were receiving 0.003 mg/kg/day. There were 2 patients who did not complete the study, one due to impaired glucose tolerance and one withdrew consent.

This intervention had a significant effect on mean IGF-I levels; Fig. 1 shows IGF-I SD scores, for AO and CO patients separately, from baseline to the endpoint at 48 weeks. Baseline values were lower in CO than in AO patients and during the first 24 weeks of GH treatment, with the increasing fixed dose, normalization was obtained in CO but mean levels in AO patients exceeded the desired upper limit of 2.0 SD score. The dose adjustment regimen, which was initiated at a low dose, caused an initial decrease in IGF-I SD score, but as GH dose was increased mean levels normalized without reaching the excessively high values seen under the fixed dose regimen. However, values under GH replacement remained lower in CO than in AO, both under the fixed dose regimen and with individualized dose adjustment.

Long-term changes in central fat accumulation and body composition

Table 1 summarizes the changes from baseline for percent total FM, percent FM in the trunk and percent total LBM. GH replacement induced significant changes in body composition which persisted over time. After 24 weeks of a fixed dose regimen, percent total FM had decreased by –3.1 ± 2.8% ($p<0.001$). The dose adjustment algorithm slightly reduced the magnitude; however, the change from baseline to week 48 was still significant (–2.7 ± 2.9%, $p<0.001$). The pattern of change was identical for percent FM in the trunk, with the 0–48 week change being slightly less pronounced than the 0–24 week change but still statistically significant (at week 24: –3.8 ± 3.3%, $p<0.001$; at week 48: –3.1 ± 3.7%, $p<0.001$). The difference between the two changes, +0.9 ± 2.5%, was not statistically significant.

Opposite, but consistent and also statistically sig-

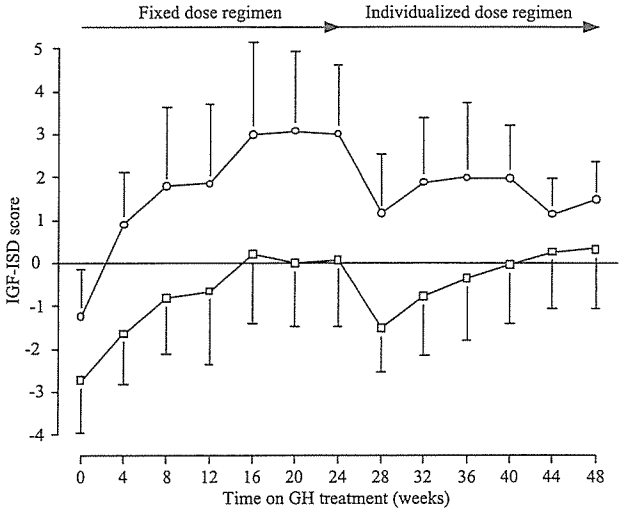

Fig. 1. IGF-I SD scores in AO (○) and CO (□) GH deficient patients during treatment with GH for 48 weeks; values are mean ± SD.

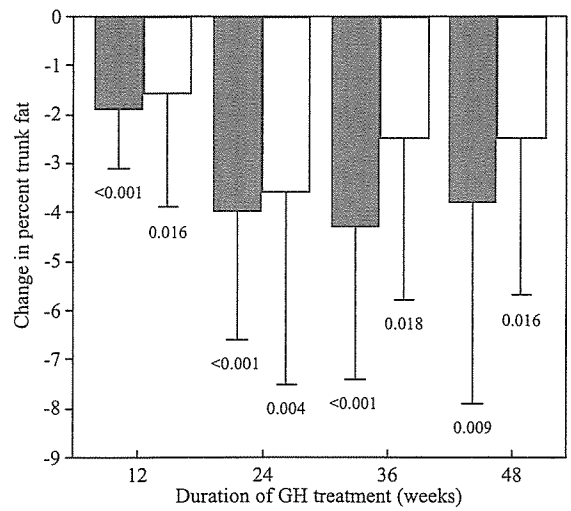

Fig. 2. Mean ± SD changes from baseline in percentage fat in the trunk during GH treatment of AO (shaded bars) and CO (clear bars) GH deficient patients, with p-values for changes from baseline

Table 1. Changes from baseline in percent body composition, measured by DXA, during GH replacement therapy

	Baseline	Change to week12	Change to week 24	Change to week 36	Change to week 48
Total Fat mass %	34.4 ± 8.3	–1.4 ± 1.6	–3.1 ± 2.8	–2.9 ± 2.8	–2.7 ± 2.9
P value		<0.001	<0.001	<0.001	<0.001
Trunk Fat mass %	33.6 ± 8.0	–1.7 ± 1.8	–3.8 ± 3.3	–3.4 ± 3.3	–3.1 ± 3.7
P value		<0.001	<0.001	<0.001	<0.001
Lean body mass %	62.8 ± 8.1	1.4 ± 1.6	3.1 ± 2.8	2.9 ± 2.8	2.7 ± 2.9
P value		<0.001	<0.001	<0.001	<0.001

P-values are for within-group difference in change from baseline.

nificant changes were seen in percent LBM. The initial increase of 3.1 ± 2.8% at week 24 ($p<0.001$) was maintained at week 48 (2.7 ± 2.9%, $p = 0.001$).

Fig. 2 shows the changes from baseline at different time points during the study period for percent FM in the trunk for AO and CO patients separately. Although on average the effect was slightly more pronounced in AO patients, the changes were very similar for the two onsets (change to week 48: AO 3.6 ± 4.1%, CO 2.5 ± 3.2%). The within-group changes from baseline were statistically significant for each onset group at all time points.

Lipid changes

Total cholesterol and LDL-cholesterol at baseline were 218 ± 34 mg/dl and 127 ± 30 mg/dl, respectively. Both were significantly lower than the baseline values at 24 and 48 weeks of treatment. Total cholesterol decreased by −24 ± 28 mg/dl at week 24 ($p<0.001$) and −17 ± 28 mg/dl at week 48 ($p = 0.007$); LDL-cholesterol decreased by −17 ± 23 mg/dl ($p<0.001$) and −16 ± 20 mg/dl ($p = 0.001$) at weeks 24 and 48, respectively. In contrast, HDL-cholesterol showed no significant difference from baseline values after 24 or 48 weeks of treatment.

Safety

There were no deaths or serious adverse reactions reported during the study and no cases of de novo tumour or tumour recurrences were observed. All patients reported at least one adverse events at some time during the study. Adverse events for which the causal relationship with GH administration could not be ruled out (adverse drug reactions) were reported in 25 (92.6%) of the patients. These events included edema, arthralgia, increases in serum inorganic phosphate and alkaline phosphatase, and decreased thyroxine levels. Two patients experienced HbA1c elevations. The first was a 60-year-old male with AO GHD and a BMI of 22.2 kg/m^2 who had an increase in the HbA1c value and abnormal glucose tolerance; this patient continued GH replacement after adequate dose reduction. The second patient was a 33-year-old female with CO GHD and a BMI of 25.2 kg/m^2 who experienced 2 episodes of increased HbA1c; the dose was reduced after the first episode, but GH treatment was eventually discontinued after a recurrent increase in HbA1c.

Discussion

The present study demonstrates that if dose adjustment is applied to individual patients with excessively elevated IGF-I concentrations, a beneficial GH treatment effect on central fat accumulation in adult Japanese GHD patients persists over the longer term. GH dosing by IGF-I titration was recommended by the GRS guidelines as early as 1998 [14], and is today the internationally accepted clinical standard. It is, therefore, of importance to show that this dose regimen is also fully applicable to Japanese adult patients, in whom clinical experience with GH replacement is much more limited compared to Caucasians.

At the end of the fixed-dose phase, the average IGF-I SD score in AO patients was well above 2.0, but returned below this upper limit after dose individualization. This was less pronounced in CO subjects, who exhibited the same pattern of IGF-I changes but at significantly lower levels. These results confirm a variety of studies in Caucasians [16–18] and also in Japanese [19], showing that adult CO GHD patients have lower baseline as well as GH-stimulated IGF-I levels than AO patients.

The changes seen in trunk FM reflected this pattern, although the differences between onsets were not statistically significant at any time point. Similar differences between AO and CO in responsiveness to GH replacement have been described in Caucasians [16, 17, 20], and surveillance reports indicate that in clinical practice GH dose in Caucasians is on average about 20% higher in CO than in AO patients [20]. This may be caused by the age and developmental difference existing between CO and AO, as CO patients are usually much younger than AO patients and many of them are still in the postpubertal/transition age when GH needs are higher than at older ages. One may thus expect that in Japanese patients also, the individual dose adjustment by IGF-I levels will, in clinical practice, produce higher GH doses for CO compared to AO patients.

The changes in body composition seen during the initial double-blind phase with a fixed-dose regimen were maintained during the open-label phase after dose adjustment. Although the decrease in percent trunk FM was less pronounced after dose-individualization, the overall change from baseline to 48 weeks was still significant. This indicates that the lower, but more physiological, replacement dose obtained by IGF-I adjustment is fully effective in achieving the desired

clinical effect. Also, the magnitude of the long-term clinical response to GH treatment did not differ very much among onsets. This was demonstrated by the changes seen in trunk fat, for which the initial changes observed under the fixed dose regimen were maintained for both onsets after dose adjustment.

