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Safety and efficacy of interferon-α in 167 patients with human T-cell lymphotropic virus type 1–associated myelopathy

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A postmarketing surveillance study was undertaken to investigate the safety and efficacy of interferon-α for human T-cell lymphotropic virus type 1 (HTLV-1)-associated myelopathy (HAM) under routine treatment conditions. A total of 273 cases from 91 medical institutions were registered into the survey. So far, 167 cases had been evaluated for safety and 152 for efficacy. The efficacy evaluation was rated based on clinical symptoms of HAM. Efficacy ratio (rate of patients assessed as "modest to markedly improved" and "mildly improved") at 4 weeks was 66.2%. Factors that significantly affected efficacy ratio at 4 weeks was initial Osame's motor disability score (OMDS) before interferon-α therapy and duration and stage of illness. Sustained improvement of OMDS for at least 5 months after stopping interferon-α was observed in 11 of 30 patients (36.7%). A total of 536 adverse drug reactions (ADRs) occurred in 146 patients, 46 of which were serious. Because some of these ADRs occurred late, it is necessary to watch out for them during long-term treatment. *Journal of NeuroVirology* (2007) **13,** 364–372.

Keywords: adverse reactions; HAM; interferon-α; postmarketing surveillance; provision factor; sustained effect

Introduction

Human T-cell lymphotropic virus type 1 (HTLV-1)-associated myelopathy (HAM) is characterized by slowly progressive spastic paraparesis and anti-HTLV-1 antibody positivity in serum and cerebrospinal fluid (CSF) (Osame *et al*, 1987; Osame and McArthur, 1992). There is no treatment that can eliminate HTLV-1 from patients; however, improvement in clinical status and motor function has been reported with some drugs, including interferon-α, corticosteroids, immunomodulators, and antiviral agents (Nakagawa *et al*, 1996). A double-blind, multicenter study has shown that the therapeutic benefit in the 3.0×10^6 international units (IU) group was significantly higher than in the 0.3×10^6 IU group in the improvement of motor dysfunction, urinary disturbance, and changes in neurologic signs (Izumo *et al*, 1996). As a result of this trial, natural

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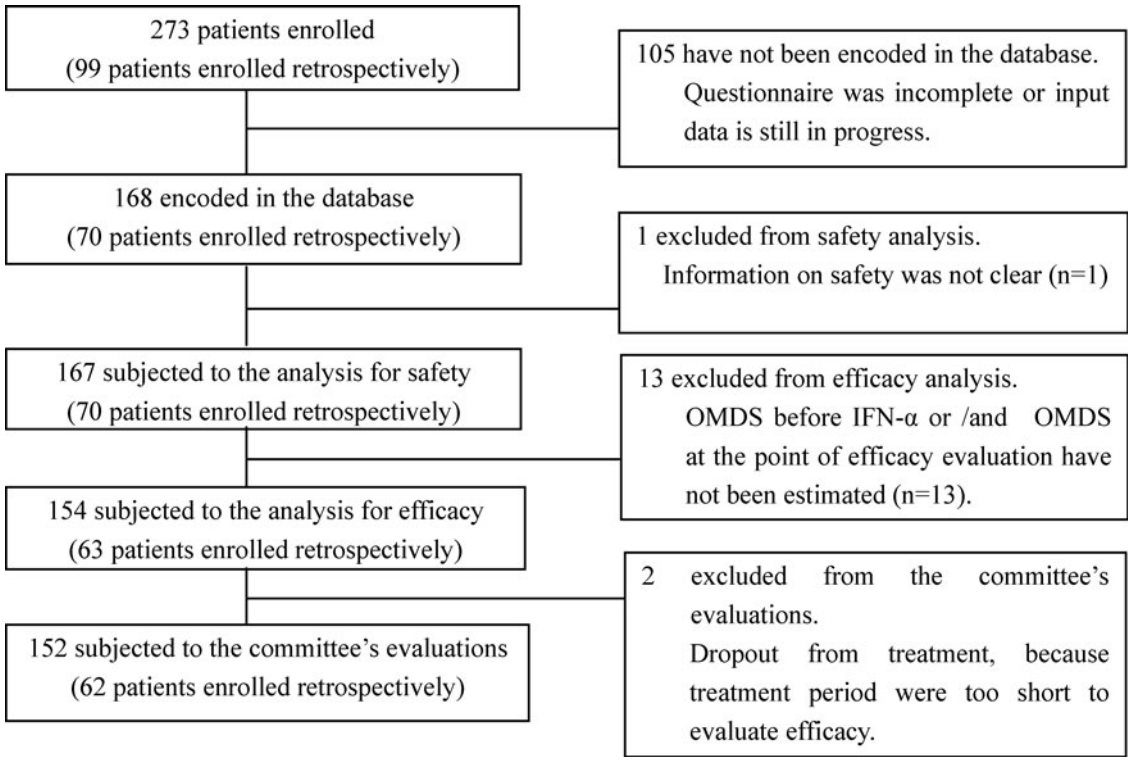

