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The Japanese Interferon Study Group (JISG) has established the efficacy of human interferon-β for serious CMV pneumonitis in kidney recipients

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The Japanese Interferon Study Group (JISG) is a research organization formed by 30 special hospitals for organ transplantation. A joint multi-centre, double-blind trial was conducted in order to investigate the efficacy of human interferon-β (HuIFN-β) against serious cytomegalovirus pneumonitis in kidney recipients.

Key words: Kidney transplantation – CMV – Pneumonitis – Interferon β

Subjects and methods

Subjects

The subjects were patients diagnosed with cytomegalovirus pneumonitis who received immunosuppressants immediately after kidney transplantations at special kidney transplant facilities. Before the start of the trial, informed consent was obtained from the patients themselves or their relatives.

Test drug

The HuIFN-β reference standard used in the trial was produced from normal human diploid fibroblasts [1] and prepared as a clinical standard drug by Toray Industries. This standard was a freeze-dried preparation that included 2.0×10^6 IU/vial, inert up to 10^7 IU/mg protein. A preparation containing 0.3×10^6 IU/vial was used for the control group. The controller confirmed the indistinguishability of the drug preparations.

Quantitative confirmation of the contents was conducted by Dr. S. Yamazaki of the N. I. H., Japan.

Allocation of the test drug

The test drug was allocated by two controllers (Dr. N. Shimizu, Internal Department, Teikyo University, and Dr. M. Kameyama, Internal Department, Sumitomo Hospital).

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Dose levels and dosing method

The dose level for both drug preparations was set at a single vial administered three times a day. The administration method involved intravenous drip infusion for 2 h of the contents of a single vial which had been dissolved in 1 ml physiological saline for injection and to which 250 ml saline had been added.

Evaluation method

The improvement in the main clinical symptoms of viral pneumonia was evaluated by separately rating the following factors.

Chest X-ray radiographs. Two radiographs for each case, taken before and after drug administration, were submitted in a blind test by the controller to the Evaluation Committee on Chest X-Ray Radiographs, which conducted the scoring. Standard radiographs shown in Table 1 and Figs. 1–6 were used as references in scoring.

Fever. Improvement rating was assessed from the body temperature (daily maximum) before and after the end of drug administration. A drop below 38 °C was evaluated as 'improved', no drop as 'unchanged', and an increase above 38 °C as 'aggravated'.

Cough. Improvement rating was assessed from the extent of coughing before and after the end of drug administration. Symptoms interfering with sleep were assessed as (+ +), presence of cough as (+),

Table 1. Evaluation criteria for chest X-ray radiographs

Score	Criterion	Figure
0	No abnormal shadow is noted	1
2	Reinforced interstitial shadow is noted, but limited to a portion of lung field of one or both lungs	2
4	Interstitial shadow extends to the periphery of both lung fields	3
6	Manifestation of frosted-glass-type shadow	4
8	Diaphragmatic shadow is noted, but cardiac shadow is unclear; or cardiac shadow is noted, but diaphragmatic shadow is unclear	5
10	Both diaphragmatic and cardiac shadows cannot be seen	6

