking.
20	Patients who received treatment for HCC	Hormone therapy was avoided
Follow-up monitoring		
21	HCC patients who underwent surgical resection or percutaneous local ablation therapy	AFP and PIVKA-2 were monitored for at least 4-month intervals for 2 years after the curative treatment
22	HCC patients who received TACE	CT/MRI and tumor marker tests were performed within 2 months after TACE
23	HCC patients who received TACE	Image studies (contrast-enhanced CT/MRI, if not contraindicated) were performed at least every 3 months
24	HCC patients who received TACE	Tumor marker tests (AFP, PIVKA-2) were monitored at least every 3 months
25	HCC patients who received TACE and who showed elevated tumor marker levels, increases in the tumor size from diagnostic imaging or the appearance of new tumors with rich blood flow	TACE was repeated, or the medical record indicates the TACE was considered

AFP, Alpha-fetoprotein; CT, computed tomography; HCC, hepatocellular carcinoma; ICG, indocyanine green; MCT, microwave coagulation therapy; MRI, magnetic resonance imaging; PEI, percutaneous ethanol injection; PIVKA-2, protein induced by vitamin K absence-2; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Clinical Symptoms and Courses of Primary HIV-1 Infection in Recent Years in Japan

Hideta Nakamura, Katsuji Teruya, Misao Takano, Kunihisa Tsukada, Junko Tanuma, Hirohisa Yazaki, Haruhito Honda, Miwako Honda, Hiroyuki Gatanaga, Yoshimi Kikuchi and Shinichi Oka

Abstract

Background The natural course of HIV-1 infection includes 10 years of an asymptomatic period before the development of AIDS. However, in Japan, the disease progression process seems faster in recent years.

Methods The study subjects were 108 new patients with primary HIV-1 infection during the period from 1997 through 2007. We evaluated their clinical symptoms and laboratory data, and then analyzed disease progression in 82 eligible patients. Disease progression was defined as a fall in CD4 count below 350/μL and/or initiation of antiretroviral therapy.

Results Ninety percent of the patients were infected via homosexual intercourse. All patients had at least one clinical symptom (mean; 4.75±1.99) related to primary HIV-1 infection, with a mean duration of 23.2 days (±14.8) and 53.3% of them had to be hospitalized due to severe symptoms. The mean CD4 count and viral load at first visit were 390/μL (±220.1) and 4.81 log10/mL (±0.78), respectively. None developed AIDS during the study period. Estimates of risk of disease progression were 61.0% at 48 weeks and 82.2% at 144 weeks. In patients who required antiretroviral therapy, the median CD4 count was 215/μL (range, 52-858) at initiation of such therapy. Among the patients with a CD4 count of <350/μL at first visit, 53% never showed recovery of CD4 count (>350/μL) without antiretroviral therapy.

Conclusion Despite possible bias in patient population, disease progression seemed faster in symptomatic Japanese patients with recently acquired primary HIV-1 infection than the previously defined natural course of the disease.

Key words: HIV-1, primary infection, disease progression

(Intern Med 50: 95-101, 2011)
(DOI: 10.2169/internalmedicine.50.4137)

Introduction

The natural course of HIV-1 infection has been well described in large cohorts from the United States and Europe before the introduction of highly active antiretroviral therapy (HAART); primary HIV-1 infection (PHI) is followed by a clinical latency, usually lasting around 10 years, which precedes the eventual collapse of the immune system (1, 2). However, there is a common feeling among clinicians at present that the natural disease progression of recently infected patients is faster than in previous years (3, 4). Disease progression depends on various factors such as HLA type (5), concomitant infections (6, 7), and available medical resources (8). In addition to these factors, events occurring during PHI could also determine the natural course of the disease. Initial studies suggested that patients with more symptoms related to primary PHI and longer duration of illness exhibit faster rates of progression to AIDS (9-13). Plasma viral load at a set point is also an independent predictor of disease progression (14, 15). However, to determine the viral set point is sometimes difficult. Therefore, for clinicians, the severity of clinical symptoms is the only predictor of subsequent disease progression. The latency be-

AIDS Clinical Center, National Center for Global Health and Medicine, Japan
Received for publication June 28, 2010; Accepted for publication September 29, 2010
Correspondence to Dr. Shinichi Oka, oka@acc.ncgm.go.jp

tween the development of PHI and commencement of HAART is also important in the present HAART era.

The main aim of this study was to evaluate the natural disease progression of recently infected Japanese patients. To determine whether or not the disease progression of recently infected patients is accelerated, their CD4 decline was compared with that of hemophiliacs infected before 1985 as the first HIV-1 infection in Japanese.

Furthermore, we also evaluated the correlation between initial CD4 count, viral load, and clinical events and subsequent changes in CD4 and/or time to start HAART in symptomatic Japanese patients with PHI.

Patients and Methods

Study site and patients with PHI

This study was conducted at the AIDS Clinical Center (ACC), National Center for Global Health and Medicine (NCGM: formerly International Medical Center of Japan). The NCGM (925 beds) is a tertiary general hospital located in central Tokyo and the ACC is the main referral clinic for treatment of HIV infected patients in Japan. As part of the follow-up service, HIV-1 infected patients usually visit the ACC on a monthly basis and CD4 count and viral load are measured at each visit. In the present retrospective study, we reviewed the medical records of 108 patients with PHI who were newly diagnosed with PHI between 1997 through 2007 at the ACC. We had conducted a clinical trial of structured treatment interruptions in patients with PHI from November 2000 through December 2002 and 26 patients were enrolled in that trial (16, 17). In terms of the data of these 26 patients, only the initial clinical and laboratory data were included in the present analysis, while all other data, such as time to events, were excluded from this study. To compare the natural CD4 decline of previously and recently infected patients, CD4 counts of 42 Japanese hemophiliacs recorded in the database in 1988 were analyzed as a previous control. Japanese hemophiliacs were infected with HIV-1 through contaminated blood products before 1985 (the estimated mean year of infection was 1983). Therefore, CD4 counts at the end of 1988 were the data at least 3 years after infection. In this comparison, the number of eligible recently infected patients was 59 patients; untreated and CD4 count at 3 years after infection was available.

Definition of PHI

PHI was diagnosed based on the presence of the following three criteria: 1) negative or incomplete western blot finding at the first visit with subsequent change to positive, 2) negative or weakly reactive enzyme-linked immunosorbent assay (ELISA) result for plasma HIV-1 RNA, and 3) confirmed HIV-1 infection on the first visit with documentation of negative ELISA result within 6 months. Symptomatic PHI was defined as PHI accompanied by at least one symptom related to acute retroviral syndrome, such as fever, lymphadenopathy, or skin rash.

Definition of disease progression

Disease progression was defined as fall in CD4 count below 350/μL and/or initiation of antiretroviral therapy. Specifically, patients with an AIDS-defined illness [listed under Centers for Disease Control and Prevention (CDC) category C], patients with AIDS requiring initiation of HAART, and those with severe symptomatic PHI on HAART were defined to have disease progression. The selection of a cutoff value of 350/μL for CD4 count was based on the fact that treatment is generally indicated during the chronic phase of infection when CD4 count falls below 350/μL (18). Patients were considered to be in immunologic progression at the first visit when the initial CD4 count was <350/μL and never subsequently reached 350/μL. For patients who showed a spontaneous increase in subsequent CD4 counts to ≥350/μL (such recovery occurred within 3 months from the first visit in all such patients), disease progression was set to have started at the time when such change in CD4 count occurred.