Figure 1 Flow chart of the analysis of the subjects.

interferon-α (SUMIFERON; Dainippon Sumitomo Pharma, Osaka, Japan) was approved as the first drug for the treatment of HAM in Japan in January 2000. The approved dosage and administration is once-daily 3.0×10^6 IU by subcutaneous or intramuscular administration. As a postmarketing surveillance, exposure data were collected, and safety and efficacy on patients prescribed interferon-α in clinical practice were evaluated. Although the survey is still ongoing, with a large number of data on the use of interferon-α under routine treatment still to be reported, we here present the interim results of the efficacy and safety of interferon-α on HAM.

Results

Subjects

This study started on 18th January 2000. All the patients with HAM who received interferon-α from 18th January 2000 to 31st March 2005 were enrolled into this surveillance. As a result, a total of 273 patient data from 91 medical institutions throughout Japan, especially from the Kyushu district where HAM is endemic, were registered. Number of registered patients was not the total number of patients who met entry criteria at the 91 institutions participated in the survey, as the survey period have shortened in some institutions for unavoidable reasons. Data from 168 patients have already been encoded in the database. One hundred sixty-seven were included for the safety evaluation and 154 for the efficacy evaluation (Figure 1).

Interferon-α administration under routine condition

Administration of interferon-α varied among the patients. The usages of interferon-α in 167 patients are summarized in Table 1. Duration of interferon-α therapy period ranged from 4 to 793 days (median : 30 days). In the majority of cases, the period was no longer than 35 days ($n = 102$). (The duration of the therapy was not shown in Table 1.)

Concomitant therapy was also quite variable among patients. Various treatments for HAM had been given during and after interferon-α therapy. The kinds of drugs and the number of patients are shown below.

Corticosteroids: $n = 50$
Muscle relaxant: $n = 110$
Ascorbic acid or mixture containing ascorbic acid: $n = 52$
Drugs for hypoactive detrussor: $n = 67$
Mecobalamin: $n = 37$
Therapy other than drugs: $n = 70$ (rehabilitation including physiotherapy: $n = 69$; acupuncture and moxibustion: $n = 1$; urinary self-catheterization: $n = 1$)

Some started therapy concomitantly with interferon-α, some started and stopped just

Table 1 Administration of interferon-α

	No. of patients
Injection route	
Intramuscular	165
Subcutaneous	2
Dosage of interferon-α at one time	
3.0×10^6 IU	163
1.5×10^6 IU	2
Alternation of 1.5×10^6 and 3.0×10^6 IU	2
Frequency and duration of interferon-α	
Daily administration within 20 days	25
Daily administration more than 21 days and less than 35 days	57
Daily administration more than 36 days	4
Initial daily administration within 21 days then followed for an additional intermittent administration	20
Initial daily administration from 21 to 35 days then followed for an additional intermittent administration	38
Intermittent (from 20 to 434 days)	10
Other	10

before interferon-α therapy, some altered their dosages or were interrupted.

Disparity of score

We assumed that each clinical symptom would change congruently with the other clinical symptoms. However, there was a disparity in symptoms in nine patients—nine patients improved in one (or more) symptom(s) with deterioration in another. Disparity in clinical symptoms was seen in connection with adverse drug reactions (ADRs) of interferon-α such as sensory disturbance or hyperesthesia, or changing of combination medicine in some patients. Because HAM is characterized by progressive spastic paraparesis, much importance was attached to improved scores compared to scores that deteriorated. The Committee evaluated efficacy mainly according to the improvement in scores.