At the end of the 48-week study period the magnitude of the opposite changes in percent FM and percent LBM (–2.7% and +3.1%, respectively) was comparable, indicating that a redistribution of body components had taken place. While this is in keeping with the literature [21], this study additionally showed that in the Japanese patients the loss of FM specifically affects the trunk. The decrease in percent trunk fat mass at 48 weeks would correspond to an average loss of about 1.0 kg in abdominal FM. In our baseline GHD population [12] trunk FM was about 9 kg in males and 10 kg in females and Ito *et al.* [13] have shown that the age-adjusted cut-off for trunk FM for increased cardiovascular complications in the normal Japanese population is 7.8 kg for males and 8.9 kg for females. Thus, with prolonged GH treatment with a physiological replacement dose there is a trend for trunk FM values to normalize, which translates into a clinically relevant reduction of predicted cardiovascular risk. This is further supported by the changes in total and LDL-cholesterol, which were consistent with long-term data in Caucasian patients [20].

The 48-week safety profile was consistent with published data [16, 20, 22, 23] and available clinic experience in Caucasians and Japanese patients. There were two patients who developed signs of glucose intolerance under GH replacement; one of these was able to continue treatment after adequate dose reduction, but the second, with a borderline high BMI value for Japanese, had to discontinue. The two cases further emphasize the importance of accurate individual GH dosing and the necessity of regular glucose monitoring under GH treatment.

In summary, individualizing the GH dose by IGF-I titration avoids excessively high IGF-I values and maintains clinical efficacy during long-term treatment. Adequate GH replacement produces a significant and clinically relevant decrease of abdominal FM in adult Japanese GHD patients. This effect persists over time and effectively reduces the cardiovascular risk associated with GHD.

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Low-dose Growth Hormone Treatment (0.175 mg/kg/week) for Short Stature in Patients with Turner Syndrome: Data from KIGS Japan

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Abstract. Turner syndrome is a common sex chromosome anomaly. Human growth hormone (hGH) is effective for treating short stature, which is a major characteristic of the disease. In this report, we analyzed the results of low-dose GH treatment for short stature in 212 Turner syndrome patients with growth hormone deficiency. These patients were enrolled in KIGS Japan. After 5 years of treatment, change in height was more than the mean growth curve in many patients, and the standard deviation (SD) for stature improved by +1.22 SDS. As the treatment progressed, the weight-for-height index (WHI) decreased in patients aged 8.1 years or older but not more than 14.8 years at the commencement of the treatment.

Key words: Growth hormone treatment, Short stature, Turner syndrome

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TURNER syndrome is one of the most common sex chromosome anomalies. Human growth hormone (hGH) is effective for treating short stature, which is a major characteristic of the disease [1]. High-dose hGH treatment (0.05 mg/kg/day) continues to be performed in Western countries [2]. In Japan, by contrast, previously the approved indication for hGH treatment was limited to "short stature in Turner syndrome patients with growth hormone deficiency and without epiphyseal closure." In addition, dose was also limited to 0.5 IU/kg/week (0.175 mg/kg/week). However, the limited indication "with growth hormone deficiency" was removed in December 1999, and high-dose hGH treatment (0.35 mg/kg/week) was approved.

Therefore, we believe it is meaningful to compile the results of low-dose hGH treatment now because most Turner syndrome patients commencing treatment from now on will undergo high-dose hGH treatment.

As such, we analyzed the results of low-dose hGH treatment in Turner syndrome patients with growth hormone deficiency, and who had been enrolled in KIGS Japan (Pfizer International Growth Study Japan).

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Subjects and Methods

Subjects

Two hundred and seventeen Turner syndrome pa-

tients were enrolled in KIGS Japan prior to the end of January 2001 and received hGH treatment. Of these, the 212 patients for whom there were records on height at the commencement of the hGH treatment and basic treatment-related information were included as subjects in this study. Genotropin® (generic name: somatropin) was used in the hGH treatment.

Evaluation method

Mean height and mean weight for each age and their standard deviations (SD) [3] were used to evaluate the height and weight of the patients. The difference between the measured height and the mean height calculated according to the patient's age was divided by the SD of the patient's age in order to determine height SDS. Height SDS calculated one to five years following the commencement of the treatment were compared with that at commencement. In addition, "height-age" was calculated based on the measured height, and the mean weight of each age was regarded as the expected weight. The ratio of the expected weight to the measured weight was regarded as the weight-for-height index (WHI*) and was calculated for up to three years following the commencement of the treatment (* the measured weight ÷ the expected weight).

Results

Patient background

The patients were aged 11.4 ± 3.3 years (mean ± SDS) (range: 3.3 to 19.2) when they commenced the hGH treatment, and the follow-up period was 3.3 ± 2.2 years (range: 0.0 to 17.5 years). Height at birth was 47.0 ± 2.4 cm (n = 131), bodyweight at birth was 2676 ± 411 g (n = 210), father's height was 167.3 ± 5.8 cm (n = 205), and mother's height was 154.7 ± 5.0 cm (n = 202). The hGH dose was 0.162 ± 0.031 mg/kg/week, and the frequency of administration was 5.14 ± 1.58 per week (Table 1).

The most common karyotype was 45,X, which accounted for 33.3% of the patients (n = 47), followed by 45,X/46,X,i(Xq) (14.9%, n = 21), 46,X,i(Xq) (8.5%, n = 12). Other types accounted for 43.3% of the patients (n = 61) (Table 2).

Twenty-eight patients underwent gonadal substitution therapy as a concomitant therapy. The patients were aged 16.4 ± 2.5 years at the commencement of the gonadal suppletion therapy, which commenced 3.7 ± 2.2 years following the hGH treatment.

Height prior to the hGH treatment was evenly distributed both above and below the mean growth curve, but at the final observation it was above the mean in many patients (Fig. 1); thus suggesting that the hGH treatment was effective. In addition, the patients were divided into two groups based on the duration of the hGH treatment (less than five years, or five years or more), and the heights at the commencement of the treatment and at the final observation were plotted on a growth curve for girls with Turner syndrome (Fig. 2). The figure clearly shows the improvements in height SDS. We examined the relationship between the age at

Table 2. Karyotype distribution

Karyotype	n (%)
45,X	41 (29.1%)
45,X/46,X,i(Xq)	22 (15.6%)
46,X,i(Xq)	14 (9.9%)
45,X/46,XX	8 (5.7%)
Others	56 (39.7%)

Table 1. Patient background

	n	Mean	SDS	Median	Range
Age at commencement of GH treatment (years)	212	11.4	3.3	11.5	3.3–19.2
Follow-up period (years)	212	3.3	2.2	3.8	0.0–17.5
Height at birth (cm)	131	47.0	2.4	47.0	37.0–51.0
Bodyweight at birth (g)	210	2676	411	2700	1305–3820
Gestation period (weeks)	208	39.1	1.6	40.0	32.0–43.0
Father's height (cm)	205	167.3	5.8	167.0	150.0–181.0
Mother's height (cm)	202	154.7	5.0	155.0	143.0–170.0
GH dose (mg/kg/week)	212	0.162	0.031	0.162	0.04–0.343
Frequency of GH administration (per week)	212	5.14	1.58	6.00	1.00–7.00

which the treatment commenced and the changes in height SDS (Table 3). Height SDS was significantly greater than for the preceding year for each of the four years following the commencement of the treatment. Height SDS five years following the commencement of the treatment was 1.22SDS. Furthermore, we divided the patients into two groups based on the age at which the treatment commenced (below 11.4 years, or 11.4 years or more) such that both groups had the same number of patients. The rates of increase up to two years following the commencement of the treatment were significantly high in the group aged less than 11.4 years ($p = 0.05$, Fig. 3).

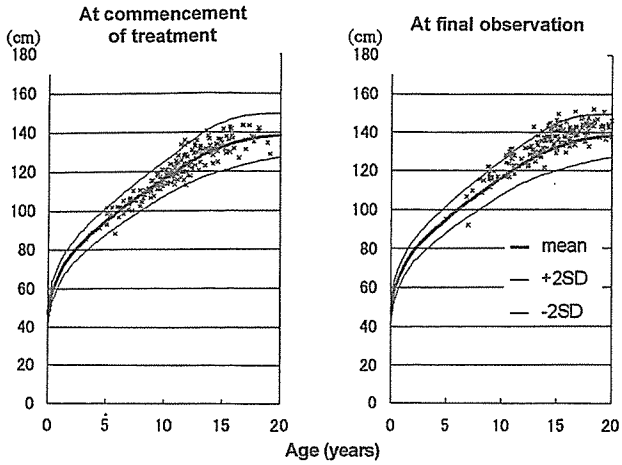

Fig. 1. Height at commencement of hGH treatment and at final observation.
Height prior to the hGH treatment was evenly distributed both above and below the mean growth curve, but at the final observation it was above the mean in many patients of Turner syndrome.

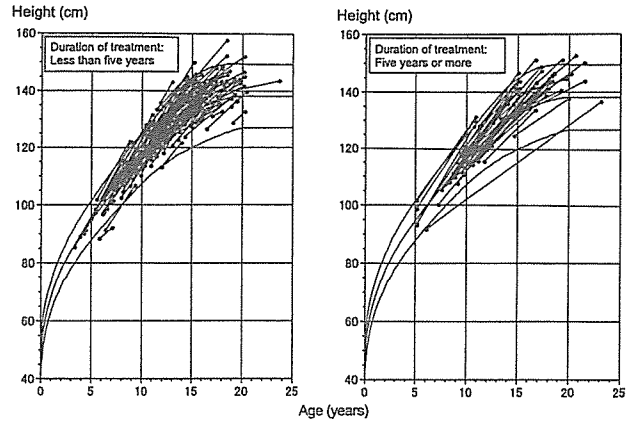

Fig. 2. Height at commencement of hGH treatment and at final observation (sorted by duration of treatment).
Subjects were divided into two groups on the basis of duration of treatment (less than five years or five years or more). Height at commencement of treatment and height at final observation were plotted on the growth curve for Turner syndrome patients.