Statistical analysis

Continuous variables are presented as mean value ± SD. Categorical variables were presented as absolute numbers and proportions. Time to events was analyzed by the Kaplan-Meier survival curves, and compared using log-rank test. For patients who did not experience the events described above, data were censored at their last visit. To evaluate the differences between patients groups, the Student t test and χ^2 test were used when appropriate. The relationships between variables were analyzed by the Spearman rank-over correlation test. Statistical significance was defined as $p<0.05$. Data were analyzed using SPSS for Windows (version 15, SPSS, Inc., Chicago, IL).

Results

Table 1 lists the demographics of the enrolled patients with PHI. All patients had at least one documented symptom consistent with PHI (median 5; range 1-11). Fever, cervical lymphadenopathy, pharyngitis, and rash were found in more than 50% of patients (Table 2). The mean duration of symptoms was 23.2 days (SD ±14.8). Fifty-eight (53.7%) patients had to be hospitalized due to severe clinical symptoms. The initial viral loads in hospitalized patients were significantly higher than those of non-hospitalized patients. A longer duration of symptoms was associated with higher initial viral load (R=0.31, p=0.002) (Fig. 1A), and lower CD 4 count (R=-0.22, p=0.03) (Fig. 1B). Consequently, a higher viral load slightly was correlated with a lower CD4 count at the first visit (R=-0.22, p=0.033) (Fig. 1C).

Disease progression was analyzed in 82 patients. None of the patients had AIDS-defining events. Estimates of the risk of disease progression were 50.6% at 24 weeks, 61.0% at 48 weeks, 67.0% at 96 weeks, and 82.2% at 144 weeks

Table 1. Baseline Characteristics of 108 Patients with Primary HIV-1 Infection in this Study

Characteristics	Total number or mean (±SD) or %	Hospitalized patients (n = 58)	Non-hospitalized patients (n = 50)	p
Age (year)	31.8±8.48	32±9.07	31±7.82	NS
Sex				
Male	102	56	46	NS
Female	6	2	4	NS
Predisposing factor				
MSM	97	53	44	NS
Heterosexual	8	3	5	NS
IDU	1	0	1	NS
Unknown	2	2	0	NS
PMH of STD	75 (69.7)	44 (40.4)	31 (29.3)	NS
Syphilis	49 (45.5)	27 (25.3)	21 (20.2)	NS
Acute hepatitis A	11 (10.1)	6 (6.1)	5 (4.0)	NS
Acute hepatitis B	36 (33.3)	22 (20.2)	14 (13.1)	NS
Amebiasis	10 (9.1)	9 (8.0)	1 (1.1)	0.035
Others	7 (6.1)	2 (2.0)	5 (4.1)	NS
No. of symptoms	4.75±1.99	4.98±1.94	4.48±2.04	NS
Duration of symptoms (days)	23.2±14.8	27.8±13.1	18.0±15.1	0.001
Laboratory findings				
CD4 count/μL	390.0±220.1	356.1±204.1	443.7±236.0	0.06
HIV RNA $\log_{10}$/mL	4.81±0.78	5.03±0.68	4.48±0.81	0.001
STI trial*	26	12	14	NS

*Patients enrolled in a clinical trial of structured treatment interruptions in recently HIV-1-infected patients. Abbreviations; MSM: men who have sex with men, PMH of STD: past medical history of sexual transmitted diseases, STI: structured treatment interpretations, IDU: intravenous drug user, Others: genital herpes infection, chlamydial urethral infection condyloma acuminata, NS: not significant

Data are presented as mean ± SD or percentage (%) unless otherwise indicated

Table 2. Symptoms and Physical Findings Observed in the Patients with >10% Frequencies (n=108)

Symptoms and physical findings	frequency (%)
Fever	91
Lymphadenopathy	63
Pharyngitis	53
Rash	50
Diarrhea	37
Fatigue	32
Headache	26
Myalgia	20
Weight loss	19
Nausea	16
Appetite loss	14
Neurological sign	13
Hepatomegaly	13
Thrush	12

(Fig. 2). Eighteen of 34 (53.3%) patients with an initial CD 4 cell count below 350 cells/μL had immunologic progression at the first visit. Their CD4 counts never increased above 350/μL until initiation of HAART. Forty-eight (58.5%) required initiation of HAART in this study. The reasons for the initiation of HAART were severe clinical symptoms related to PHI in 16 patients and immunologic progression in 32 patients. The median CD4 count of those patients at initiation of HAART was 215/μL (range, 52-858).

We analyzed the clinical course in 66 patients (excluding 26 patients who enrolled in a clinical trial of structured treatment interruptions in PHI and 16 patients who received HAART for PHI) to determine the factors associated with disease progression. Half of these patients (33 patients) required hospitalization. As shown in Fig. 3A, the mean time to disease progression of the hospitalized patients [57.4 weeks, 95% confidence interval (95%CI); 34.9-79.8 weeks] was shorter than that of the non-hospitalized (33 patients, 94.4 weeks, 95%CI; 71-117 weeks, p=0.002). Among the 32 patients with CD4 count >350/μL at first visit, 24% had documented disease progression within 1 year, whereas among 34 patients with CD4 count <350/μL at first visit, 76.4% showed disease progression (Fig. 3B). The mean times to disease progression for the two groups were 111.9 weeks (95%CI; 92.8-131) and 39.5 weeks (95%CI; 18.6-60.5), respectively (p<0.001). Disease progression in 39 patients with high viral load (≥5.0 $\log_{10}$/mL) was not significantly different (p=0.41) from that in 27 patients with low viral load (<5.0 $\log_{10}$/mL) (Fig. 3C). The number of symptoms was not significantly different in each group (Fig. 3D). The mean time to disease progression was 69.8 weeks (95% CI; 47.2-92.5) in patients with a high viral load and 80.4 weeks (95%CI; 54.9-105.8) in those with a low viral load.