Efficacy at 4 weeks after starting interferon-α therapy

The committee's evaluations were made on 152 cases, whereas 154 met the efficiency analysis criteria. Because two were administered interferon-α less than 6 days, the committee judged them as dropout of the treatment. Only one patient was not observed sensory disturbance at 4 weeks after interferon-α, but based on the improvement of Osame's motor disability score (OMDS), this patient evaluated as "modest to markedly improved." As comments concerning efficacy were not necessarily to be filled, it was not clear whether physicians measured time required to walk 10 m or noticed a patient's self-defined complaints.

The rates for modest to markedly improved, mildly improved, stable, slightly deteriorated and deteriorated were 29.2%, 37.0%, 27.9%, 2.6%, and 1.9%, respectively. Efficacy ratio was defined as the percentage of patients assessed as "modest to markedly improved" and "mildly improved" in the total number of patients subjected to the efficacy analysis. Efficacy ratio was 66.2%. As a result of statistical analysis, the efficacy ratio was statistically higher in the patients with lower OMDS (Table 2). The efficacy ratio was particularly low in patients with more than 8 in OMDS. There were no relationships between efficacy ratio and background factors (sex, age, age of onset of HAM, duration of illness, previous therapy, concomitant drugs for HAM, and concomitant therapy other than drugs for HAM (data not shown) other than OMDS. Neither corticosteroids nor muscle relaxant were not correlated with efficacy ratio (Table 3). In patients in progression phase, ratio of improvement was higher than that in stable phase, but efficacy ratio was not statistically significant ($P = .277$) (Table 2).

As shown in Table 1, two patients received interferon-α by subcutaneous and another two received lower dose (1.5×10^6IU). Efficacy at 4 weeks of patients who received by subcutaneous route were modest to markedly improved = 1, stable = 1; and who received lower dose were modest to markedly improved = 2.

Efficacy at the time of withdrawal of interferon-α

Interferon-α therapy was continued over 35 days in 61 of 154 patients. Because OMDS at the time of withdrawal was not documented in 13 of 61 patients, the committee made efficacy evaluations based on the remaining 48 cases. The results are as follows: modest to markedly improved: 33.3% (16 of 48 patients); mildly improved: 39.6% (19 of 48 patients); stable: 12.5% (6 of 48 patients); slightly deteriorated: 4.2% (2 of 48 patients); and deteriorated: 10.4% (5 of 48 patients). In Table 4, the results of the evaluation at the time of withdrawal are represented against those at 4 weeks after starting interferon-α. Most of these 48 patients (85%, 41 of 48 cases) were rated as modest to markedly improved or mildly improved at 4 weeks after starting interferon-α. Fourteen patients were administered interferon-α over 6 months. Two deteriorated in OMDS and urinary disturbance scores, respectively, during withdrawal of interferon-α and remained unchanged after repeated administration. Three responded to treatment temporarily but returned to base line at the end of treatment. Nine patients were rated as "modest to markedly improved" or "mildly improved" (data not shown).

Sustained effects after interferon-α withdrawal

Sustained effects of interferon-α were evaluated in 50 patients who improved at least by 1 point in OMDS during administration of interferon-α or within 1 week of withdrawal. We defined the sustained effects as the period from the day of withdrawal to the first day at which patients showed relapse in OMDS. OMDS after stopping interferon-α were not documented in 14 cases. Six cases retained their improved rating but their follow-up period was less than 5 months. Thus, the duration of sustained

Table 2 Correlation with corticosteroids, muscle relaxant and efficacy evaluations