Table 3. Delta height SDS following GH treatment

		n	Mean	SD	Median	Range
At commencement	Height SDS	212	0.13	0.89	0.12	−2.83–2.58
	Age		11.44	3.35	11.49	3.31–19.08
One year later	Height SDS	189	0.55	0.85	0.54	−2.89–2.96
	Delta Height SDS		0.40	0.29	0.38	−0.27–2.12
	Age		12.42	3.36	12.54	4.31–20.22
Two years later	Height SDS	129	0.78	0.84	0.79	−1.82–2.94
	Delta Height SDS		0.63	0.41	0.60	−0.74–1.86
	Age		13.10	3.16	13.09	5.87–21.07
Three years later	Height SDS	99	1.03	0.80	1.07	−1.59–3.28
	Delta Height SDS		0.83	0.51	0.83	−0.53–2.03
	Age		13.81	3.28	13.83	6.89–22.03
Four years later	Height SDS	50	1.23	0.71	1.25	−0.12–3.28
	Delta Height SDS		1.11	0.48	1.08	0.18–2.18
	Age		14.45	2.94	13.88	9.02–23.07
Five years later	Height SDS	36	1.13	0.74	1.15	−0.41–2.44
	Delta Height SDS		1.22	0.46	1.20	0.39–2.34
	Age		14.60	2.29	14.62	10.02–19.95

Delta height SDS: Height SD at each observation — Height SD at commencement

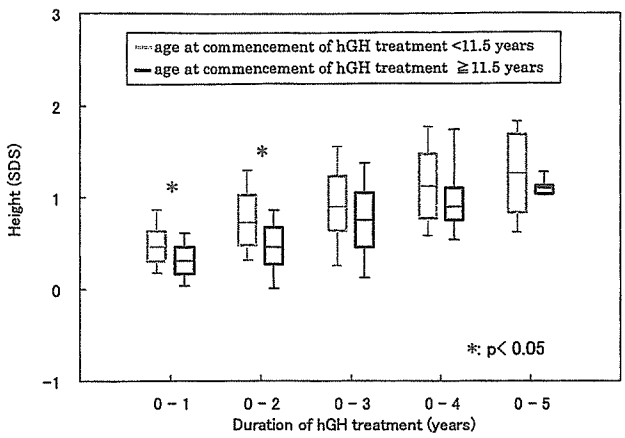

Fig. 3. Height SDS (sorted by age at commencement of hGH treatment).

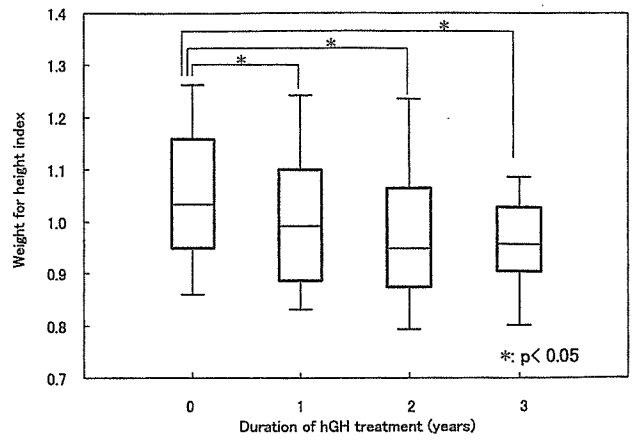

Fig. 4. Change of WHI at duration of hGH treatment.

Changes in physical constitution

We analyzed changes in physical constitution using WHI. Mean body weights for Turner syndrome patients up to 17 years and 0 months have been reported. We could therefore calculate WHI in cases in which height was up to 135.9 cm, which is the reported mean height of patients aged 17 years and 0 months (in cases without genital bleeding). In order to create a uniform analysis population, we selected subjects who were aged 8.1 to 14.8 years (*i.e.* within the range of mean ± 1SDS), and on the basis of height growth during the treatment. We calculated WHI up to three years following the commencement of the treatment (Fig. 4). WHI was 1.059 ± 0.165 (n = 135) at commencement, 1.008 ± 0.164 (n = 103) one year following commencement, 0.983 ± 0.163 (n = 60) two years following commencement, and 0.972 ± 0.139 (n = 33) three years following commencement, and as such, WHI following commencement of the treatment was significantly lower than that at commencement ($p = 0.05$).

Discussion

Short stature and gonadal dysfunction in Turner syndrome patients are indications for hormonal therapy. Therefore, various therapies to improve the patient stature have been attempted. The most commonly used therapy in addition to anabolic steroid treatment and sex steroid treatment is hGH treatment. Increases in height can be expected from hGH due to its pharmacological action, and there are many reports on hGH treatment in many countries. In particular, Rosenfeld *et al.* reported that an increase of 10.3 ± 4.7 cm in height was achieved by hGH treatment in combination with anabolic steroid treatment [4].

As such, hGH treatment is considered effective for treating short stature in Turner syndrome patients. However, in Japan reports are mainly on the results of clinical trials [5] or results compiled by the Foundation for Growth Science in Japan [6]. There is no report on the results of any cohort study. Thus, we compiled the results of treatment using Genotropin, a recombinant human growth hormone, in Turner syndrome patients. There are various karyotypes in Turner syndrome. 60.2% [7] of all Turner syndrome patients enrolled in KIGS International (which is the parent organization for KIGS Japan), 54.6% of patients studied by Lippe *et al.* [8] and 46.0% of patients studied by Kleczkowska *et al.* [9] were karyotype 45,X. In our study, karyotype 45,X was lower than in these studies in foreign countries. This is thought to be due to technical problems such as the larger number of cells that are required for chromosomal analysis.

However, it was reported that Turner syndrome patients who have an X isochromosome cannot secrete enough hGH, so bone maturation is delayed [10]. In other words, different karyotypes may respond to hGH differently. In our study, although there was no great difference between the karyotypes with respect to the response to hGH treatment (data not shown), it is necessary to continue to put effort into correctly diagnosing the karyotype.

In this study, the mean improvement in height was 1.22SDS following short-term hGH treatment (five

years). Height SDS increased more in patients who commenced the treatment at an earlier age. In principle, hGH treatment can be continued until epiphyseal closure occurs. Therefore, it is important in the future to examine the extent to which height prognosis will improve in cases in which Turner syndrome was diagnosed early and the treatment commenced during infancy. As mentioned earlier, high-dose treatment has been approved as a health insurance-covered treatment, and therefore it is expected that the effect of hGH treatment on improvements in height SDS will increase.

In this study, we examined the effect of low-dose hGH treatment in patients with GH deficiency. We did not, however, examine the relationship between the effect of hGH treatment and the extent of GH deficiency. Further studies are necessary to verify it.

hGH treatment in Turner syndrome patients not only promotes growth but also improves physical constitution [11]. We therefore calculated expected bodyweight in order to calculate WHI. We used WHI to evaluate bodyweight because it is difficult to specify normal bodyweight for Turner syndrome patients, and body mass index (BMI) is not appropriate for longitudinal evaluation of bodyweight in school-aged children. WHI significantly decreased during the three years of treatment, suggesting that hGH has a beneficial effect on physical health.

Currently in Japan, high-dose hGH treatment is performed in Turner syndrome patients. In the future it is necessary to further compile the results of low-dose hGH treatment, and to accumulate data on high-dose hGH treatment.

With respect to the data used in this report, we obtained consent from the patients or parents of the patients for the secondary use of their medical data. (This consent was obtained when KIGS Japan entered agreement for participation in this study with them.)

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Steroid Treatment for Severe Childhood IgA Nephropathy: A Randomized, Controlled Trial

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A previous trial showed that treatment of children with severe IgA nephropathy (IgAN) using prednisolone, azathioprine, heparin-warfarin, and dipyridamole for 2 yr early in the course of disease reduced the severity of immunologic renal injury and prevented any increase in the percentage of sclerosed glomeruli. This study compared the effects of prednisolone, azathioprine, warfarin, and dipyridamole (combination) with those of prednisolone alone in 80 children with newly diagnosed IgAN that showed diffuse mesangial proliferation. Patients were randomly assigned to receive either the combination or prednisolone alone for 2 yr. The primary end point was the disappearance of proteinuria, defined as urinary protein excretion <0.1 g/m^2 per d, and the secondary end points were urinary protein excretion at the end of treatment, the change in the percentage of sclerosed glomeruli during the trial, and adverse effects. The two study groups were similar in terms of baseline characteristics. Thirty-nine of the 40 patients who received the combination and 39 of the 40 who received prednisolone completed the trial. Thirty-six (92.3%) of the 39 patients who received the combination and 29 (74.4%) of the 39 who received prednisolone reached the primary end point by the 2-yr follow-up point ($P = 0.007$ log-rank). The percentage of sclerosed glomeruli was unchanged in the patients who received the combination but increased from 3.1 ± 4.8 to 14.6 ± 15.2% in the prednisolone group ($P = 0.0003$). The frequency of adverse effects was similar in the two groups. It is concluded that combination treatment may be better for severe IgAN than treatment with prednisolone alone.