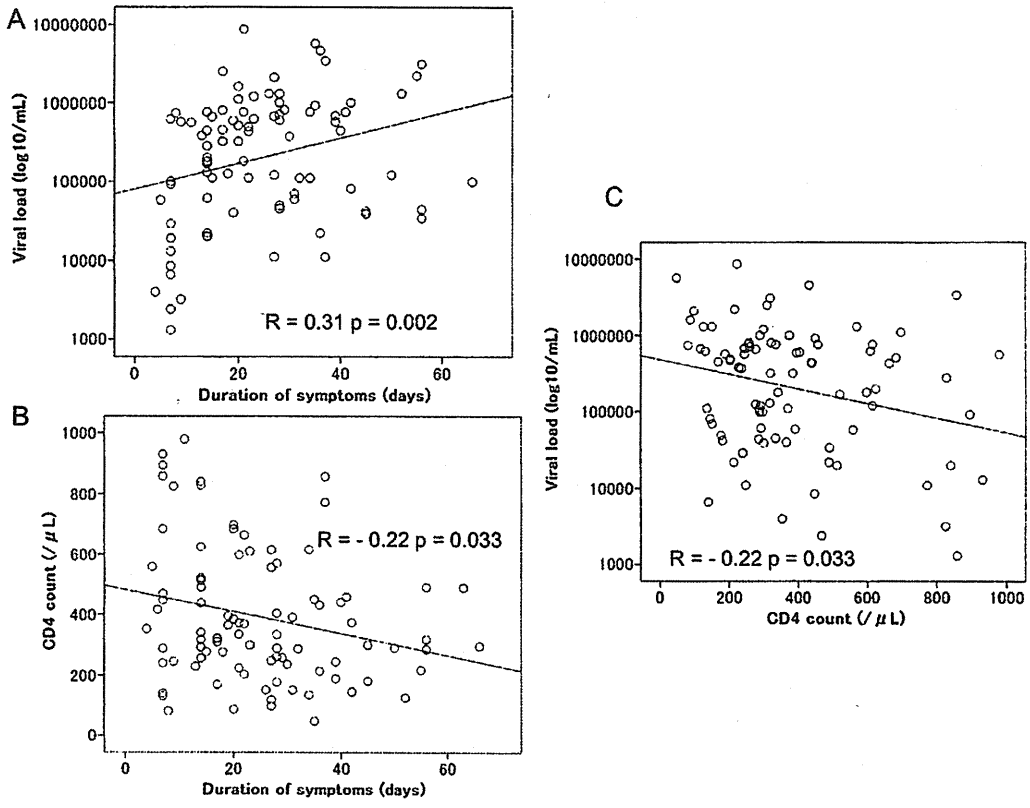

Figure 1. Correlations among plasma viral load, CD4 count, and clinical symptoms. A; Plasma viral load correlated with duration of symptoms (R=0.31, p=0.002). B; CD4 count correlated inversely with duration of symptoms (R=-0.22, p=0.033). C; plasma viral load correlated inversely with CD4 count (R=-0.22, p=0.033).

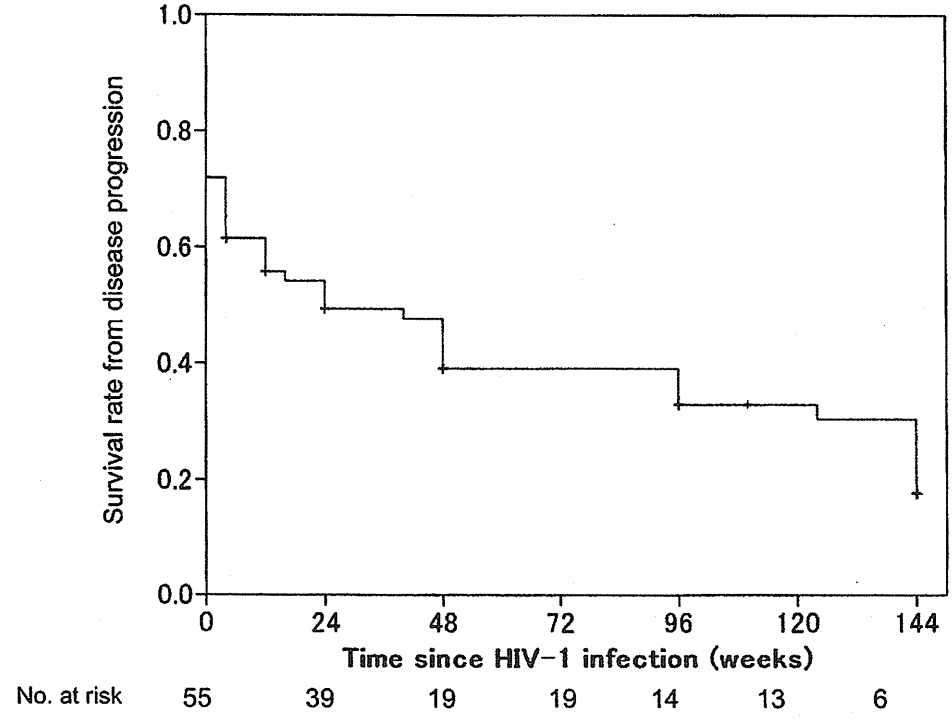

Figure 2. Progression-free survival in 82 patients. Progression was defined as CD4 count <350/μL or initiation of HAART. No. at risk: the number of CD4 count >350/μL or HAART naïve patients

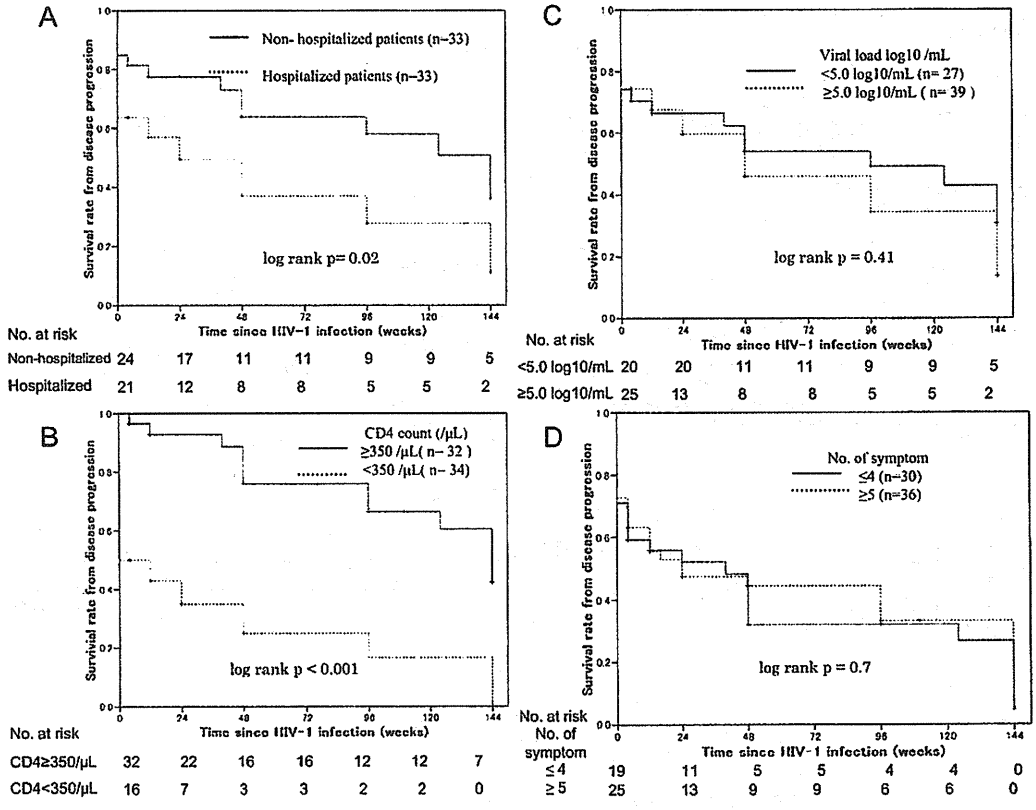

Figure 3. Progression-free survival among 66 patients according to rate of hospitalization, baseline CD4 count, and viral load. No. at risk: the number of CD4 count >350/μL or HAART naïve patients. A; Solid line: patients who required hospitalization due to PHI, dashed line: patients who did not require hospitalization (p=0.02, by log-rank test). B; Solid line: patients with CD4 count >350/μL at first visit, dashed line: patients with CD4 count <350/μL (p<0.001). C; Solid line: patients with viral load <5.0 log_{10}/mL, dashed line: patients with viral load ≥5.0 log_{10}/mL (p=0.41). Disease progression was defined as CD4 count <350/μL or initiation of HAART. D; Solid line: patients with the number of PHI symptoms ≤4, dashed line: patients with the number of PHI symptoms ≥5 (p=0.7, by log-rank test).