		Committee's evaluation (%)						
	No. of patients	*Modest to markedly improved*	*Mildly improved*	*Stable*	*Slightly deteriorated*	*Deteriorated*	*Efficacy ratio (%)*	*P value*
Stage of HAM								.277*
Stable phase	90	19 (21.1)	38 (42.2)	31 (34.4)	1 (1.1)	1 (1.1)	57 (63.3)	
Progress phase	58‖	23 (39.7)	18 (31.0)	10 (17.2)	3 (5.2)	2 (3.4)	41 (70.7)	
Uncertain	6	3 (50.0)	1 (16.7)	2 (33.3)			4 (66.7)	
OMDS before treatment								.132†
								.031§
2	11	4 (36.4)	3 (27.3)	2 (18.2)	1 (9.1)	1 (9.1)	7 (63.6)	
3	10	4 (40.0)	4 (40.0)	2 (20.0)			8 (80.0)	
4	44‖	5 (11.4)	24 (54.5)	11 (25.0)	1 (2.3)	2 (4.5)	29 (65.9)	
5	36	13 (36.1)	13 (36.1)	9 (25.0)	1 (2.8)		26 (72.2)	
6	14	7 (50.0)	4 (28.6)	3 (21.4)			11 (78.6)	
7	8‖	4 (50.0)	2 (25.0)	1 (12.5)			6 (75.0)	
8	14	4 (28.6)	5 (35.7)	5 (35.7)			9 (64.3)	
9	6	2 (33.3)	1 (16.7)	3 (50.0)			3 (50.0)	
10	4	1 (25.0)	1 (25.0)	2 (50.0)			2 (50.0)	
11	5			4 (80.0)	1 (20.0)			
12	2	1 (50.0)		1 (50.0)			1 (50.0)	

*Fisher's exact test.
†Chi-square test.
§Cochran-Armitage test.
‖Number included patients whose efficacy evaluations were not determined due to dropout from treatment.

effects was evaluated in the remaining 30 cases. Of the 21 cases that relapsed during the follow-up period, 2 maintained their score for at least 5 months but relapsed later on. Nine cases showed sustained improvement until the 6-month follow-up ended. Therefore, the proportion of patients achieving sustained improvement at least 5 months after discontinuation of interferon-α was calculated as 36.7% (11/30) (Table 5). Eight patients relapsed during interferon-α treatment, which mostly occurred during interruption of interferon-α or when frequency of administration was decreased.

The administration periods are shown in Table 5. Because patients who had been administered interferon-α for long periods included those who have not completed its follow-up period, the relationship between administration period and sustained effects are not clear based on the present data.

Adverse drug reactions

ADRs, including abnormality of laboratory tests, were observed in 146 of 167 patients (87.4%). Incidence rates of the survey were higher than we had previously reported in double-blind, multicenter study (50.0%, 8 of 16 patients assigned to 3.0×10^6 IU). The most frequently reported ADRs was pyrexia (65.9%, 110/167 patients). Other major ADRs were decreased white blood cell count (47.9%, 80/167 patients) and decreased platelet count (25.1%, 42/167 patients). There were no reports that anti-interferon neutralizing antibodies appeared. Pyrexia usually occurred in the early days after starting treatment; on the day of starting interferon-α: 68 of 110 cases (62%), within 3 days after starting: 89 of 110 cases (81%). Decreased white blood cell count and decreased platelet count occurred from 7 to 21 days after starting (51 of 80 cases [64%], and 26 of 42 cases

Table 3 Comparison of backgrounds of patients enrolled into the survey and efficacy evaluation

		Committee's evaluation (%)						
	No. of patients	*Modest to markedly improved*	*Mildly improved*	*Stable*	*Slightly deteriorated*	*Deteriorated*	*Efficacy ratio (%)*	*P value* †
Corticosteroids								.836
With	34	10 (29.4)	12 (35.3)	9 (26.5)	2 (5.9)	1 (2.9)	22 (64.7)	
Without	120§	35 (29.2)	45 (37.5)	34 (28.3)	2 (1.7)	2 (1.7)	80 (66.7)	
Muscle relaxant								.728
With	87	30 (34.5)	27 (31.0)	26 (29.9)	3 (3.4)	1 (1.1)	57 (65.5)	
Without	67§	15 (22.4)	30 (44.8)	17 (25.4)	1 (1.5)	2 (3.0)	45 (67.2)	

†Fisher's exact test.
§Number included patients whose efficacy evaluations were not determined due to dropout from treatment.

Table 4 Relation of committee's evaluation of efficacy at the time of withdrawal and 4 weeks after starting interferon-α.