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IgA nephropathy (IgAN) is the most common variety of primary glomerulonephritis in the world today. It was initially considered a benign disease with a favorable prognosis, but then data from long-term follow-up studies revealed that the disease progressed to renal failure in 20 to 50% of adult patients (1,2). Although there has been a prevailing belief that the prognosis of IgAN is more benign in children, recent studies do not support this (3). Children who have IgAN and in whom diffuse mesangial proliferation is evident on renal biopsy have a high risk for progressive renal deterioration (4). On the basis of a multicenter, randomized trial, we reported previously that treatment of childhood IgAN with diffuse mesangial proliferation using prednisolone, azathioprine, heparin-warfarin, and dipyridamole for 2 yr early in the course of disease reduced the severity of immunologic renal injury and prevented any increase in the percentage of sclerosed glomeruli (5). Corticosteroids uncombined with other drugs have been widely used to treat IgAN in pediatric patients (6–8). However, it has not been clear whether similar effects can be obtained using prednisolone alone in children with severe IgAN.

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Materials and Methods

The study was a prospective, unblinded, randomized, controlled clinical trial that involved 20 Japanese pediatric renal centers (The Japanese Pediatric IgA Nephropathy Treatment Study Group). The study protocol was in accordance with the standards of the ethics committee at each center, and all patients' parents gave informed consent to participate.

Patients

Patients were eligible for the study when they had a new diagnosis of having IgAN with diffuse mesangial proliferation by renal biopsy and when the following criteria were satisfied: (1) Age ≤15 yr at study entry, (2) no previous treatment with corticosteroids or immunosuppressive drugs, and (3) sufficient renal biopsy tissue available for histologic evaluation (minimum of 10 glomeruli).

The pathologist at each study center examined each renal biopsy specimen by light and immunofluorescence microscopy. The histologic sections were reviewed by two independent investigators who were unaware of the patients' clinical data at entry into the study. A diagnosis of IgAN was based on the presence of IgA as the sole or predominant Ig in the glomerular mesangium without systemic disease (9). Diffuse mesangial proliferation was defined on the basis of the World Health Organization criteria (>80% of glomeruli showing moderate or

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severe mesangial cell proliferation, *i.e.*, more than three cells per peripheral mesangial area) (10). Mesangial cell proliferation always was accompanied by increased mesangial matrix. The intensity of mesangial IgA deposits was graded semiquantitatively on a scale of 0 to 3+: 0, none; 1+, slight; 2+, moderate; and 3+, intense.

Study Design

After study eligibility was established and informed consent was obtained, patients were assigned randomly to one of the two treatment groups. Randomization was done by a sealed-envelope technique in blocks of four. The patients who were assigned to group 1 received prednisolone, azathioprine, warfarin, and dipyridamole treatment for 24 mo. Prednisolone was given orally at a dose of 2 mg/kg body wt per day (maximum 80 mg/d) every day in three divided doses for 4 wk, followed by 2 mg/kg every 2 d given as a single dose in the morning for 4 wk, 1.5 mg/kg every 2 d given as a single dose in the morning for 4 wk, and 1 mg/kg every 2 d given as a single dose in the morning for 21 mo. Azathioprine was given orally at a dose of 2 mg/kg body wt per day in a single morning dose for 24 mo. When a patient's leukocyte count decreased to $<4 \times 10^9$/L, azathioprine was discontinued until the leukocyte count increased to $>4 \times 10^9$/L. Warfarin was given in a single morning dose to maintain the Thrombotest at 30 to 50% for 24 mo. Dipyridamole was given orally at a dose of 5 mg/kg body wt per day in three divided doses for a total dose of not more than 400 mg/d for 24 mo. The patients who were assigned to group 2 received prednisolone alone under the same treatment protocol as that for group 1. The use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers was prohibited.

On entry into the study, all patients underwent a physical examination, and their complete medical histories were obtained. Initial clinical and laboratory results were forwarded to the coordinating center. Patients were followed up once a month during the study. At each follow-up visit, the patients were asked about their symptoms and were monitored for any adverse effects of therapy. Tests and measurements that were carried out at each visit comprised blood count (including hemoglobin, white blood cells, and platelets), Thrombotest, serum creatinine, blood urea nitrogen, serum IgA concentration, urinary protein excretion, hemostix test, BP, body weight, and body height. Hypertension was defined as present when the systolic or diastolic BP exceeded the upper normal limit for Japanese healthy children (mean + 2 SD).

At the time of study enrollment, all patients were asked to undergo repeat renal biopsies at the end of treatment. Two independent investigators who were blinded to the treatment status reviewed the second biopsies. No arrangement was made about treatment after the end of the 24-mo study period, and this was left to the judgment of each physician.

Statistical Analyses

On the basis of the data of our previous randomized, controlled study (5), we decided that the primary end point was the disappearance of proteinuria, as defined by urinary protein excretion <0.1 g/m^2 per d (11), and the secondary end points were urinary protein excretion at the end of treatment, change in the percentage of sclerosed glomeruli during the trial, and adverse effects. We predicted that the disappearance rate of proteinuria would be 65% in the combination group and 50% in the prednisolone alone group. Thirty-six patients were required for each study group, based on a selection design (12) in which the probability of correctly selecting the better treatment is 0.9 when it is superior by an absolute difference of 15% in the disappearance rate of proteinuria.

The results were analyzed with StatView J-4.02 software. The distribution of clinical and morphologic attributes between the treatment groups was examined by Fisher exact test. Continuous characteristics at the start of treatment were compared using the Mann-Whitney U test. Differences between study entry and study end in each treatment group were tested by the Wilcoxon signed rank test. The disappearance rate of proteinuria was analyzed by the Kaplan-Meier method, and the two groups were compared by intention-to-treat analysis by log-rank test. A two-tailed $P < 0.05$ was taken as the level of significance.

Results

Between January 1994 and December 1998, 83 children received a new diagnosis of having IgAN that showed diffuse mesangial proliferation. All 83 children met the criteria for inclusion in the trial. Eighty of the 83 patients were willing to enter the study (Figure 1). Of these, 40 were assigned to group 1 (prednisolone, azathioprine, warfarin, and dipyridamole) and 40 were assigned to group 2 (prednisolone alone). The clinical and laboratory characteristics of the patients in the two groups were similar (Table 1). Twenty-three (57.5%) patients in group 1 and 27 (67.5%) in group 2 presented with asymptomatic proteinuria and microscopic hematuria detected by a school screening program.

One patient in group 1 was lost to follow-up in the first month as a result of withdrawal of consent. Prednisolone was discontinued in four patients in group 2 as a result of adverse effects (three patients, in the 13th, 14th, and 21st months) and noncompliance (one patient in the 13th month). One of the three patients was lost to follow-up in the 22nd month. Three patients in group 1 did not complete the azathioprine therapy because of adverse effects (in the first, second, and 11th months) but completed the planned prednisolone, warfarin, and dipyridamole therapy. Thirty-nine patients each in groups 1 and 2 completed the 2 yr of treatment (Figure 1). All 40

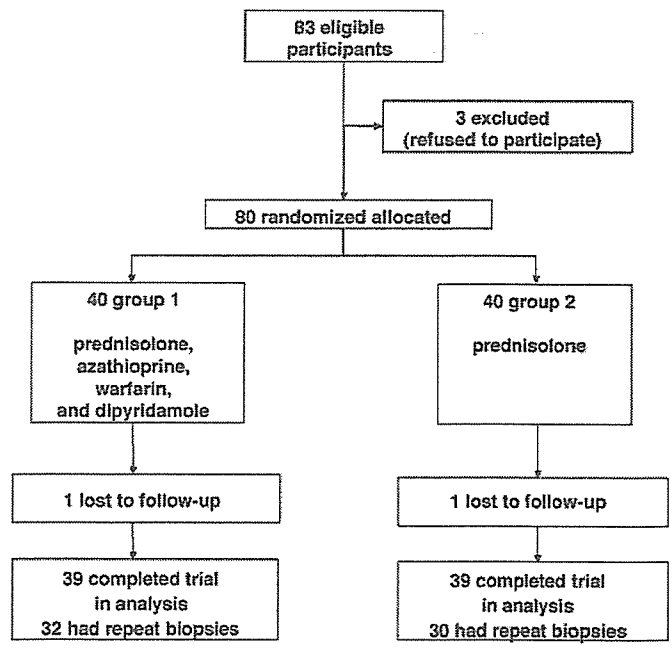

Figure 1. Trial profile.