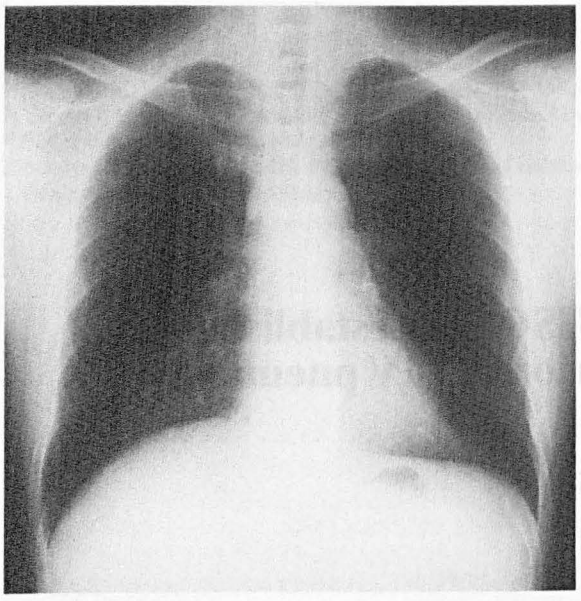

Fig. 1

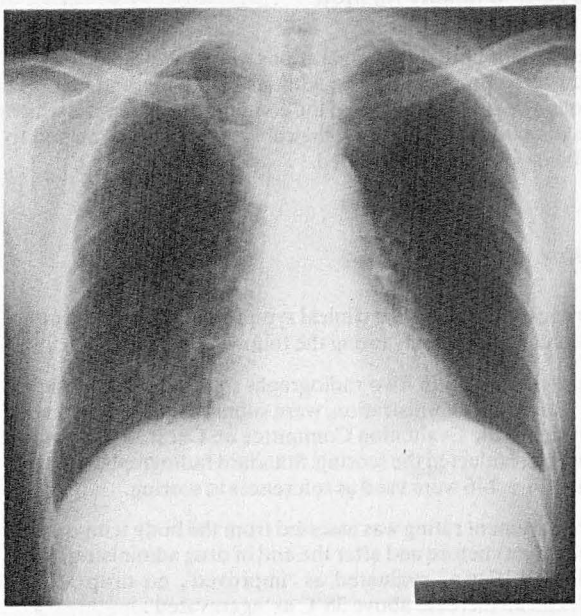

Fig. 2

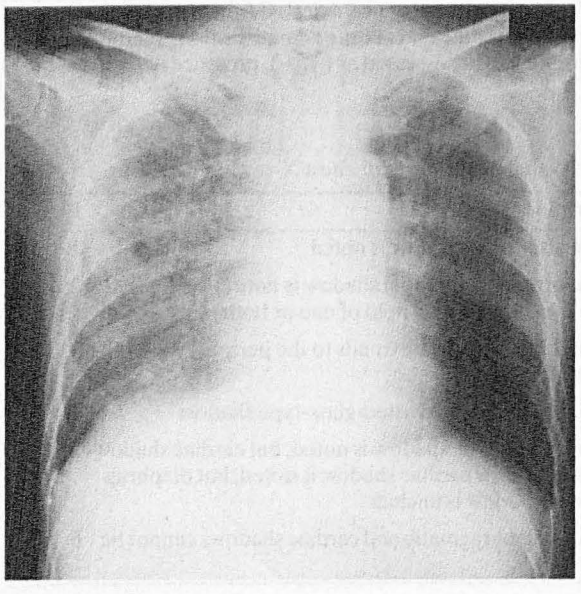

Fig. 3

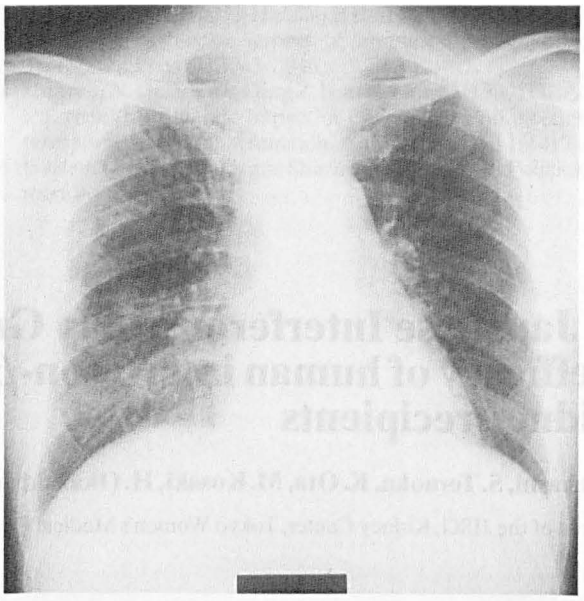

Fig. 4

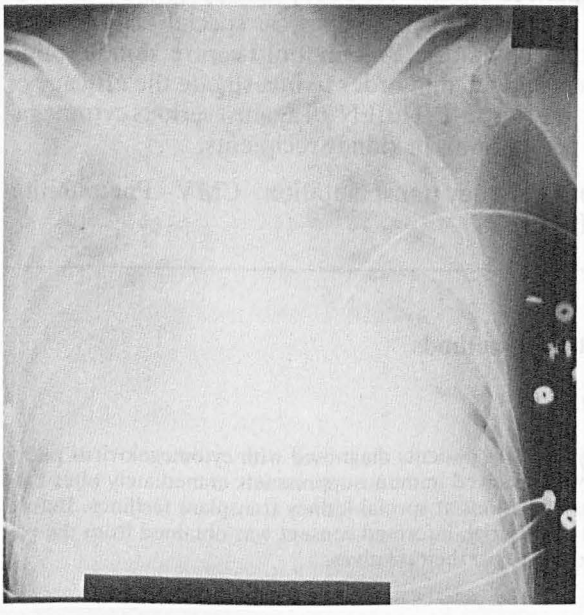

Fig. 5

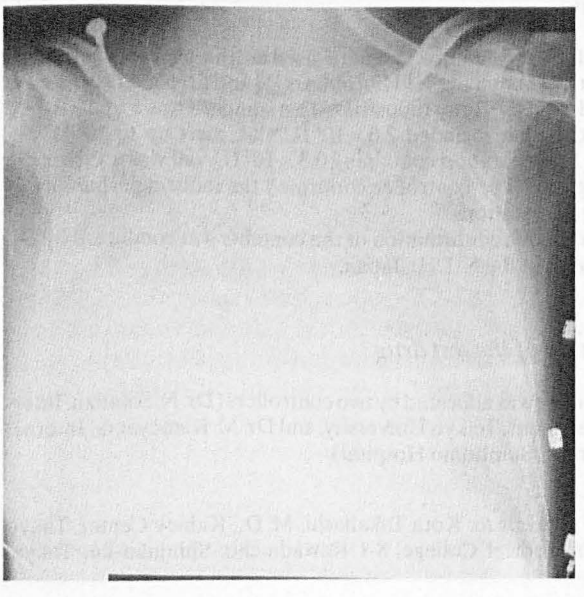

Fig. 6

Table 2. Background factors

			6.0 M group ($n = 18$)	0.9 M group ($n = 23$)	Test	
					U	Fisher
Sex	Male		12 (67)	16 (70)	NS	NS
	Female		6 (33)	7 (30)		
Age (years)	~19		2 (11)	2 (9)	NS	NS
	20–29		6 (33)	8 (35)		
	30–39		7 (39)	4 (17)		
	40–49		2 (11)	7 (30)		
	50~		1 (6)	2 (9)		
Severity	Slight		1 (6)	3 (13)	NS	NS
	Moderate		8 (44)	10 (43)		
	Severe		9 (50)	10 (43)		
Weight (kg)	~49		4 (22)	6 (26)	NS	NS
	50–59		9 (50)	13 (57)		
	60~		5 (28)	4 (17)		
Complications		No	10 (56)	17 (74)	NS	NS
		Yes	8 (44)	6 (26)		
	Acute rejection	No	15 (83)	22 (96)	NS	NS
		Yes	3 (17)	1 (4)		
	Chronic rejection	No	17 (94)	20 (87)	NS	NS
		Yes	1 (6)	3 (13)		
Donor	Living donor		12 (67)	15 (65)	NS	NS
	Cadaveric donor		6 (33)	8 (35)		

Numbers in parentheses are percentages

and no symptoms as (–), and cases with improvement by more than one stage were taken as improved.

Hypoxaemia. Improvement rating was assessed from the PO_2 (room air) before and after the end of drug administration. A PO_2 value below 50 mm Hg was evaluated as (+ +), 50–70 mm Hg as (+), and more than 70 mm Hg as (–), and cases with improvement by more than one stage were taken as improved.