Committee's evaluation at 4 weeks	*Number of patients*	*Committee's evaluation at the time of withdrawal**				
		Modest to markedly improved	*Mildly improved*	*Stable*	*Slightly deteriorated*	*Deteriorated*
Markedly improved	16	13 (81.3)	1 (6.3)			2 (12.5)
Moderately improved	25	3 (12.0)	17 (68.0)	3 (12.0)	2 (8.0)	—
Stable	6	—	1 (16.7)	3 (50.0)		2 (33.3)
Deteriorated	1	—	—	—		1 (100.0)

*Only patients administrated interferon-α over 35 days were evaluated.

[62%], respectively). These manifestations have been already recognized adverse events especially with interferon therapy.

Forty-six serious ADRs (Table 6) appeared in 24 patients. Eighteen patients stopped or temporarily stopped interferon-α, whereas five patients continued. Outcome of the most cases were reported as resolved (79.2%, 19/24). In spite of stopping interferon-α, consciousness disturbance remained in one patient with cerebral hemorrhage and gait disturbance remained in one patient with flaccid paralysis. In two patients, outcomes were not obtained due to changing of hospital. One patient (female, 70 years old) died of circulatory shock, which occurred 1 month after stopping interferon-α. She had been taking interferon-α for 4 weeks, and had high fever 9 days after withdrawal. Her doctor suspected infection and the fever resolved after administration of antibiotics. One month after stopping interferon-α, she suddenly went into circulatory shock, and died. Her doctor reported that the causation of the shock and interferon-α was uncertain.

Long-term administration of interferon-α

Interferon-α was administered for more than 6 months in 15 of 167 patients (median was 320 days, range 184–793 days). The manner of administration was as follows: daily administration (range: 14 to 61 days) followed by intermittent, $n = 14$; intermittent (twice a week for 434 days), $n = 1$. The reasons for discontinuation of interferon-α in 15 patients were; intended schedule has been completed ($n = 5$), change of hospital ($n = 3$), adverse event not related to interferon-α ($n = 3$; suicide attempt in one, hyperthyroidism in one, and gastrointestinal hemorrhage concomitant with gastric cancer in one), ineffectiveness ($n = 2$), adverse drug reaction ($n = 1$, a slight decrease in platelet and white blood cell count and anemia). One patient who continued interferon-α for more than 416 days dropped out in the middle of the survey due to unforeseen circumstances not related to the study involving the participating institution.

ADRs were observed in 12 of 15 patients (80.0%). Many of them appeared during initial daily administration, and most of them were well-known ADRs such as pyrexia and decreased white blood cell or platelet counts. ADRs that appeared after 6 months were hyperthyroidism (290 days after starting interferon-α), hyperglycemia and elevated glycosylated hemoglobin (210 days), back pain (229 days), chest pain (348 days), cerebral hemorrhage (263 days), and decreased white blood cell count (355 days); one patient had persistently decreased white blood cell and platelet counts and anemia until withdrawal at 755 days. The evaluation at 4 weeks were modest to markedly improved = 6; mildly improved = 7; stable = 1; evaluation not possible = 1 (the patient was excluded from efficacy analysis due to a lack of efficacy evaluation at 4 weeks) (Table 4). One of six patients rated as modest to markedly improved at 4 weeks deteriorated during interruption of treatment and did not improve after restarting interferon-α.

Table 5 Duration of sustained effects in OMDS and administration period of interferon-α

	No. of patients	*Administraion period (days)*†
Patients with relapse	21	
Relapsed during administration	8	
Relapsed after stopping administration	13	
Time of relapse (months after stopping interferon-α)		
<1 month	6	28 (18–68)
1 to <3 months	1	64
3 to <5 months	4	29 (22–122)
5 months and above	2	72, 192
Patients without relapse*	9	28 (11–88)

*OMDS after stopping interferon-α were maintained at levels higher than the base line until the follow-up was completed.
†Value represents median days (range) if the number of patients were more than 2.