Table 1. Baseline characteristics

Characteristics	Combination (n = 40)	Prednisolone (n = 40)	P
Demographic			
age (yr; mean [SD])	11.5 (3.2)	11.1 (2.8)	0.57
gender (M/F)	22/18	21/19	0.99
mo of disease (mean [SD])	11.5 (14.1)	14.8 (16.6)	0.30
mo from biopsy (mean [SD])	1.6 (1.4)	1.5 (1.4)	0.47
Initial presentation			
asymptomatic proteinuria and hematuria	25 (62.5%)	33 (87.5%)	0.14
macroscopic hematuria	12 (30.0%)	5 (12.5%)	
edema	3 (7.5%)	2 (5.0%)	
BP (mmHg, mean [SD])			
systolic	116 (11)	114 (13)	0.23
diastolic	64 (11)	63 (11)	0.62
Renal function			
urinary protein excretion (g/m^2 per d; mean [SD])	1.30 (1.17)	1.14 (1.12)	0.44
hematuria in morning urine[a] (mean [SD])	3.0 (0.6)	3.0 (0.8)	0.64
blood urea nitrogen (mmol/L; mean [SD])	5.2 (2.6)	4.7 (1.3)	0.74
serum creatinine (μmol/L; mean [SD])	49 (19)	43 (14)	0.22
estimated creatinine clearance (ml/min per 1.73 m^2; mean [SD])	147 (34)	157 (33)	0.24
serum IgA (mg/dl; mean [SD])	274 (117)	248 (109)	0.33
Renal biopsy			
no. of glomeruli (mean [SD])	22.9 (14.8)	21.9 (10.4)	0.80
glomeruli showing sclerosis (%; mean [SD])	3.9 (8.0)	2.7 (5.0)	0.97
glomeruli showing crescents (%; mean [SD])	17.8 (18.0)	19.3 (17.1)	0.65
glomeruli showing capsular adhesions (%, mean [SD])	5.5 (8.2)	3.9 (5.2)	0.66
intensity of mesangial IgA deposits[b] (mean [SD])	2.1 (0.5)	2.2 (0.6)	0.49

[a]Hematuria was quantified using dipsticks, and macroscopic hematuria was quantified as 4.
[b]The intensity of deposits on immunofluorescence microscopy was graded semiquantitatively on a scale from 0 to 3+: no, 0; slight, 1+; moderate, 2+; and intense, 3+.

patients in both groups were included in the Kaplan-Meier analysis of treatment effect (Figure 2).

Changes in Proteinuria, Hematuria, Renal Function, and Serum IgA Concentrations

At the end of the 2-yr treatment period, 36 (92.3%) of the 39 patients in group 1 and 29 (74.4%) of the 39 patients in group 2 reached the primary end point (urinary protein excretion <0.1 g/m^2 per d). Kaplan-Meier analysis demonstrated that the disappearance rate of proteinuria was significantly higher in group 1 than in group 2 at the 2-yr follow-up point (log-rank P = 0.007; Figure 2). The difference in the disappearance rate of proteinuria between the two groups at the end of the 2-yr treatment period was 17.9% (95% confidence interval 1.8 to 34.0%).

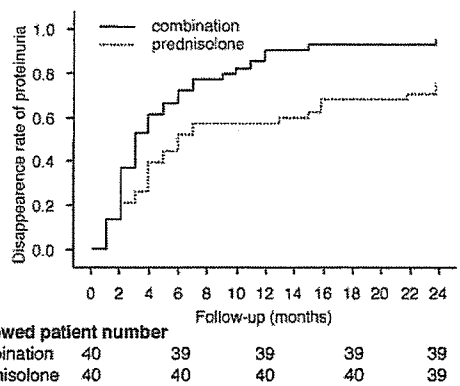

Figure 2. Disappearance of proteinuria as defined by urinary protein excretion <0.1 g/m^2 per d.

Mean urinary protein excretion in group 1 was reduced from 1.29 g/m^2 per d at the start of treatment to 0.10 g/m^2 per d at the end (P < 0.0001), and that in group 2 was also reduced from 1.16 to 0.12 g/m^2 per d (P < 0.0001; Table 2). The intergroup difference in the reduction of mean urinary protein excretion at the end of treatment was NS. The presence of blood in morning urine, quantified using dipsticks, a colorimetric test for hemoglobin (13), showed significant reduction in both groups (Table 2). The mean serum IgA concentration in group 1 decreased from 276 ± 118 mg/dl at the start of treatment to 194 ± 85 mg/dl at the end (P = 0.0001), and that in group 2 also decreased from 245 ± 109 to 194 ± 90 mg/dl (P = 0.0003). BP and creatinine clearance were normal at the end of the trial in all patients. The mean body mass indexes in both groups increased significantly even though they were within normal range during the study period (Table 2).

Table 2. Effect of 2 yr of treatment

Parameter	Start of Treatment	End of Treatment	*P*
Clinical data			
Urinary protein excretion (g/m^2 per d; mean [SD])			
combination (n = 39)	1.29 (1.19)	0.10 (0.15)	<0.0001
prednisolone (n = 39)	1.16 (1.13)	0.12 (0.16)	<0.0001
Urinary protein excretion <0.1 g/m^2 per d			
combination (n = 39)	0	36 (92.3%)	<0.0001
prednisolone (n = 39)	0	29 (74.4%)	<0.0001
Hematuria in morning urine[a] (mean [SD])			
combination (n = 39)	3.0 (0.5)	0.4 (0.8)	<0.0001
prednisolone (n = 39)	3.0 (0.8)	0.6 (1.0)	<0.0001
Estimated creatinine clearance (ml/min per 1.73 m^2; mean [SD])			
combination (n = 39)	148 (33)	156 (26)	0.64
prednisolone (n = 39)	156 (32)	155 (32)	0.95
Estimated creatinine clearance <60 ml/min per 1.73 m^2			
combination (n = 39)	0	0	
prednisolone (n = 39)	0	0	
Serum IgA (mg/dl; mean [SD])			
combination (n = 39)	276 (118)	194 (85)	0.0001
prednisolone (n = 39)	245 (109)	194 (90)	0.0003
Body mass index (mean [SD])			
combination (n = 39)	18.7 (4.0)	20.0 (3.0)	0.0007
prednisolone (n = 39)	19.1 (3.7)	21.8 (4.3)	<0.0001
Pathologic data			
Time of repeat biopsy from end of treatment (mo; mean [SD])			
combination (n = 32)	1.2 (3.0)		
prednisolone (n = 30)	1.8 (3.6)		
No. of glomeruli (mean [SD])			
combination (n = 32)	24.5 (15.5)	26.8 (16.5)	0.67
prednisolone (n = 30)	24.2 (10.1)	26.2 (14.8)	0.68
Glomeruli showing sclerosis (%; mean [SD])			
combination (n = 32)	5.0 (9.1)	4.6 (7.9)	0.74
prednisolone (n = 30)	3.1 (4.8)	14.6 (15.2)	0.0003
Glomeruli showing crescents (%; mean [SD])			
combination (n = 32)	17.3 (16.6)	1.7 (3.0)	<0.0001
prednisolone (n = 30)	19.1 (17.1)	0.9 (1.9)	<0.0001
Glomeruli showing capsular adhesions (%; mean [SD])			
combination (n = 32)	5.2 (7.0)	5.3 (8.1)	0.62
prednisolone (n = 30)	3.6 (5.4)	5.0 (7.5)	0.60
Intensity of mesangial IgA deposits[b] (mean [SD])			
combination (n = 31)	2.1 (0.4)	1.5 (1.0)	0.006
prednisolone (n = 29)	2.2 (0.5)	1.8 (1.2)	0.03

[a]Hematuria was quantified using dipsticks and macroscopic hematuria was quantified as 4.
[b]The intensity of deposits on immunofluorescence microscopy was graded semiquantitatively on a scale from 0 to 3+: no, 0; slight, 1+; moderate, 2+; and intense, 3+.

Changes in Pathologic Features

Thirty-two patients in group 1 and 30 in group 2 underwent repeat renal biopsies at the end of treatment (Table 2). The mean percentage of glomeruli that showed segmental or global sclerosis was unchanged in group 1 but increased from 3.1 ± 4.8% at the start of treatment to 14.6 ± 15.2% at the end of treatment in group 2 (P = 0.0003). The percentage of glomeruli that showed crescents was significantly reduced in both groups (P < 0.0001, respectively). The percentage of glomeruli that showed capsular adhesions was unchanged in both groups.

Immunofluorescence was not available for the repeat biopsy at the end of treatment for one patient each in groups 1 and 2. The initial renal biopsy revealed intense or moderate mesangial deposits of IgA in all patients. Mesangial IgA deposits became

significantly less intense at the end of treatment in both groups ($P = 0.006$ and 0.03, respectively).

Adverse Effects

The adverse effects in both treatment groups are shown in Table 3. Ten patients in each group showed adverse effects, and the total number of cases of adverse effects that were observed in each group was 14. One patient in each group showed aseptic necrosis of the femoral head (as a result of prednisolone). Other adverse effects that affected group 1 patients were glaucoma (as a result of prednisolone; two patients), headache (as a result of dipyridamole; three patients), leukopenia (as a result of azathioprine; four patients), bleeding (one patient), anemia (as a result of azathioprine; one patient), and elevation of transaminase concentration (two patients). Other adverse effects as a result of prednisolone that affected group 2 patients were hypertension (five patients), glucosuria (three patients), glaucoma (two patient), cataract (two patients), and elevation of transaminase concentration (one patient). Hypertension was improved only by restricted sodium diet and tapering of prednisolone based on the study design without antihypertensive drugs. All of these adverse effects except for aseptic necrosis of the femoral head and cataract subsided after the treatment.

Azathioprine was discontinued until the adverse effects subsided in two patients with leukopenia and one patient with elevation of transaminase concentration in group 1. However, these three patients completed the planned prednisolone, warfarin, and dipyridamole therapy. Prednisolone was discontinued in one patient with glucosuria and hypertension, one patient with glaucoma and hypertension, and one patient with glaucoma in group 2 by doctors in charge.

