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ORIGINAL ARTICLE

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Efficacy and tolerability of once-weekly administration of 17.5 mg risedronate in Japanese patients with involutional osteoporosis: a comparison with 2.5-mg once-daily dosage regimen

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Abstract In this multicenter, randomized, double-blind controlled trial, the efficacy and safety of once-weekly dosing with 17.5 mg risedronate was compared with once-daily dosing with 2.5 mg risedronate in Japanese patients with involutional osteoporosis. A total of 496 patients were randomized to receive either once-weekly (n = 249) or once-daily (n = 247) treatment. All patients were supplemented with 200 mg/day calcium. Following 48 weeks of treatment, the mean (±SD) percent changes, from baseline, in the bone mineral density of the lumbar spine (L2-L4 BMD) in the once-weekly and once-daily treatment groups were 5.36 ± 4.27% and 5.87 ± 4.47%, respectively. The difference between the groups was –0.5% (95% confidence interval: –1.35% to 0.35%), demonstrating that the effect on BMD of once-weekly treatment was not inferior to that of once-daily treatment. The time-course reductions in biochemical markers of bone resorption (urinary N- and C-telopeptide of type I collagen) and bone formation (bone-specific alkaline phosphatase) were similar for the two dosing regimens. There were no differences in the incidence of new vertebral fractures or the worsening of existing fractures between the once-weekly (2.2%) and once-daily (2.7%) dosing regimens. No significant differences were observed between the two dosing regimens in the incidence or the type of adverse events. However, 10.1% of the patients in the once-daily group withdrew due to adverse events as compared to 5.2% in the once-weekly group. Moreover, drug-related adverse events, including upper gastrointestinal disorders and abnormal changes in laboratory parameters, tended to be less in the once-weekly dosing regimen than in the once-daily dosing regimen. In conclusion, once-weekly oral dosing with 17.5 mg risedronate was well tolerated in Japanese osteoporotic patients, and showed equivalent efficacy to once-daily oral dosing with 2.5 mg risedronate. This once-weekly regimen is expected to provide a more convenient therapeutic option as an alternative to daily dosing and to enhance patient compliance in long-term therapy for osteoporosis.

Key words bisphosphonate · bone mineral density · once-weekly regimen · osteoporosis · risedronate

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Introduction

Risedronate, a pyridinyl bisphosphonate with potent antiresorptive activity, has been shown to reduce vertebral fracture risk and increase bone mineral density (BMD) in both Caucasian [1–6] and Japanese osteoporotic patients [7,8]. The recommended once-daily dosage regimen of risedronate in Europe and North America is 5 mg, whereas,

in Japan, a 2.5-mg once-daily regimen is recommended due to an ethnic difference in pharmacokinetics. It has been demonstrated in the Japanese population that the maximum plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC) of risedronate after dosing with 2.5 mg and 5 mg were two to three times higher compared with these values in Caucasians [9,10], and the efficacy of a 2.5-mg once-daily regimen in Japanese osteoporotic patients was similar to that of a 5-mg once-daily regimen in Caucasian patients [7,8,11].

Because gastrointestinal absorption of risedronate is decreased in the presence of food, probably by its forming of a complex with divalent cations (e.g., Ca^{2+}) contained in food [9,12], patients are instructed to take risedronate immediately after rising in the morning, and to avoid taking food and drink other than water for at least 30 min post-dosing. In addition, patients are instructed to avoid lying down for at least 30 min post-dosing, because prolonged retention of the drug in the upper gastrointestinal tract may lead to mucosal irritation.

Osteoporosis is a chronic disease requiring long-term therapy, and many osteoporotic patients are elderly. Some patients, especially when they are taking multiple medications, may have difficulty maintaining compliance with a once-daily dosage regimen, which can complicate patient compliance. Although many patients are able to adapt to a once-daily dosage regimen, some patients may prefer a less frequent dosage regimen, e.g., once weekly. A less frequent dosage regimen may be more convenient and may enhance patient compliance. Having a choice of a once-daily and a less frequent dosage regimen will also provide physicians with more flexibility in addressing the needs of individual patients, and may enhance patients' willingness to accept long-term therapy for osteoporosis.

In a nonclinical study using animal osteoporotic models [13,14], it has been shown that intermittent dosing, including a once-weekly regimen of risedronate and other bisphosphonate agents, prevented bone loss to an extent comparable with that of a once-daily regimen; the study suggested that the efficacy depended on the total dosage in a unit period of time, irrespective of the dosing frequency.