Table 6 Serious adverse drug reactions (multiple answers possible)

Adverse drug reactions	*Total number (%)*	*Degree of seriousness*
Epiglottitis	1 (0.6)	Been considered medically serious
Anemia	1 (0.6)	Resulted in or prolonged hospitalization
Pancytopenia	1 (0.6)	Resulted in or prolonged hospitalization
Thrombocytopenia	1 (0.6)	Been considered medically serious
Anorexia	2 (1.2)	Resulted in or prolonged hospitalization
Decreased appetite	1 (0.6)	Resulted in or prolonged hospitalization
Hypokalemia	1 (0.6)	Been considered medically serious
Depression	2 (1.2)	Resulted in or prolonged hospitalization: 1 Been considered medically serious: 1
Cerebral hemorrhage	1 (0.6)	Resulted in or prolonged hospitalization, sequelae
Headache	3 (1.8)	Resulted in or prolonged hospitalization: 2 Been considered medically serious: 1
Flaccid paralysis	1 (0.6)	Resulted in or prolonged hospitalization, sequelae
Clonus	1 (0.6)	Resulted in or prolonged hospitalization
Dysesthesia	1 (0.6)	Resulted in or prolonged hospitalization
Hyperesthesia	1 (0.6)	Resulted in or prolonged hospitalization
Shock	1 (0.6)	Fatal
Hypotension	1 (0.6)	Resulted in or prolonged hospitalization
Nausea	2 (1.2)	Resulted in or prolonged hospitalization: 2
Hepatic function abnormal	1 (0.6)	Resulted in or prolonged hospitalization
Rash	1 (0.6)	Resulted in or prolonged hospitalization
Hemorrhage subcutaneous	1 (0.6)	Resulted in or prolonged hospitalization
Systemic lupus erythematosus	1 (0.6)	Resulted in or prolonged hospitalization
Fever	3 (1.8)	Resulted in or prolonged hospitalization: 3
Malaise	1 (0.6)	Resulted in or prolonged hospitalization
Decreased platelet count	4 (2.4)	Resulted in or prolonged hospitalization : 4
Decreased granulocyte count	1 (0.6)	Been considered medically serious
Decreased white blood cell count	8 (4.8)	Resulted in or prolonged hospitalization: 5 Been considered medically serious: 3
Increased alanine aminotransferase	2 (1.2)	Resulted in or prolonged hospitalization
Increased aspartate aminotransferase	1 (0.6)	Resulted in or prolonged hospitalization

Discussion

In this study, we evaluated data on 167 patients with HAM who were given interferon-α, and confirmed interferon-α's efficacy and safety under routine clinical conditions. Although there is no limitation with regards to duration of treatment using interferon-α, the most frequent dosage regimen is 3.0×10^6 IU injected intramusculary every day for 4 weeks then discontinued. This is the same regimen used in a double-blind, multicenter study previously reported by Izumo *et al* (1996).

ADRs were observed in 87.4% of the patients, most of these were well-known ADRs of interferon-α, such as pyrexia, decreased white blood cell count, or decreased platelet count. Because interferon-α has been administered to many patients with hepatitis C, hepatitis B, and malignant tumors, various kinds of ADRs, both with frequent or rare occurrence, have been reported (Thierry and Jacques, 1994). There were no characteristic ADRs that frequently occurred in patients with HAM in this survey. The frequency of ADRs was high in comparison with that of double-blind, multicenter study. This result might be caused by different background of studies.

It has been reported that patients with HAM sometimes have complications such as HTLV-1–associated bronchopneumonopathy (HAB) (50%), HTLV-1–associated arthropathy (HAAP) (17%), Sjögren's syndrome (25%), and cataract (21%) (Nakagawa *et al*, 1995). In this survey, ADRs such as dry mouth, crackles on pulmonary auscultation, and reduced visual acuity were reported but the frequencies of these ADRs were not high. It seems that interferon-α does not influence complications of HAM at the present time. In view of the relationship between safety and efficacy, some of the common ADRs seem to affect efficacy. Because the efficacy of interferon-α in this survey was evaluated based on the improvement of clinical symptoms, careful observation was needed to distinguish ADRs such as malaise, muscular weakness, asthenia, hyperesthesia, and sensory disturbance from ineffectiveness of interferon-α. Whether or not patients respond to interferon-α should be decided based on the course of disease, not on the temporary deterioration caused by ADRs.

Flaccid paralysis and clonus, common symptom of HAM, were reported as ADRs by their physicians, as these ADRs occurred in relation with administration and restored by withdrawal of interferon-α.