Discussion

Like our previous randomized, controlled trial (5), this study showed that the combination therapy for 2 yr significantly reduced the level of urinary protein excretion, serum IgA concentration, and mesangial IgA deposition and prevented any increase of sclerosed glomeruli in children with newly diagnosed IgAN that showed diffuse mesangial proliferation. In contrast, treatment with prednisolone alone for 2 yr did not prevent a further increase of sclerosed glomeruli, although it reduced the level of urinary protein excretion, serum IgA concentration, and mesangial IgA deposition. Disappearance of proteinuria (primary end point) was observed in 36 (92.3%) of the 39 patients in the combination therapy group and in 29 (74.4%) of the 39 patients in the prednisolone alone group. Kaplan-Meier analysis demonstrated that the disappearance rate of proteinuria was significantly higher in group 1 than in group 2 at the 2-yr follow-up point (log-rank $P = 0.007$; Figure 2). The difference in the disappearance rate of proteinuria between the groups at the end of the 2-yr treatment period was 17.9% (95% confidence interval 1.8 to 34.0%). On the basis of the selection design (11), we therefore were able to select the combination treatment as the better of the two. This selection also was supported by the intergroup difference in the change in the percentage of sclerosed glomeruli during the trial. These findings suggest that combination treatment may be better for IgAN that shows diffuse mesangial proliferation than prednisolone monotherapy. Most of the patients who reached the primary end point did so within the first 12 mo (Figure 2). Therefore, we may be able to modify the duration and/or dose for prednisolone treatment to reduce adverse effects.

Table 3. Adverse effects

Adverse Effect	Combination ($n = 40$)	Prednisolone ($n = 40$)
Hypertension	0	5 (12.5%)
Glucosuria	0	3 (7.5%)
Aseptic necrosis of femur	1 (2.5%)	1 (2.5%)
Glaucoma	2 (5.0%)	2 (5.0%)
Cataract	0	2 (5.0%)
Headache	3 (7.5%)	0
Leukopenia	4 (10.0%)	0
Bleeding	1 (2.5%)	0
Anemia	1 (2.5%)	0
Elevation of transaminase concentration	2 (5.0%)	1 (2.5%)

The most appropriate treatment for patients with IgAN is controversial. The present standard treatment is focused on two perspectives: Anti-inflammatory drugs to fight the systemic immune reaction and renal histologic activity, including corticosteroids and immunosuppressors, and antisclerogenic drugs to inhibit progressive renal fibrosis (14). The rationale for using prednisolone and azathioprine in IgAN is that corticosteroids and immunosuppressive agents reduce IgA production and minimize the abnormal immune response and inflammatory events after glomerular IgA deposition. Warfarin and dipyridamole are used to inhibit the mediators of glomerular damage. Corticosteroids, immunosuppressive agents, antiplatelet drugs, and anticoagulants have been used singly or in combination in children and adults with IgAN (7,15–19). However, clinical trials that were conducted in the early period have not provided convincing evidence of any beneficial effect of drugs (20,21).

Corticosteroids have been widely used to treat moderate to severe IgAN, particularly in pediatric patients. To date, information concerning not only the effectiveness but also the safety of corticosteroid therapy over a long time course has been largely defective. It has been difficult to assess the results of treatment trials with these agents in terms of preservation of renal function, as a result in part of wide variations in the length of therapy and the dosing regimens used and also to the use of corticosteroids in combination with other drugs (22). Recently, however, some evidence has been obtained for the role of corticosteroids in the treatment of IgAN (2,22). In adults with IgAN, an Italian prospective, randomized, controlled trial demonstrated that a 6-mo course of steroid treatment protected against deterioration of renal function with no notable adverse effects during follow-up (23). Recently, the long-term follow-up data of the trial showed that corticosteroids significantly reduced proteinuria and protected against renal function deteri-

oration (24). With regard to children, our previous study (5) is the only randomized, controlled trial so far to have demonstrated that treatment that includes corticosteroid for 2 yr early in the course of disease reduces immunologic renal injury and prevents any further increase of glomerular sclerosis. Up to now, however, it has been unknown whether corticosteroid alone is sufficient for treatment of IgAN in children, and there has been no reliable evidence for its effectiveness in this group of patients (22).

The difference in the effectiveness between the two treatment regimens in our study was thought to be due to the total effect of azathioprine, warfarin, and dipyridamole. Although the exact mechanism by which this regimen prevents glomerular sclerosis remains unknown, immunosuppressive agents may play a major role. To investigate this issue, a controlled trial is currently in progress to compare the effects of prednisolone, immunosuppressive agents, warfarin, and dipyridamole with those of prednisolone and immunosuppressive agents in children with severe IgAN.

The beneficial effects of prednisolone, azathioprine, warfarin, and dipyridamole treatment were accompanied by relatively few serious adverse effects that were attributable specifically to the drugs, except for aseptic necrosis of the femoral head. Three patients did not complete the treatment because of adverse effects of azathioprine. However, these adverse effects subsided after withdrawal of azathioprine, and three of the patients completed the planned prednisolone, warfarin, and dipyridamole therapy. Aseptic necrosis of the femoral head was observed in one patient in each of the groups. This is a severe adverse effect with sequelae. To reduce its frequency and severity, we may be able to modify the corticosteroid regimen. Five of the 40 patients in group 2 (prednisolone alone) showed hypertension, but none of the 40 patients in group 1 (combination) did so. Dipyridamole therapy therefore may prevent the development of hypertension in children who receive prednisolone.

Our serial pathologic observations (25,26) have revealed that the extent of glomerulosclerosis increases with time in patients who show persistent proteinuria. In this study, treatment was started early in the course of disease because the duration of the disease before treatment was short and the extent of glomerulosclerosis was low as a result of the school screening program. Accumulated experience indicates that long-term corticosteroid and/or immunosuppressive treatment during the insidiously progressive stage of the disease does not confer any benefit in adult patients (27). Because of the variable rate of progression to renal failure and the probable multifactorial pathogenesis of IgAN, the effectiveness of any treatment can be evaluated properly only by a controlled trial.

In a controlled trial, it is important to select adequate end points. Although in a clinical trial of progressive IgAN the ultimate end point is development of chronic renal insufficiency, most pediatric patients do not develop it during the 2-yr study period (22). Our previous trial (5) and experience also support this. Therefore, studies of pediatric patients with IgAN may differ markedly from studies of adults with regard to the apparent risk for progressive disease and, hence, the need for therapy (22). For this reason, we decided that the primary end point of this study was the disappearance of proteinuria.

Although the 2-yr study period may be too short to confirm the long-term benefit of the prednisolone, azathioprine, warfarin, and dipyridamole regimen, the results obtained so far suggest that the combination therapy may slow the rate of progression to chronic renal failure, because it prevents the progression of glomerular sclerosis. After 2 yr of treatment, all of the patients are still being followed to examine the long-term effects of the combination treatment on the rate of progression to chronic renal failure.

Conclusion

Treatment of children with severe IgAN using prednisolone alone for 2 yr reduces the severity of immunologic renal injury but does not prevent any further increase of glomerular sclerosis. Therefore, treatment with prednisolone, azathioprine, warfarin, and dipyridamole for 2 yr early in the course of disease may be better than prednisolone alone for this group of patients.

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医師主導治験で生じる副作用情報等を中心とした問題点

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Difficulties Managing Safety Information on Adverse Drug Reactions in Investigator-initiated Clinical Trials

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はじめに

医師主導治験は，その実施のために，平成15年7月30日，「医薬品の臨床試験の実施の基準（Good Clinical Practice，GCP）に関する省令の一部を改正する省令」（平成15年厚生労働省令第106号）が施行され，これらを遵守するための通知[1]が発出される等，準備が進められてきた。平成16年7月22日，「医薬品の臨床試験の実施の基準の運用について」[2]が通知された後，同年末，小児科領域では初めて，クエン酸フェンタニル医師主導治験の治験届が提出された。

ここでは，まず，わが国の小児科領域での医師主導治験の現況を簡単に振り返り，医師主導治験が今後も必要なものであるのかどうかを考える。それらを踏まえ，医師主導治験を実施することにより，新たに，当時の法令に基づき，これまで製薬企業が収集し，検討後規制当局へ報告していた副作用等報告が，自ら治験を実施する医師にも求められることとなったこと等，その内容を検討したい。更に，自ら治験を実施する医師に掛かる過度の負担と考えられるものについて，特に，副作用情報等を中心とした問題点について，従来の製薬企業の治験の場合と比較しながら，まとめ，考え，これまでに講じられた解決策を含め，クエン酸フェンタニル医師主導治験の治験調整医師としての経験を踏まえた私見を述べたい。

国内小児科領域医師主導治験の現況

臨床現場で必要とされている，あるいは実際に使用されているにもかかわらず，何らかの理由で製薬企業が主体となって治験が実施されていない，即ち，その科学的根拠を明らかにできていない医薬品，この場合，多くは適応外使用ということになるが，や治療法というものが存在する。このような医薬品や治療法において，質の高いEvidenceを創ることを目的とし，GCP下で医師自らが主体となって，根拠に基づいた医療（Evidence-based Medicine，EBM）を確立するために，臨床試験を実施することがある。「製造販売承認申請を目的とした」医師主導臨床試験，言い換えれば，これが医師主導治験である。