Final global improvement rating. Based on changes in overall clinical symptoms and results of clinical laboratory tests, the global improvement rating was assessed on a six-point rating scale as 'markedly effective', 'effective', 'slightly effective', 'ineffective', 'aggravated', or 'unassessable'.

Results

Number of cases

The total number of cases in the present trial was 43, including 19 in the 6.0 M group and 24 in the 0.9 M group. Two cases were excluded from analysis, including one case where, because of inattention by the physician-in-charge, the patient received the same dose twice and one case where clinical efficacy was evaluated as unassessable because the patient contracted pulmonary tuberculosis either simultaneously with or following CMV pneumonitis. The patient background factors of the 41 evaluated cases are listed in Table 2.

Fig. 1–6. Standard radiographs for the radiograph rating described in Table 1

Efficacy

The improvement ratings with regard to chest radiographs, fever, cough and hypoxaemia are listed in Tables 3–6, respectively. Final global improvement rating is listed in Table 7.

The efficacy rate in the 6.0 M group was 50% (9/18 cases), showing a statistically significant tendency compared with the 17% in the 0.9 M group (7/17 cases) (*U*-test: $Z_0 = 1.653$, $P_0 = 0.098$).

Safety

Side effects were noted in 83% (15/18 cases) of the 6.0 M group and in 61% (14/23) of the 0.9 M group. The breakdown is listed in Table 8.

Table 3. Rating of chest X-ray radiographs

Group	Improved	Unchanged	Aggravated	Unassessable	Total[a]	Proportion improved (%)
6.0 M	7	5	6	0	18	39
0.9 M	7	4	9	1	21	33

U test, NS; Fisher, NS

[a] Only 39 cases were analysed because radiographs were missing in two cases

Table 4. Fever rating

Group	Improved	Unchanged	Aggravated	Total[a]	Proportion improved (%)
6.0 M	8	7	1	16	50
0.9 M	4	4	4	12	33

U test, NS; Fisher, NS

[a] Only 28 cases were analysed because in 13 of the 41 cases fever was absent before and after administration of the test drug

Table 5. Cough rating

Group	Improved	Unchanged	Aggravated	Total[a]	Proportion improved (%)
6.0 M	10	3	0	13	77
0.9 M	2	9	1	12	17

U test, $Z_0 = 0.987$, $P_0 = 0.003$; Fisher, $P_0 = 0.008$

[a] Only 25 cases were analysed because in 16 of the 41 cases no coughs occurred before and after administration of the test drug

Table 6. Hypoxaemia rating

Group	Improved	Unchanged	Aggravated	Unassessable	Total[a]	Proportion improved (%)
6.0 M	8	1	3	1	13	62
0.9 M	5	1	4	7	17	29

U test, NS; Fisher, NS

[a] Only 30 cases were analysed because in 11 of the 41 cases no abnormal PO_2 values were noted before and after administration of the test drug

Table 7. Final global rating

	Markedly effective	Effective	Slightly effective	Ineffective	Aggravated	Total	Efficacy rate (%)
6.0 M	6	3	2	4	3	18	50
0.9 M	2	2	8	4	7	23	17

U test, $Z_0 = 1.653$; $P_0 = 0.098$ (+)

Table 8. Side effects

	6.0 M group ($n = 18$)	0.9 M group ($n = 23$)
Fever	15 (83)	14 (61)
Chill	9 (50)	7 (30)
Headache	4 (22)	4 (17)
Fatigue	3 (17)	7 (30)
Anorexia	3 (17)	5 (22)
Nausea, Vomiting	3 (17)	1 (4)
Number of cases	15 (83)	14 (61)

Numbers in parentheses are percentages
None of the differences between the two groups was statistically significant

Table 9. Abnormal laboratory test values

	6.0 M group ($n = 18$)	0.9 M group ($n = 23$)
Decrease in RBC	0 (0)	1 (4)
Drop in Hb	0 (0)	1 (4)
Drop in Ht	0 (0)	1 (4)
Decrease in PLT	2 (11)	5 (22)
Decrease in WBC	2 (11)	8 (35)
Granulcytopenia	0 (0)	1 (4)
Rise in GOT	1 (6)	3 (13)
Rise in GPT	2 (11)	5 (22)
Rise in ALP	1 (6)	1 (4)
Rise in S-Cr	1 (6)	0 (0)
Number of cases	6 (33)	11 (48)

Numbers in parentheses are percentages
None of the differences between the groups was found to be statistically significant

Abnormal laboratory test values were noted in 33% (6/18 cases) of the 6.0 M group and in 48% (11/23) of the 0.9 M group (Table 9).