Comparison of percentage of recently infected patients with CD4 counts >350/μL at 3 years after infection and that of hemophiliacs as the first HIV-1 infected population in Japanese is shown in Fig. 4. The percentage (13.5%) of recently infected patients was significantly lower than that (47.6%) of Japanese hemophiliacs (p<0.001), clearly indicating the rapid decline of CD4 count in recently infected patients.

Discussion

In this study, we demonstrated rapid disease progression of symptomatic PHI Japanese patients in this decade. However, when we divided our study subjects into two groups according to the first half (1997-2002) and the latter half (2003-2007), disease progression of each group was not different (data not shown). In contrast, disease progression surrogated with natural CD4 decline of recently infected patients was significantly accelerated compared with Japanese hemophiliacs infected with HIV-1 before 1985. However, there are two quite different backgrounds; one is the route of infection and the other is the year of infection. Almost all hemophiliac patients are also co-infected with hepatitis C but do not have other sexually transmitted diseases (STDs). In contrast, most patients in the present study were infected via homosexual intercourse with many other STDs that may facilitate acceleration of the disease progression (7). In the present study, 69.7% patients had a past medical history of STDs, and the mean number of STDs was 1.08/patient (0: 31.3%, 1: 37.4%, 2: 23.2%, 3: 8.1%). In this regard, most published data on disease progression were obtained from men who have sex with men (MSM) cohorts (1, 2). Therefore, it is unlikely that the recent rapid disease progression is due to Japanese MSM. Whether or not the rapid disease progression in the recently HIV-1-infected Japanese can be generalized is to be elucidated in future studies.

Some HLA types are protective against disease progression such as HLA-B57 (19) and HLA-B51 (20) because HLA-restricted cytotoxic T lymphocytes (CTLs) play an important role on viral control. On the other hand, virus can easily escape from CTLs (17, 21). In some prevalent HLA types, escape virus can transmit and accumulate in the population (21). In this situation, some HLA types are no more

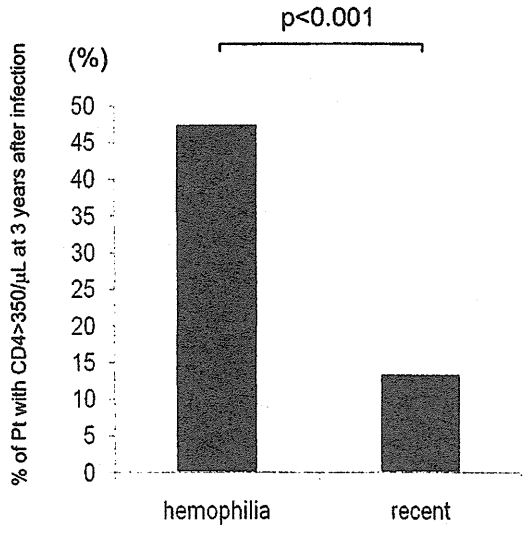

Figure 4. Comparison of percentage of previously and recently infected patients with CD4 counts >350/μL at 3 years after infection. In this analysis, Japanese hemophiliacs (designated "hemophilia" in the figure) were regarded as a previously infected patient, because they were infected with HIV-1 before 1985. The number of hemophiliacs was 42 patients. The eligible number of recently infected patients (designated "recent" in the figure) was 59 patients; infected with HIV-1 after 1997, untreated, and CD4 count at 3 years after infection.

protective. The HLA distribution is different in Americans compared to Japanese. Another possible hypothesis for the different disease progression is that Japanese hemophiliacs were exposed to HIV-1 through contaminated blood products imported from US as the first Japanese population infected with the virus around 1983. However, in recent years, most HIV-1 infection in Japanese is transmitted from Japanese patients. It can be postulated that current HIV-1 in Japan has adapted to the Japanese population, indicating acquisition and accumulation of escape virus from immune pressure of the otherwise protective HLA in Japanese population (21). From a negative point of view, the situation is similar to the epidemic of drug-resistance virus in treatment of naïve patients (22). The clinical relevance of the prevalence of immune escape virus in Japanese is a potentially serious matter in terms of the natural course of HIV-1 infection.

In the present study, all patients have had at least one symptom associated with PHI. During the follow-up period, no patient developed AIDS, whereas around 70% of the patients experienced immunologic progression as defined by a CD4 count <350/μL. It is noteworthy that the majority of these patients exhibited immunologic progression within 3 years and, surprisingly, >60% of them were documented within the first year. HAART was initiated in nearly 60% of patients during this period, including initiation for PHI-related severe symptoms in 20% of these patients. Previous studies on PHI have suggested that the number, duration, and/or severity of symptoms can predict faster disease progression to AIDS (23, 24). Our findings are compatible with these previous studies. Considered together, these results suggest that the duration of illness rather than the number of symptoms is more likely to be a major determinant of immunological progression. The estimated risks of disease progression were more than 50% by week 24 and 80% by week 144. Comparison with those observed elsewhere during the natural course of HIV-1 infection (24), these disease progression rates are surprisingly high. Among the patients with CD4 counts >350/μL at first visit, a quarter of them showed disease progression within 1 year. In contrast, in patients with CD4 count <350/μL, three quarters of them showed disease progression within the same period. Goujard et al (25) suggested possible recovery of CD4 count after the primary infection phase even in patients with very low count because it fluctuates during that period. In contrast, our results suggest that patients with a CD4 count of <350/μL during primary infection should be monitored carefully because spontaneous recovery of CD4 cell count during primary infection was rare. This cautionary remark could also apply to patients with a CD4 count of >350/μL because they exhibited nearly 60% risk of disease progression within 3 years. These observations may allow more targeted clinical monitoring and timely initiation of HAART. The impact of a short-term HAART during symptomatic primary infection on the subsequent disease progression needs to be elucidated in future study.

Although we included all recent seroconverters during the study period, it could be argued that this study carries some institution bias (i.e., a high proportion of cases with severe disease). However, the present finding of a surprisingly rapid disease progression in our patient population is new. Whether or not the natural course of disease progression has recently become accelerated in other countries or other cohorts is a matter of great interest.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

The authors thank all clinical staffs of the AIDS Clinical Center. This study was supported in part by a Grant-in-Aid for AIDS Research from the Ministry of Health, Labour, and Welfare of Japan.

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INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Open-Label Randomized Multicenter Selection Study of Once Daily Antiretroviral Treatment Regimen Comparing Ritonavir-Boosted Atazanavir to Efavirenz with Fixed-Dose Abacavir and Lamivudine

Miwako Honda[1], Michiyo Ishisaka[1], Naoki Ishizuka[2], Satoshi Kimura[3], Shinichi Oka[1] and behalf of Japanese Anti-HIV-1 QD Therapy Study Group

Abstract

Background The side-effects of anti-retroviral drugs are different between Japanese and Caucasian patients. Severe central nerve system (CNS) side-effects to efavirenz and low rate of hypersensitivity against abacavir characterize the Japanese.