厚生労働科学研究費補助金治験推進研究事業を実施するために設立された，日本医師会治験促進センターの援助を受けている医師主導治験は，国内小児科領域で，現時点で4件ある。新生児及び小児の全身麻酔の補助として用いられるクエン酸フェンタニルは，添付文書上フェンタニル自体，2歳以下では禁忌，小児等への安全性も確立していない等となっている。しかしながら，小児科臨床現場では，なくてはならない品目であり，適応外使用解決のために，医師主導治験の治験届が，平成16年12月に提出され，実施されるに至った。日本の小児科領域医師主導治験の先駆けであるが，平成18年6月30日に治験を終了したものの，当初予想されなかった，さまざまな問題に直面しているところでもあり，副作用情報等以外でも，実情が，そのまま医師主導治験に関する問題提起となり得る状況にある。新生児けいれんに対する静脈内投与フェノバルビタールは，小児科領域の中でも，対象が新生児であること等種々の理由により，最も治験が実施しにくいであろうと考えられている分野での治験の実施となった。現在，平成18年12月までの予定で治験中である。難治性小児悪性固形腫瘍の塩酸イリノテカンは，以前からの，この専門分野の医師等の努力が結実し，小児科領域では最も整備されている分野での臨床試験の実施となったと言うことができるであろう。現在，治験中である。脳卒中様症状を主体とする，ミトコンドリア病の病型（Mitochondrial Encephalomyopathy Lactic Acidosis Stroke，MELAS）のL-アルギニンは，オーファンドラッグでも最たるものと考えられるが，現在，まもなく治験がはじまるところであると聞いている（平成18年7月）。

国内小児科領域医師主導治験実施の必要性

前項でも述べたが，わが国の小児科領域における医師主導治験は，特に，医薬品の適応外使用解決と深く結びついていると考えられる[3]。小児科領域での医薬品の適応外使用は，たいへん大きな問題であって，こどもたちに最良な薬物療法を提供するためには，是非解決して行かなければならないことである。この領域で，医薬品を適応外使用している理由を2つ挙げるとすれば，1に，日常頻用されるが，何らかの理由で適応取得されずに放置されたものと，2に，希少疾病のために，これまでにも積極的には適応取得されなかった，あるいは最新の治療であるため治験が追いつかないということに集約されると私は考えている。前者であれば，品目によっては，今更治験が必要とは言えないものも多いであろうが，中にはきちんとした評価を必要とする品目もあるに違いないし，

後者であれば，必然として，何らかの形での臨床試験で評価することは必須となろう。小児科領域での医師主導治験は，これら医薬品の適応外使用を解決する手段の一つとして，今後も実施されていかれなければならない性質のはずのものである。もちろん，日本の小児科領域で，医師主導治験を円滑に進めるためには，小児科領域での治験のインフラストラクチャーを整備し，治験を計画するための，例えば，有効性のエンドポイントやサロゲートエンドポイントを決定する等，方法論確立の議論も十分になされなければならない。医師主導治験を実施できるよう環境を整えようとすることは，インフラストラクチャー整備や方法論の確立等への解決にも繋がる。更に，小児科領域での，臨床研究全体の基盤も整備され，臨床研究自体のレベルの向上にも結びつくこととなろう。

医師主導治験における治験調整医師と治験責任医師

これより，医師主導治験における，副作用情報等に関する話をする。これらを語る際には，副作用情報等をとりまとめて，後述する厚生労働大臣への報告義務を担うことになるのが，治験調整医師であり，治験責任医師であるので，医師主導治験における治験調整医師と治験責任医師の位置付けについて，よく知っておく必要があることから，以下確認する。

GCP第2条では，治験責任医師は，実施医療機関において，治験に係る業務を総括する医師となっており，自ら治験を実施する者とは，その所属する実施医療機関において，自ら治験を実施するために治験の計画を届け出た治験責任医師をいうとなっている。GCP第26条では，自ら治験を実施する者は，一の治験実施計画書に基づき，複数の実施医療機関において，共同で治験を実施する場合には，当該実施医療機関における，当該治験実施計画書の解釈，その他の治験の細目について，調整する業務を治験調整医師，又は治験調整委員会に委嘱することができると説明されている。

クエン酸フェンタニル医師主導治験は，国内6医療機関の共同治験であり，治験責任医師として各医療機関1名ずつの医師で構成されている。治験調整業務は，国立成育医療センターで執り行い，2名の医師が治験調整医師となっている。

医師主導治験副作用情報等の取扱いの実際

治験中に得られる安全性情報については，すみやかに報告するための基本的な指針[4]が日米EU医薬品規制調和国際会議(International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH)での合意に基づき発出されているところであるが，それを踏まえた上で，まず，医師主導治験で取り扱う安全性情報の厚生労働大臣への報告対象，及び報告期限について，整理しておく。

薬事法第80条2では，治験の依頼をした者，又は自ら治験を実施した者は，当該薬物の副作用によるものと疑われる疾病，障害，又は死亡の発生等，厚生労働省令で定めるものを知ったときは，その旨を厚生労働省令で定めるところにより，厚生労働大臣に報告しなければならないとなっている。薬事法施行規則第273条では，これらの厚生労働大臣への報告期限について，死亡や死亡につながるおそれのある症例で，治験薬概要書から予測できないもの，即ち，未知のものは7日，入院又は入院期間の延長，障害，障害につながるおそれのある症例やこれらに準じて重篤である症例等で，未知のものは15日，死亡や死亡につながるおそれのある症例で，治験薬概要書から予測できる，即ち，既知のものは15日，その他の重篤で，既知のものは，報告不要であることが記されている。

製薬企業が主体となって実施する治験では，製薬企業が治験依頼者となるが，医師主導治験の場合には，治験依頼者は存在せずに，治験実施の主体が自ら治験を実施するもの，即ち，治験責任医師そのものということになる。医師主導治験では，製薬企業主体の治験で治験依頼者が行っていた，副作用情報等の取り扱いを含む多くの業務を，治験責任医師や治験調整医師がやらなければならないということである。

更に，副作用情報等には，どのようなものがあるのか，具体的にみてみる。

治験中に取り扱う安全性情報には，当該治験そのもので起きた副作用情報，外国で使用されている薬剤では外国で発現した副作用等情報(多くは国際的な統一規格である，Council for International Organization of Medical Sciences Form, CIOMS Form (CIOMS Form)を用いて国際的に情報交換されている)，当該治験薬に関する国内外の学術雑誌等に掲載された研究報告，あるいは当該治験薬に関連する企業において実施された研究報告等の情報，並びに外国で使用されている薬剤では，治験薬と同一成分に対してなされた外国における措置報告，更に，国内既承認の医薬品で，かつ承認事項の一部変更（一変）等の申請のための治験中であれば，国内で市販されている，同一成分の医薬品に対してなされた措置報告等が挙げられる。

ここで，実際の業務手順を説明する。

まず，当該治験で起きた副作用情報についてであるが，幸い，クエン酸フェンタニル医師主導治験において，治験そのもので重篤な有害事象は発現しなかった。したがって，発現した場合に取るはずであった手順について述べることにする。

医療機関で有害事象が発生した場合，その有害事象が重篤かどうかによって，その後の扱いが異なる。重篤な有害事象の取扱いに関する医療機関内での手順については，GCPに従い，医療機関で定められているので，ここでは省略する。

はじめに，有害事象が発現した場合，治験責任医師等はその有害事象について，重篤性，既知未知，因果関係の有無を判断し，重篤と判断した場合には重篤な有害事象報告書に症例の内容を記載するとともに，当該治験で定めた様式に規制当局への報告の必要性等を記載し，治験調整医師へ連絡する。この際，規制当局への報告期限を勘案し，治験責任医師等は重篤な有害事象の発現を認めてから極めて速やかな対応が必要とされる。

治験責任医師等からの連絡を受けた治験調整医師は，そ

の報告の内容，及び治験責任医師等の判断を確認し，全治験責任医師に当該報告を通知する。その際，治験調整医師は各治験責任医師の当該報告に対する意見を調整する目的で，意見返信用の様式も準備した。

治験調整医師からの連絡を受けた治験責任医師は，その報告の内容，情報元の治験責任医師，及び治験調整医師の意見を確認し，各自の意見を治験調整医師に返信する。治験調整医師は全治験責任医師からの意見を取りまとめ，規制当局への報告の必要がある場合には，法令で定められた報告書を準備し，規制当局へ提出するという手順を取る予定であった。

治験依頼者による治験では，規制当局への報告期限の起算日は治験依頼者が対象となる副作用等の発現を知った日とされているが，医師主導治験では治験責任医師自身が知った日が起算日となるため，報告書作成に至る各ステップでの持ち時間が極めて重要となる。そこで，本治験では，日本医師会治験促進センターの情報管理支援システムであるFaxサーバを使用したが，その詳細についてはここでは省く。他稿を参照いただきたい。

次に，当該治験以外の安全性情報について，治験責任医師自らも情報入手に努めるが，実際には治験薬提供者から治験薬に関する情報の一環として，安全性情報を入手することが現実である。なお，その際，治験薬提供者，及び個々の治験責任医師の負担を軽減するため，治験調整医師が代表して情報を入手し，評価案を作成することとした。