Clinical trials investigating the efficacy and safety of once-weekly dosage regimens of risedronate in patients with postmenopausal osteoporosis have been conducted outside Japan. The results demonstrated that 35 mg risedronate given once weekly was therapeutically equivalent to a 5-mg daily dose in increasing lumbar spine BMD, and the vertebral fracture incidences, as well as safety profiles, were also similar in both treatment groups [15,16]. Similar results have been reported for an alendronate 70-mg once-weekly dosage regimen [17,18]. A risedronate 35-mg once-weekly regimen, and an alendronate 70-mg once-weekly regimen have been approved for the treatment of osteoporosis and are widely used in Europe and North America.

In the present study, we investigated the effects of once-weekly treatment with 17.5 mg risedronate (seven times the approved daily dose of 2.5 mg in Japan) on lumbar spine BMD and tolerability in Japanese patients with involutional osteoporosis, to examine equivalence in efficacy and safety between once-weekly and once-daily treatments.

Patients and methods

Study design

This randomized, double-blind, parallel group, controlled trial was conducted at 47 medical institutions throughout Japan between November 2002 and July 2004. The study protocol was approved by the Institutional Review Board of each institution before initiation of the study, and all patients enrolled gave written informed consent before entering the study. The study was conducted in compliance with the Japanese Good Clinical Practice and in accordance with the ethical principles of the Declaration of Helsinki.

Eligible patients were randomly assigned to receive either a 17.5-mg once-weekly dose or a 2.5-mg once-daily dose of risedronate for 48 weeks (1 week being defined as one cycle). Blinding to the study drug was maintained by a double-dummy technique using risedronate 17.5-mg tablets, risedronate 2.5-mg tablets, and corresponding placebo tablets. The active drug and placebo were made indistinguishable from each other. As the mode of administration of the study drug in 1 week, patients in the 17.5-mg once-weekly group took one each of the 17.5-mg risendronate tablet and a 2.5-mg placebo tablet (two tablets in total) on rising in the morning of day 1, and one 2.5-mg placebo tablet once daily on rising every morning on days 2 to 7. Patients in the 2.5-mg once-daily group took one each of a 17.5-mg placebo tablet and a 2.5-mg risendronate tablet (two tablets in total) on rising in the morning of day 1, and one 2.5-mg risendronate tablet once daily on rising every morning on days 2 to 7. Each patient was requested to avoid taking any food or beverage other than water, as well as to avoid lying down for at least 30 min post-dosing. All patients were supplemented with 1.54 g calcium lactate daily (equivalent to 200 mg elemental calcium) throughout the study period, to compensate for any dietary shortage of calcium. The daily dose of calcium was based on the result of the National Nutrition Survey conducted by the Ministry of Health, Labor, and Welfare (recommended daily allowance of calcium for Japanese, 600 mg; actual intake, 585 mg on average in 1995) and on determination of the necessary amount in the elderly, estimated in a calcium balance study (700–800 mg) [19]. The calcium lactate was administered after the evening meal. Risedronate and the placebo tablets were supplied by Takeda Pharmaceutical (Osaka, Japan). Throughout the study period, concomitant use of any drug known to affect bone metabolism was prohibited.

Patient selection and number of patients

Ambulatory patients of either sex, older than 50 years of age, with documented involutional osteoporosis, according to the diagnostic criteria for primary osteoporosis [20,21],

were eligible. The lumbar spine (L2-L4) BMD of eligible patients was less than 70% of the young adult mean (YAM) in patients without fragility fracture, or less than 80% of the YAM in those with fragility fracture. The actual cutoff values of L2-L4 BMD for instruments used for the determination of BMD by dual-energy X-ray absorptiometry (DXA) were set as follows: the BMD values corresponding to 70% of the YAM for Hologic QDR (Hologic, Waltham, MA, USA), Norland XR (Norland, Fort Atkinson, WI, USA), and Lunar DPX (Lunar, Madison, WI, USA) instruments were 0.708, 0.728, and 0.834 g/cm^2, respectively, and those corresponding to 80% of the YAM were 0.809, 0.832 and 0.954 g/cm^2, respectively.

Exclusion criteria were any secondary osteoporosis or other diseases with reduced bone mass; recent use of drugs known to affect bone metabolism (e.g., treatment with bisphosphonates within 48 weeks before starting the study medicine); serious renal, hepatic, or cardiac diseases; drug hypersensitivity; gastrointestinal diseases; history of radiotherapy to the lumbar spine or pelvis; and malignant tumor for which chemotherapy was being received. Those with morphologic problems that grossly interfered with accurate L2-L4 BMD determination, such as severe spinal scoliosis, fracture, deformity, or osteosclerotic changes in L2-L4, were excluded from the study.