Objective The objective of this study was to select a once daily regimen for further non-inferior study comparing the virological efficacy and safety of the first line once daily antiretroviral treatment regimens in the current HIV/AIDS guideline.

Methods The study design was a randomized, open label, multicenter, selection study. One arm was treated with efavirenz and the other with ritonavir-boosted atazanavir. A fixed-dose lamivudine plus abacavir were used in both arms. The primary endpoint was virologic success (viral load less than 50 copies/mL) rate at 48 weeks. Patients were followed-up to 96 weeks with safety as the secondary endpoint. Clinicaltrials.Gov (NCT 00280969) and the University hospital Medical Information Network (UMIN000000243).

Results A total of 71 participants were enrolled. Virologic success rates in both arms were similar at week 48 [efavirenz arm 28/36 (77.8%); atazanavir arm 27/35 (77.1%)], but were decreased at week 96 to 55.6% in the efavirenz arm and 68.8% in the atazanavir arm (p=0.33). At the 96-week follow-up, 52.8% of the EFV arm and 34.3% of the ATV/r arm reached total cholesterol more than 220 mg/dL and required treatment. None of the patients developed cardiovascular complications in this study by week 96.

Conclusion There was no significant difference in the efficacy of efavirenz and ritonavir-boosted atazanavir combined with lamivudine plus abacavir at 48 weeks. The evaluation of safety was extended to 96 weeks, which also showed no significant difference in both arms.

Key words: HIV, antiretroviral treatment, efavirenz, atazanavir, abacavir, lamivudine

(Intern Med 50: 699-705, 2011)
(DOI: 10.2169/internalmedicine.50.4572)

Introduction

The use of a non-nucleoside transcriptase inhibitor (NNRTI) or ritonavir-boosted protease inhibitor as the key drug, combined with two nucleoside reverse-transcriptase inhibitors (NRTI), as the backbone drugs, is recommended as an initial therapy in human immunodeficiency virus type 1 (HIV-1) infection. For the key drug, when efavirenz (EFV) or ritonavir-boosted atazanavir (ATV/r) is selected, once daily therapy is possible. EFV is a widely used NNRTI, however, in some clinical studies conducted in Asia, a higher rate of adverse events, especially central nervous system-related symptoms, has been noted (1-3).

In terms of backbone drugs, didanosine (ddI), stavudine (d4T) and zidovudine (ZDV) were widely used NRTIs.

[1]AIDS Clinical Center, National Center for Global Health and Medicine, Japan, [2]Division of Preventive Medicine, Research Institute, National Center for Global Health and Medicine, Japan and [3]Tokyo Teishin Hospital, Japan
Received for publication September 22, 2010; Accepted for publication December 6, 2010
Correspondence to Dr. Miwako Honda, honda-1@umin.ac.jp

However, their mitochondrial toxicity made long-term use difficult (4-7). Due to HLA-B*5701-related hypersensitivity, abacavir (ABC) is listed as the second line drug under the United States Department of Health and Human Services (DHHS) guidelines. However, HLA-B*5701 is quite rare among Japanese, and thus the incidence of hypersensitivity to ABC in Japanese patients is lower than that of Caucasians (8-10). Although tenofovir (TDF) is widely used as the first line drug, the dose-dependent nephrotoxicity is a major concern in Japanese because Japanese body weight is lighter than that of Caucasians (11, 12).

The present study was designed in 2006, when the combination of TDF, lamivudine (3TC) or entiricitabine (FTC), and EFV was the first line regimen of antiretroviral treatment (13). To explore the optimal antiretroviral combination for the best clinical outcome among Japanese HIV-1 patients (14), a selection study was designed to compare the efficacy and safety of once daily treatment with EFV or ATV/r combined with a fixed-dose ABC and 3TC (ABC/3TC).

Objective

The objective of this study was to select a once daily regimen for further non-inferior study comparing the virological efficacy and safety of the first line once daily antiretroviral treatment regimens in the current HIV/AIDS guideline.

Subjects and Methods

Study design

The study was designed as a randomized, open label, multicenter selection study, which means the superior regimen at the end point is to be selected as alternate arm to compare with the current first line regimen in the next step. Therefore, this study was not to compare superiority or non-inferiority of both arms. As the selection study, the main objective is to select a treatment regimen for further pivotal study and the secondary objective is safety. The primary endpoint was the proportion of patients in each arm who achieved virologic success (HIV-1 RNA less than 50 copies/mL in plasma) at week 48. The secondary endpoints were death, AIDS and serious non-AIDS events, non-AIDS defining cancer, treatment-related serious or grade 3 to 4 adverse events, and discontinuation of antiretroviral treatment before week 96.

The inclusion criteria of this study were those who were treatment-naïve, HIV-1 positive Japanese men with a CD4+ count ranging from 100 to 300 cell/mm^3. The exclusion criteria included current active AIDS, acute retroviral syndrome and persistent active hepatitis B infection (HBs-Ag positive). Patients with a history of 3TC treatment for hepatitis B infection were also excluded. After obtaining informed consent, eligible participants were randomized into once daily 600 mg EFV or 100 mg RTV and 300 mg ATV (EFV arm vs ATV/r arm). All participants received a fixed dose of 600 mg of ABC and 300 mg 3TC (ABC/3TC).

At baseline, the demographic characteristics and a complete medical history were recorded, physical examination was performed, and various laboratory tests were obtained (CD4+ count, HIV-1 RNA, complete blood count, biochemistry, liver and renal function tests, and total cholesterol). Participants were examined at baseline, then every 4 weeks until week 96. Careful clinical examination was provided at each visit, including history taking of any adverse event, adherence to treatment, and physical examination. Furthermore, blood tests were obtained including complete blood count, biochemistry, liver and renal function tests, CD4+ count and HIV-1 RNA. When HIV-1 RNA became less than 50 copies/mL, participants were rescheduled to be seen every 4 to 12 weeks. All participants underwent clinical examination at week 48 as the primary endpoint, then every 12 weeks until week 96 as the secondary follow-up period for evaluation of safety.

The study recruitment period was started on September 1st of 2005 for 2 years. The study protocol was originally designed to follow patients for 48 weeks, however, during the study period, cardiovascular adverse events of ABC-containing regimen were reported (15, 16). Considering the importance of adherence to safety, the follow-up period was extended to 96 weeks.

Independent data and safety monitoring board reviewed virology and safety data by treatment allocation were obtained when all participants had completed 24 weeks of the study. A total of 18 academic medical institutions in Japan participated in this study. The study protocol was approved by the ethics committee of each site and was registered at Clinicaltrials. Gov (NCT00280969) and the University Hospital Medical Information Network (UMIN000000243).

Statistical analyses

The estimated proportion of virologic failure, representing HIV-1 RNA of more than 50 copies/mL at 48 weeks of treatment, was 30% over one year. To choose one treatment group with a probability of 0.90, if it is superior to another treatment by >10%, if any, a sample size of 40 participants per group was necessary according to the selection design (17).