The efficacy ratio of interferon-α at 4 weeks was 66.2%. Although the subjects' background, the study design, number of patients enrolled, and evaluation method in this survey differed from those in a previous double-blind, multicenter study, the outcome was almost of the same degree. The efficacy ratio was higher in the lower motor disability grade group and the rate of improvement ratio was higher in

patients with shorter duration of illness and in the progression phase.

Fifteen patients were administered interferon-α over a period of 6 months and the committee's evaluation at the time of withdrawal was made in 14 of them. Nine patients were able to maintain their improved condition under long-term treatment. We have reported that HTLV-1 provirus load correlates with the clinical symptoms of HAM (Nagai *et al*, 1998; Matsuzaki *et al*, 2001) and that HTLV-1 provirus load decreases during interferon-α treatment (Saito *et al*, 2004) and returns to the original state after stopping the treatment (Nakagawa *et al*, 2004). The result that many of the patients showed improvement while on interferon-α coincided with our previous study, although HTLV-1 provirus load was not measured in these patients. On the other hand, the sustained effect after withdrawal is much longer than what we supposed. The reduction in HTLV-1 provirus load disappeared 2 to 4 weeks after stopping treatment of 3.0×10^6 IU per day of interferon-α with a total number of 12 to 31 (Saito *et al*, 2004; Nakagawa *et al*, 2004), whereas another study showed that improvement of motor performance was sustained over 6 months after long-term and high-dose administration (Yamasaki *et al*, 1997). Long-term administration of interferon-α may have some advantage in maintaining the improved condition during treatment, although whether or not it has additional effects, including a sustained effect, is still unclear. In addition, some patients whose OMDS improved during daily administration deteriorated after the frequency was reduced. Thus, the most suitable protocol for interferon-α administration in HAM needs to be defined in the future. Further investigation is needed to find factors that can influence its effects including the duration of treatment.

Clinical implication and study limitations

This study has clinical value in the points of investigating the actual use of interferon-α and confirming the efficacy and ADRs of interferon-α for HAM on the basis of a large number of patients under routine treatment. However, we recognize that this study is preliminary because of patients' treatment situation were quite varied and long-term follow-up have been in a few patients so far. Thus, the most suitable protocol for interferon-α administration in HAM needs to be defined in the future. Further investigation is needed to find factors that can influence its effects and ADRs including the duration and doses of the treatment.

Methods

Subjects

Diagnosis of HAM was performed by the treating neurologist on the basis of World Health Organization diagnostic criteria for HAM (Osame, 1990). The demographic and clinical characteristics of 167 patients are summarized in Table 7. The age was ranged from 22 to 80 years. The median age was 60 years. There were 120 female patients (72%) and 47 male patients (28%). Duration of illness ranged from 4 months to 51 years. Osame's motor disability score (OMDS) before starting interferon-α ranged from 2 to 12 (median = 5).

Table 7 Demographic and clinical characteristics of patients who were evaluable for safety

Characteristic	*Number of patients*
Total number of patients	167
Sex, male/female	47/120
Age (years)	
20–29	3
30–39	9
40–49	19
50–59	46
60–69	73
70–79	16
80–89	1
Duration of illness (years)	
0–4	46
5–9	38
10–14	32
15–19	13
20+	24
Uncertain	14
Stage of HAM	
Stable phase/progress phase	98/61
Uncertain	8
OMDS before treatment	
2	12
3	11
4	49
5	36
6	14
7	8
8	14
9	8
10	4
11	6
12	3
Uncertain	2
Previous therapy	
Yes/no	138/27
Uncertain	2

Study design

Data on the patients were collected and encoded in a database by Dainippon Sumitomo Pharma. The survey was carried out as a post-marketing surveillance for SUMIFERON as required by legal regulations. Prior to the survey, we organized the Committee on HAM Treatment with Interferon-α consisting of four neurologists (Osame, Itoyama, Izumo, and Kira). Data on HAM patients were collected from medical institutions. As the subjects of the survey were those who received interferon-α since January 2000, partial cases were enrolled from a past medical record (Figure 1). After starting the survey, enrollment were carried out prospectively. All enrolled cases were examined at the specialist committee. Demographic and