治験調整医師（たいてい1～2名である）が，上記した内容の副作用等情報を治験薬提供者より受け，例えばCIOMS Form，措置報告や研究論文であれば，それらを要約し，事象について，既知未知や重篤度を評価する。更に，治験調整医師は，規制当局への報告要否も検討し，当該治験の手順書で規定された様式に整理し，治験責任医師にこれらの情報を回覧した後，挙げられた意見を調整する。必要であれば，前述したように，法令に則り，7日報告や15日報告に対応し，規制当局への報告書を準備した。7日報告や15日報告の期限は，本来治験責任医師が知った日より起算されるが，当該治験では治験調整医師がそのことを知った日から起算することとし，この期間内に規制当局たる，医薬品医療機器総合機構へ報告することになる。このすべてのやり取りには，週末や祝日も日数としてカウントされる。前述のように，当該治験では，これらの煩雑な業務を少しでも早く確実に実行していくために，日本医師会治験促進センターのFaxサーバを使用した。

がん領域での，メシル酸イマチニブ医師主導治験では，外国でも広く使用されている医薬品と同一成分であるため，1ヶ月で200件以上の膨大な副作用情報を処理したと聞く。これらを踏まえてのことと，容易に予想されるが，実施している国立がんセンターの医師自ら，平成17年4月の時点（治験届は平成16年11月及び12月）で，医師主導治験の実施を巡る副作用報告等をも含む，法令改正のための要望書[5]を提出した程である。

クエン酸フェンタニル医師主導治験の副作用情報等の報告数は，治験届が平成16年12月17日に提出されて以来，平成17年10月25日までに，CIOMSは36例，追加報告も含めて37件，このうち未知・死亡や死亡につながるおそれのため，7日報告が2件，未知・その他重篤とされた15日報告，あるいは既知・死亡や死亡につながるおそれとされた15日報告が18件，報告不要が17件であった。外国研究報告及び措置報告は計26件（追加報告も含めて，外国研究報告が24件，措置報告が5件の計29件），このうち，報告対象は，研究報告とされ15日報告に相当が2件，研究報告の中で内容的には症例報告であった15日報告に相当が1件，措置報告とされ15日報告に相当が2件，報告不要が24件であった。その後，平成18年6月30日の治験終了時までには，CIOMS Formが全74例78件，外国研究報告及び措置報告は48件，追加報告を併せて52件となった。結果的に規制当局に報告不要であったとしても，治験調整医師は，受け取った情報を吟味，既知未知，重篤度を評価，規制当局への報告が必要であるか否かを判断，内容を整理後，治験責任医師に回覧して，意見を調整することまでの作業は同様に発生する。しかも，これらの業務は診療の合間に行うことになる。

医師主導治験副作用情報等の取扱いに関する問題点

医師主導治験では，実施する医師に，診療及びこれまでの製薬企業主体の治験を実施する上で，やらなければならない作業に加えて，新たな負担がかかっており，それが過度なものであることが問題なのである。

特に，副作用情報等の取扱いについては，そのノウハウを持たない，自ら治験を実施する者にも，製薬企業と同様に，それらを規制当局に報告する義務が生じたことも問題の一つである。しかもしばしば，自ら治験を実施する者の報告する内容と，製薬企業の報告する内容とが重複している。

前述したように，クエン酸フェンタニル医師主導治験の副作用情報等の報告数のみを見ると，がん領域のメシル酸イマチニブ程ではないにせよ，単純計算では，1週間に2件見当で，副作用情報等を処理していたことになる。医師主導治験における副作用情報等の取扱いは，その医薬品の臨床的位置付けの違いもあるであろうし，その治験毎取扱い上の取り決めが異なっているので，報告数での単純比較には意味がないと個人的には思うものの，治験調整医師から，治験責任医師に通知して，意見を調整した報告のうち，必要があれば（当時の）法令に則り，7日報告や15日報告に対応するために，副作用等報告書を準備し，最終的に規制当局に提出するという一連の流れをも振り返ると，私たちの行ったクエン酸フェンタニル医師主導治験でも，十分余裕を持って副作用情報等の対応ができたとは言い難い。特に，7日報告のやり取りは，時間的にも相当厳しいものとなった。

個人的には，副作用情報等の報告のうち，CIOMS Formによるものは，その事象の概要を探るには有用であろう。したがって，潜在している，その被験薬に関わるかも知れない，何か大きな副作用の発現に気付くという可能性は高いと思わ

れるが，特に外国での市販後の情報では細かい経緯が把握しにくく，この情報で内容を十分検討することは難しいと感じる。外国研究報告は，クエン酸フェンタニルの場合，例えば，臨床研究において評価対象とされる医薬品ではなく，併用薬として使用されている等の報告が多く，やはり，この報告を基に，事象の内容を十分に検討できるかと言われると，これも難しく感じる。

国立がんセンターの藤原は，第2回治験のあり方に関する検討会において，薬事法施行規則の規定する重篤（既述）と臨床的な重篤は異なる，各種届出の様式が定められている，面会を求められることもある等（医師主導治験実施における問題があること）を強調していたことも付記しておく[6]。

医師主導治験副作用情報等の取扱いに関する問題点解決の糸口

医師主導治験で生じる副作用情報等の取扱いについては，医師主導治験実施中にも，製薬企業は従来どおり，当該治験薬と成分が同一性を有すると認められるものによる有害事象については，責任を持つべきである。自ら治験を実施する者は，その治験で発生した有害事象を中心に主体性をもって考えていくべきであり，その他の情報を，製薬企業としばしば重複してハンドリングする必要はないであろうと，個人的には考えていた。

このように考えるに至った理由は，自ら治験を実施する者にとって，既述したような煩雑な作業，例えば，製薬企業と重複して報告される，副作用情報のハンドリング等が，明らかに必要と考えられるより多くの範囲にわたって生じており，他の診療業務にまで支障が出るような状態の連続を，自ら実際に経験していたことにもよる。

平成17年3月には，厚生労働省による，治験のあり方に関する検討会も発足した。治験のあり方という広い範囲の議論であるが，その中で，前述のとおり，医師主導治験における副作用報告等についても取り上げられており，改善の方向で進んできた。特に，平成17年9月29日に開催された第6回では，中間まとめ（その1）案，平成17年10月26日の第7回では，中間まとめ（その1）が出された[7,8]。

中間まとめによれば，多施設共同治験における治験中の副作用・感染症（以下副作用等）症例報告の対象について，国内既承認の医薬品の効能・効果等の一部変更のための治験では，原則として，治験を実施する医療機関内で発生したものであって，①未知の副作用等による死亡，又は死亡のおそれのある症例，②未知の副作用等による重篤な症例，③既知の副作用等による死亡，又は死亡のおそれのある症例を規制当局への報告対象とする。一方，海外における当該被験薬による副作用等症例報告については，当該治験薬の承認を有する製薬企業が，副作用等症例報告に関する義務を有していることを踏まえ，報告対象から除外することとする。なお，添付文書の改訂等に係る措置報告，及び当該被験薬に係る研究報告については，従前のとおり報告対象とするとなっており，私たちの経験からも導き出されたであろう策にも似る。これに併せて種々の通知が発出された[9,10,11,12]。

これらの整備で，私たちが体験し，困難を感じていた，製薬企業としばしば重複して報告していた副作用等報告の一部，即ち外国症例報告，多くはCIOMS Formである，については，自ら治験を実施する者が報告する義務はなくなった。しかしながら，クエン酸フェンタニル医師主導治験の場合には，先に示したように，研究報告及び措置報告もCIOMS Formと同程度の数存在していたので，正直に言えば，自ら治験を実施する者の負担軽減感は，副作用情報等に関して，それ程大きくなかったように感じる。クエン酸フェンタニルの経験のみから言えば，既述したように，CIOMS Formにしても，研究報告及び措置報告にしても，報告された内容から判断できることは，非常に限られたものであることが多いと思われたので，医師主導治験で，このような経験が蓄積，分析されていく過程で，もう少し踏み込んだ，副作用等報告のあり方が議論できるようになるとよいと考える。それでも，医師主導治験については，副作用等報告に限らず，現時点では，実施しながら問題点を洗い出し，整備していこうとする姿勢があり，このことが，自ら治験を実施する者の目的達成の意欲を刺激していることは事実であろう。因みに，がん領域での，メシル酸イマチニブ医師主導治験では，開始後しばらくの副作用等報告の約9割がCIOMS Formであると聞いており，この場合には，医師主導治験の，自ら治験を実施する者の負担軽減として，かなり大きなものになったと思われる。

なお，小児科領域の医師主導治験では，経験することはなかったが，医師主導治験で生じる，副作用情報等の問題点については，以下も治験のあり方に関する検討会の中間まとめで示され[7,8]，整備された。薬事法第80条の2及び関連通知で，一の実施計画書に基づき多施設共同治験を実施し，治験届を連名で提出した場合には，副作用等報告書も連名で提出することが可能とされている。当初一旦治験届提出後，新たに治験を実施する医療機関が追加された場合には，当該追加医療機関は，他の治験実施医療機関とは別に副作用等報告書を作成し，提出しなければならないこととなっていたが，この報告書については，各医療機関における副作用に対する判断，評価及び対応等が同じであれば，各医療機関すべてからの報告を一つにまとめて，連名で規制当局に提出することができる旨が周知された。

更に，副作用情報等が主体ではなかったにせよ，平成18年1月26日に，治験のあり方に関する検討会の中間まとめ（その2）が取りまとめられ，それを受けて，「医薬品の臨床試験の実施の基準に関する省令の一部を改正する省令」（平成18年厚生労働省令第72号）が公布され，平成18年4月1日から施行されたことを付け加えておく[13,14]。

おわりに

ここでは，医師主導治験副作用情報等の問題点や解決策を中心に話をした。

本来，今後も必要とされよう，医師主導治験を円滑に進め