To assess differences in proportions, we used Fisher's exact test and calculated exact confidence intervals (CIs). We conducted intent-to-treat analysis and used the T test to compare the efavirenz arm and the ritonavir boosted atazanavir arm, unless the data showed skewed distribution, in which case the Wilcoxon's test was used. All analyses used a two-sided alfa of 0.05. No adjustment for each test was made for multiple comparisons due to the fact that we have several tests to compare the efficacies and safeties of two groups. All analyses, unless otherwise specified, were determined a priori and were hypothesis driven. Statistical analyses were performed using SAS version 9.1.

Table 1. Baseline Characteristics of Participants

Variable	efavirenz	atazanavir/r	p
Number of patients	36	35	NS
Age (yrs) median	35	36	NS
HIV-RNA (log_{10} copies/mL)			
median	4.6	4.4	NS
range	2.8–5.4	3.0–5.3	
CD4 count (cells/mm^3)			
median	220	226	NS
range	121–323	103–324	
Total Cholesterol (mg/dL)			
median	155.5	159.5	NS
range	122–208	112–215	
Total bilirubin (mg/dL)			
median	0.6	0.5	NS
range	0.3–1.7	0.3–1.5	
ALT (IU/L)			
median	24	20	NS
range	8–71	8–78	
Creatinine (mg/dL)			
median	0.80	0.75	NS
range	0.6–1.03	0.6–1.02	

Results

Participants

In the study recruitment period, 71 participants were randomly assigned to two groups (36 in EFV arm and 35 in ATV/r arm). The baseline characteristics of the subjects are listed in Table 1. Among the 71 participants, 62 (87.3%) for the primary endpoint and 58 (80.6%) for the secondary endpoint completed the study protocol. By week 96, 9 participants had withdrawn due to clinical events, 2 declined to continue the study for personal reasons, one died by accident and 3 were transferred to other non-participating institutions.

Primary endpoint

At week 48, by intent-to-treat, missing-equals-failure analysis, 28 of 36 participants (77.8%, 95% CI: 60.9-89.9) in the EFV arm and 27 of 35 (77.1%, 95% CI: 59.9-89.9) in the ATV/r arm achieved the goal of HIV-1 RNA less than 50 copies/mL. There was no significant difference between the two arms (p=0.95).

Virologic success over time

Figure 1 shows the intent-to-treat analysis of participants who reached virologic success. At week 96, the rates of virologic success in the EFV arm were 55.6% (20 of 36) and 68.6% (24 of 35) in the ATV/r arm (p=0.33). The number of participants with a baseline HIV-1 RNA level of more than 100,000 copies/mL was 5 in the EFV arm and 2 in the ATV/r arm. One participant in each arm withdrew from the study at week 4 due to skin rash. The rest of the participants achieved virologic success in the EFV arm (4 out of 4) and in ATV/r arm (1 out of 1).

Secondary endpoints

In the EFV arm, 7 of 36 participants did not complete the study; 5 of the 7 developed psychiatric symptoms, including suicidal idealization, insomnia and irritation, 2 developed skin rashes and the remaining 2 were lost to follow-up because they were transferred to non-affiliated hospitals. In the ATV/r arm, 6 of 35 patients could not complete the study; one died by accident for unknown reason (the cause of death according to the coroner's report was not related to the cardiovascular system), 2 participants required treatment change (this was due to suicidal idealization in one and to skin rash in the other), one participant withdrew by own wish, one enrolled into another study, and one was transferred to another non-affiliated medical care facility.

Figure 2 shows the change of total cholesterol, liver function and total bilirubin from the baseline. At enrollment in the study, the median total cholesterol in the EFV arm was 155.5 mg/dL (range: 122-208) and in the ATV/r arm was 159.5 mg/dL (range: 112-215). The total cholesterol was not more than 220 mg/dL in any of the participants of both arms at baseline, and there was no significant difference between the two arms. During the study period, the total cholesterol increased to more than 220 mg/dL and required treatment with hypolipidemic agents in 52.8% of the EFV arm and 34.3% of the ATV/r arm. There was a significant increase in total cholesterol from the baseline in both arms ($p < 0.05$). There was no significant change in liver function tests during the study. New onset grade 3 hyperbilirubinemia was noted in 27 of 35 (77.1%) of the ATV/r arm but in none of the EFV arm. None of the hyperbilirubinemia in the ATV/r arm was associated with altered liver function, altered renal function, nephrolithiasis, or cholelithiasis.

Discussion

This study was designed as selection study, which means the superior regimen at the endpoint is to be selected as an alternate arm to compare with the current first line treatment in the next step. By definition of the selection study, the superior arm does not require statistical significance (17). At week 48, 77.8% of ATV/r arm and 77.1% of EFV arm reached HIV-VL of less than 50 copies/mL. Based on the definition of the selection study, the combination ABC/3TC/EFV was selected to compare the current first line treatment while the efficacy of each arm was almost even in this study.

In this clinical trial of 71 participants over a period of 96 weeks, no cardiovascular events or severe hypersensitivity reaction against ABC was observed. In this study, the efficacy of EFV combined with ABC/3TC and ATV/r combined with ABC/3TC was similar. Therefore, ABC based regimen can be selected as a safe combination to compare the efficacy of the first line combinations, such as EFV plus TDF/FTC or ATV/r plus TDF/FTC (18-20), in the next step for the best clinical benefits in Japanese patients.

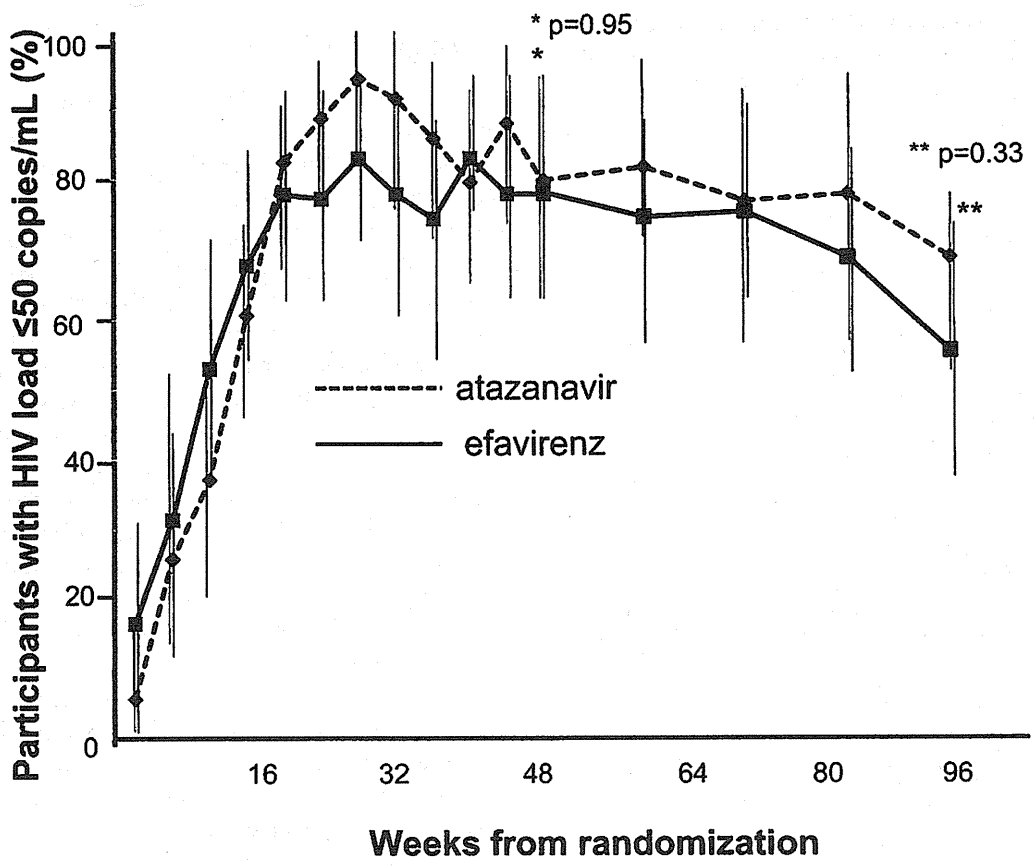

Figure 1. Proportions of participants with HIV-RNA less than 50 copies/mL.
The efficacies of the efavirenz arm and ritonavir-boosted atazanavir arm were compared with intent-to-treat analysis. There were no significant difference between arms at both week 48 (p=0.95) and week 96 (p=0.33).