No difference between the groups was noted in the incidence of side effects and abnormal laboratory test values.

Discussion

The results of kidney transplantation have improved dramatically in recent years with the progress in the development of immunosuppressive drugs. However, infection is still the most common post-transplant complication, often becoming a factor that is decisive in patient survival.

HuIFN-β is a biosubstance with a wide antiviral spectrum, which is marketed as a radical remedy for hepatitis B in Japan, where it is widely used.

The efficacy of interferon on cytomegalovirus infections has been demonstrated by the results of in vitro and in vivo tests [2]. While interferon administration has been used in an attempt to prevent viral infections immediately after kidney transplantation, there have only been case reports from several open studies on manifest cytomegalovirus pneumonitis, and the degree of therapeutic efficacy in clinical application has not been clarified.

We investigated objectively the efficacy of the drug in a randomized, double-blind, comparative trial. The dose levels used in the present trial were based on the experience from an open study conducted by Takahashi et al. [3]. Since the use of a completely inactive placebo for the control drug poses many ethical problems, and since no approval was obtained from the physicians participating in the trial, a preparation containing less than one-sixth the dose for the treatment group was used for the control group.

While the results showed a clear difference in efficacy between the 6.0 M and the 0.9 M groups, there was no difference in side effects and normal laboratory test values, demonstrating the utility of the drug against cytomegalovirus pneumonitis in the 6.0 M group. Ganciclovir is presently used as the first drug of choice among remedies for cytomegalovirus infections, but based on the results established for HuIFN-β, we wanted to provide with the present study another drug of choice, in addition to ganciclovir, for the therapy of serious cytomegalovirus pneumonitis following kidney transplantation. We are confident that either separate or concomitant use of both drugs can lead to further improvement in therapeutic results following kidney transplantation.

Note

JISG comprises:

1. Participating institutions (in order of number of patients entered): Sapporo City General Hospital; Tachikawa Sogo Hospital; School of Medicine, Chiba University; Kidney Center, Tokyo Women's Medical College (K.T., S.T. and K.O.); Institute of Medical Science, University of Tokyo; Hachioji Medical Center, Tokyo Medical College (M.K.); Hamamatsu University School of Medicine; Nagoya Second Red Cross Hospital; Shiga University of Medical Science; Kyoto Prefectural University of Medicine; Kinki University School of Medicine; Hyogo College of Medicine; Hyogo Prefectural Nishinomiya Hospital; Hiroshima University School of Medicine; Matsuyama Red Cross Hospital; National Nagasaki Chuo Hospital; Fukuoka Red Cross Hospital; and Makiminato Chuo Hospital.
2. Steering committee: K.Ota (Chairman), S.Teraoka, K.Takahashi; H.Okazaki, Sendai Shakaihoken Hospital; M.Kosaki, Hachioji Medical Center, Tokyo Medical College; S.Oshima, Shakaihoken Chukyo Hospital.
3. Evaluation Committee for Chest X-ray Radiographs: K.Simizu, Internal Department, Tokyo Women's Medical College; K.Hara, 3rd Internal Department, Nagasaki University, S.Teraoka, K.Takahashi, K.Ota; T.Tamaki, Hachioji Medical Center, Tokyo Medical College.
4. Participant for Virology: Y.Minamishima, Department of Virology, Miyazaki Medical College.
5. Data Analysis Center: The Controller Committee (N.S., M.K.)

6. Clinical Monitoring Center: Y. Kuwabara, A. Sada, N. Naruse, Toray Industries.

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