Table 8 Osame's motor dysfunction score and urinary disturbance score

Grade	*Motor disability*	*Urinary disability—increased frequency of urination, feeling of residual urine, urinary incontinence*
0	Normal walking and running	Normal
1	normal gait but runs slow	slight
2	abnormal gait	obvious
3	abnormal gait and unable to run	severe
4	need support while using stairs	
5	need one hand support in walking	
6	need two hands support in walking	
7	need two hands support in walking but is limited to 10 m	
8	need two hands support in walking but is limited to 5 m	
9	enable to walk but able to crawl on hands and knees	
10	crawls with hands	
11	unable to crawl but can turn sideways in bed	
12	unable to turn sideways but can move the toes	
13	complete bedridden (unable to move the toes)	

outcome data for each patient were collected by providing standardized questionnaires. Physicians accomplished the questionnaires based on existing patient records.

Survey items of the questionnaires are as follows:

1. Background of the patients (sex, date of birth, date of symptom onset, initial symptom and stage of HAM, complications, medical history, presence of allergy). Stage of HAM was classified into either of two phases according to the disease course: stable phase: no progression of OMDS at the entry point; progressive phase: remarkable progression of OMDS at the point.
2. Administration of interferon-α (dose, route, duration of treatment (start and stop dates), reasons for stopping).
3. Therapeutic conditions (combination medicine (purpose, dosage, route, period), combination therapy (purpose, period), drug used before and/or after interferon-α).
4. Transition of clinical symptoms. OMDS based on the degree of gait disturbance, urinary disturbance score based on the degree of increased frequency of urination, feeling of residual urine, urinary incontinence (Table 8), and degree of sensory disturbance. Sensory disturbance were assessed whether the symptom(s) eased or not. Data on these clinical symptoms before therapy, 2 and 4 weeks, then every month after starting therapy were filled out until 6 months after stopping the therapy. In addition, if physicians found any change in their patients besides these clinical symptoms (i.e., time required to walk 10 m), these findings were written down as free comments.
5. Clinical laboratory findings, health-related events the patient experienced since starting interferon-α (date of onset, seriousness, necessity of treatment, outcome, causality between interferon-α). When physicians did not deny the relationship between interferon-α and these findings or events, we defined them as ADRs.

Efficacy evaluation

Because the duration of interferon-α therapy varied among patients, we set two different evaluation points as follows:

1. Evaluation at 4 weeks after starting treatment. When duration of treatment was less than 4 weeks, the evaluation was made at the time of withdrawal of interferon-α. We defined the evaluation at this point as a primary efficacy evaluation. Patients without this primary efficacy evaluation were excluded from efficacy analysis.
2. When a patient received interferon-α for more than 5 weeks, in addition to 4 weeks' evaluation, efficacy evaluation was made at the time of withdrawal of interferon-α.

To evaluate efficacy in a standardized manner, evaluations were made by the committee. Efficacy was rated according to five categories, namely the change in OMDS, urinary disturbance score, degree of sensory disturbance, degree of gait disturbance, and comments concerning efficacy (e.g., time and steps required to walk 10 m). Evaluations were made according to the following scale:

Modest to markedly improved: patients showing one or more than one grade improvement in OMDS.
Mildly improved: patients with OMDS unchanged, but exhibiting improvement in one or more than one items mentioned above other than OMDS.
Stable: patients with all provisions mentioned above unchanged.
Slightly deteriorated: patients with OMDS unchanged, but expressing deterioration in one or more than one items mentioned above other than OMDS.
Deteriorated: patients with one or more than one grade deterioration in OMDS.

If cases had taken interferon-α therapy for less than 6 days, evaluation were not determined, because the administration period is too short to evaluate interferon-α efficacy for HAM.

Some patients took one or more concomitant therapies, which may potentially affect clinical evaluations. However, because the aim of this study was to investigate safety and efficacy under routine treatment conditions, efficacy was evaluated

regardless of whether other concomitant therapy was utilized.

Those who lack necessary data such as OMDS were excluded from the efficacy analysis.

Data analysis

Demographic and clinical characteristics were statistically analyzed. Two categorical variables were compared using Fisher's exact test. Continuous variables were compared using the Cochran-Armitage test, and chi-square tests were used to compare categorical variables. All P values presented were two-sided, and $P \leq .05$ was considered to indicate statistical significance. All statistical analyses were performed with the SAS 8.2 statistical programs (SAS Institute; Cary, NC, USA).

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