In February 2008, the United States National Institution of Allergy and Infectious Disease announced that the data and safety monitoring board of ACTG 5202 recommended a modification of the study design because they found that among participants with high viral loads (100,000 or more copies/mL) at the time of screening, treatment combinations that included ABC/3TC were not as effective in controlling the virus as those of regimens containing TDF/FTC (19, 21). At that point, all of the present 71 participants were already enrolled in the study and the baseline HIV-1 RNA of 7 participants was more than 100,000 copies/mL. Of these 7 participants, 2 had already withdrawn from the study by week 4, and the rest of participants had reached HIV-1 RNA of less than 50 copies/mL. The safety monitor board made no recommendation to amend the protocol.

As a primary endpoint, 77.8% of the EFV arm and 77.1% of the ATV/r had reached virological success, however, total cholesterol in 58.1% of the EFV arm and 46.9% of the ATV/r arm increased to more than 220 mg/dL, which required treatment. Thus, the overall proportion of participants with good viral suppression and without severe adverse events or treatment modification was 39.6% for the EFV arm and 62.3% for the ATV/r arm. Considering the reasons for treatment modification, the neuro-psychiatric side effects required a regimen change in the EFV arm. Although several studies concluded that the neuro-psychiatric side effects are transient in nature, one study reported that treatment had to be changed in 16% of patients on EFV due to neuro-psychiatric side effects (22-24). Although there was no significant difference even with the small sample size, 5 out of 36 (13.9%) participants on EFV in our study required treatment change, compared with only 1 out of 35 (2.9%) of the ATV/r arm. This aspect of our study was similar to that reported in the Euro SIDA study (24). In the Swiss Cohort study, the treatment-limiting CNS adverse events was 3.8 (95% CI 2.7-5.2) per 100 person-years and it was clearly related to EFV (25). Considered together, these results emphasize the need for close observation of patients treated with EFV.

The incidence of hyperbilirubinemia in the present study was 77.1% in the ATV/r arm but none of these patients was above grade 4. Furthermore, none of the patients in this study developed liver function abnormality, altered renal function, renal stones, or cholelithiasis. As reported by Torti et al and Josephson et al, such clinical outcome can be used as a marker of adherence to ATV therapy (26, 27).

Limitations of this study include a small sample size.

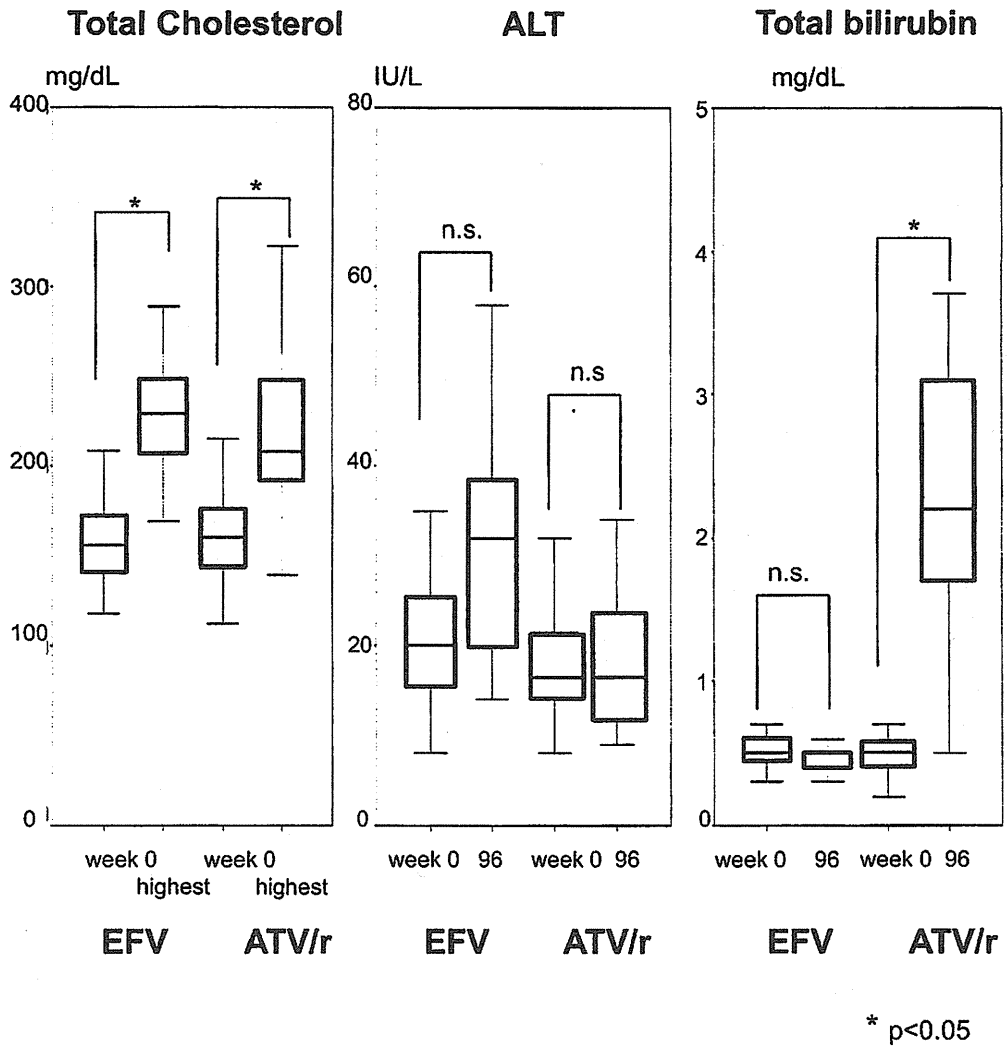

Figure 2. Changes from baseline in total cholesterol, ALT and total bilirubin.
ALT and total cholesterol at week 96 were compared with the baseline values. Since participants who developed hyperlipidemia were treated with lipid-lowering agents during the study period, the highest levels registered in each participant during the follow-up were collected for analysis. There were no significant differences in total cholesterol and ALT between the two arms, while hyperbilirubinemia was significantly higher in the ATV/r arm. Modification of treatment due to hyperbilirubinemia was not required in any of the patients of the ATV/r arm. In these box-and-whisker plots, the lines within the boxes represent median values; the upper and lower lines of the boxes represent the 25th and 75th percentiles, respectively; and the upper and lower bars outside the boxes represent the 90th and 10th percentiles, respectively.

Considering many studies on HIV treatment held in western countries that enrolled few Asian HIV-1 patients, it is important to collect data from Asian population. The current United States Department of Health and Human Services guidelines recommend TDF/FTC as the first line regimen, while the European AIDS Clinical Society recommends 3TC and ABC addition to TDF and FTC alone (28, 29). TDF/FTC is a known potent antiretroviral agent, however, its long-term efficacy and safety remain unclear (11, 12). Considering that the combinations of NRTI are limited, the efficacy and safety of ABC in the low HLA-B*5701 population need to be evaluated for wider treatment options for HIV-1 patients (9, 10).

Conclusion

This study was designed as a selection study to compare the virologic efficacy and treatment safety of EFV and ATV/r, both with ABC/3TC, in Japanese patients. The results showed no significant differences in efficacy between the two regimens at week 48. The evaluation of safety was extended to 96 weeks, which also showed no significant difference in both arms. The results of the present study have already been applied as the basis of a follow-up study that is

currently being conducted in Japan to compare NRTI combinations of ABC/3TC and TDF/FTC with ATV/r as key drugs.

The authors state that they have no Conflict of Interest (COI).

Members of the Japanese Anti-HIV-1 QD Therapy Study Group: Koji Watanabe[1], Tamayo Watanabe[1], Yasuhisa Abe[1], Ikumi Genka[1], Haruhito Honda[1], Hirohisa Yazaki[1], Junko Tanuma[1], Kunihisa Tsukada[1], Hiroyuki Gatanaga[1], Katsuji Teruya[1], Yoshimi Kikuchi[1], Misao Takano[1], Mikiko Ogata[1], Mizue Saida[2], Toshio Naito[2], Yoshiyuki Yokomaku[3], Motohiro Hamaguchi[3], Keiko Ido[4], Kiyonori Takada[4], Toshikazu Miyagawa[5], Shuzo Matsushita[5], Takeyuki Sato[6], Masaki Yoshida[7] Takafumi Tezuka[8], Yoshiya Tanabe[8], Isao Sato[9], Toshihiro Ito[9], Masahide Horiba[10], Mieko Yamada[11], Mikio Ueda[11], Kazufumi Matsumoto[12], Takeshi Fujii[12], Mariko Sano[13], Shin Kawai[13], Munehiro Yoshino[14], Takuma Shirasaka[14], Satoshi Higasa[15], Tomoyuki Endo[16], Norihiro Sato[16], Katsuya Fujimoto[16], Rumi Minami[17], Masahiro Yamamoto[17], Yukiko Nakajima[18]

[1]National Center for Global Health and Medicine, [2]Juntendo University, [3]National Hospital Organization, Nagoya Medical Center, [4]Ehime University, [5]Kumamoto University, [6]Chiba University, [7]The Jikei University, [8]Niigata University, [9]National Hospital Organization, Sendai Medical Center [10]East Saitama National Hospital, [11]Ishikawa Prefectural Hospital, [12]Institute of Medical Science, The University of Tokyo, [13]Kyorin University, [14]National Hospital Organization, Osaka Medical Center, [15]Hyogo College of Medicine, [16]Hokkaido University, [17]National Hospital Organization, Kyushu Medical Center, [18]Kawasaki City Hospital

Acknowledgement

This study was supported in part by a grant from the Japanese Foundation for the Promotion of International Medical Research Cooperation and National Center for Global Health and Medicine.

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INTERNAL MEDICINE

□ CASE REPORT □

Primary HIV Infection with Acute Transverse Myelitis

Yohei Hamada[1], Koji Watanabe[1], Takahiro Aoki[1], Noritoshi Arai[2], Miwako Honda[1], Yoshimi Kikuchi[1] and Shinichi Oka[1]

Abstract

Primary HIV infection (PHI) is associated with various neurological disorders. However, acute transverse myelitis (ATM) complicating PHI has not been reported after the introduction of the combination antiretroviral therapy (cART). We encountered one patient with known PHI with clinical presentation of ATM. Treatment with cART and corticosteroids successfully improved symptoms, and no recurrence was noted after discontinuation of cART. In conclusion, concurrent use of cART and corticosteroids was effective against PHI accompanied by ATM and could be withdrawn after improvement of ATM.

Key words: acute transverse myelitis, primary HIV infection, cART

(Intern Med 50: 1615-1617, 2011)
(DOI: 10.2169/internalmedicine.50.5186)

Introduction

Primary HIV infection (PHI) is associated with various neurological disorders (1, 2). However, PHI complicated with acute transverse myelitis (ATM) had only been reported before the availability of combination antiretroviral therapy (cART) (3). We report a case of ATM, successfully treated with cART and corticosteroids.

Case Report

A 30-year-old homosexual man visited a local hospital with 5-day history of systemic skin eruption, high fever and sore throat. Although these symptoms disappeared spontaneously within one week, PHI was suspected because of the positive result of 4th generation HIV diagnostic test. He was referred to the clinic of our hospital for further management. PHI was confirmed by the negative result of Western blot analysis and high HIV-RNA level (6.38 log copies/mL) with a CD4 count of 601/μL. No treatment for HIV infection was provided because the patient was asymptomatic at that stage. However, he subsequently developed urinary retention and abnormal sensation in the lower limbs, and he returned to the clinic 2 days later. On admission, neurological examination showed normal function of the cranial nerves and no nuchal stiffness. Motor system assessment showed no paresis. The deep tendon reflexes were exaggerated in the lower extremities but normal in the upper extremities. Pathological reflexes such as Babinski reflex and Chaddock sign were not noted. Sensory system examination showed bilateral hypoesthesia and hypalgesia below the level of Th7, and deep sensation was preserved in all extremities. Urinary retention was observed and anal muscle tone was reduced. The cranial and entire spinal magnetic resonance imaging (MRI), with and without gadolinium enhancement, showed no abnormal findings. Examination of the cerebrospinal fluid (CSF) showed mild pleocytosis (cell count: 8.0/μL, mononuclear cells 6.0/μL), a normal protein level (29 mg/dL), and normal IgG index (0.62). The CSF level of myelin basic protein (MBP) was elevated to 1857.3 pg/mL (normal range: <102 pg/mL). Herpes simplex virus, varicella zoster virus, cytomegalovirus and Epstein-Barr virus DNA were negative in the CSF on polymerase chain reaction assay.

ATM was diagnosed by the typical neurological findings with spinal cord inflammation, which was proceeded by PHI. Upon the diagnosis, cART of lopinavir/ritonavir plus abacavir/lamivudine and methylprednisolone pulse treatment (1000 mg for 3 days) were initiated (Fig. 1). The treatment resulted in immediate and rapid improvement of clinical symptoms, and all symptoms disappeared by treatment day 6. The MBP level (less than 31.2 pg/mL) and cell count

[1]AIDS Clinical Center, National Center for Global Health and Medicine, Japan and [2]Department of Neurology, National Center for Global Health and Medicine, Japan
Received for publication January 20, 2011; Accepted for publication March 29, 2011
Correspondence to Dr. Yohei Hamada, yhamada@acc.ncgm.go.jp