The number of patients required to demonstrate significant noninferiority of the once-weekly treatment with 17.5 mg risedronate compared with the once-daily treatment with 2.5 mg was estimated to be 190 in each group, based on several assumptions. The difference between the once-daily and once-weekly treatments in mean percent changes in L2-L4 BMD at week 48 was estimated to be 0.2%, based on the data obtained in a North American study [15], provided that the efficacy of a 5-mg daily dose in Caucasians was equivalent to that of a 2.5-mg daily dose in Japanese. The SD common to both treatment groups was estimated to be 4.5%, based on the data obtained at the end of week 48 in a preceding Japanese phase III comparative study [7], in which the effect on lumbar spine BMD of a 2.5-mg daily dose of risedronate was compared with that of etidronate. Using these assumptions, we calculated the number of patients required to attain a power of 80% to demonstrate noninferiority by showing a two-sided 95% confidence interval (CI) with the noninferiority margin, Δ = 1.5% [11]. The actual number of patients included in the study was 496 (once-weekly, $n = 249$; once-daily, $n = 247$) in consideration of the potential number of early patient discontinuations.

Measurement of efficacy

The primary efficacy endpoint was the percent change in mean L2-L4 BMD from baseline to week 48. The anteroposterior L2-L4 BMD was determined at baseline and after 12, 24, 36, and 48 weeks of treatment, or at the time of withdrawal from the study. DXA was carried out with a QDR type, an XR type, or a DPX type of DXA instrument. The validity of each DXA measurement was assessed by the Central Assessment Committee of DXA, without any information being provided on the patients.

Lateral and anteroposterior thoracic and lumbar spine radiographs were obtained at baseline and after 48 weeks of treatment, and vertebral fractures were evaluated by the Central Assessment Committee according to the diagnostic criteria for primary osteoporosis [20,21]. A vertebra was considered to be fractured if the ratio of the central vertebral height to the anterior (C/A) or posterior vertebral body height (C/P) was less than 0.8, or the ratio of the anterior to posterior vertebral body height (A/P) was less than 0.75, or if the anterior, central, and posterior vertebral heights were decreased by more than 20% compared with those of the adjacent vertebral body. If any one of the three vertebral height ratios, C/A, C/P, or A/P, had decreased by 20% or more from the baseline, or if any one of the three vertebral heights (normalized using T4 height), A, C, or P, had decreased by 20% or more from the baseline, a new or worsening vertebral fracture was judged to be present [22].

Biochemical markers of bone turnover were assessed at baseline and after 4, 12, 24, 36, and 48 weeks of treatment. Bone resorption was evaluated by several markers. Urinary total deoxypyridinoline was determined using high-performance liquid chromatography [23], and urinary N-telopeptide of type I collagen (NTX) was measured by enzyme-linked immunosorbent assay (ELISA), using Osteomark (Ostex International, Seattle, WA, USA), and urinary C-telopeptide of type I collagen (CTX) was measured by ELISA, using Frelisa β CrossLaps (Nordic Bioscience Diagnostics, Herley, Denmark). All urinary parameters were corrected for creatinine excretion. Serum bone-specific alkaline phosphatase (BAP), a bone-formation marker, was determined by enzyme immunoassay, using Osteolinks "BAP" (QUIDEL, San Diego, CA, USA).

Safety assessment

Subjective symptoms and objective signs related to adverse effects were monitored by noting patients' complaints at each visit. Standard laboratory tests, including hematology, blood biochemistry, and urinalysis, were conducted at regular intervals during the study.

Statistical analysis

Noninferiority of the 17.5-mg once-weekly treatment compared with the 2.5-mg once-daily treatment was examined by two-sided 95% CI for the difference between groups showing mean percent change in L2-L4 BMD from baseline to week 48 with the noninferiority margin, Δ = 1.5%. If the lower limit of two-sided 95% CI of the between-group difference in mean percent change in L2-L4 BMD was not less than −1.5%, then the once-weekly treatment was considered to be noninferior to the once-daily treatment. The value, Δ = 1.5% was chosen based on the results of a placebo-controlled dose-ranging study of risedronate in Japanese patients with osteoporosis [11], in which the difference from placebo, in

mean percent change from baseline in L2-L4 BMD, after daily treatment with 2.5 mg risedronate for 36 weeks, was 4.5%, and the lower limit of the two-sided 95% CI was 2.3%. For the present study, $\Delta = 1.5\%$ represents approximately one-third of the point estimate of the mean difference from placebo, and less than the lower limit of two-sided 95% CI of the mean difference from placebo. The difference from placebo may become greater after 48 weeks' treatment. The primary efficacy analysis (showing a two-sided 95% CI) was performed on data from the primary efficacy population (PEP) who had evaluable data for L2-L4 BMD at both baseline and week 48. In addition, two-sided 95% CI was also shown on data from the per-protocol set (PPS) of patients, to confirm the robustness of the result.

For the secondary efficacy variable – vertebral fracture rate – two-sided 95% CI for the between-group difference was constructed using the full analysis set (FAS). For the percent changes from baseline in bone turnover markers, descriptive statistics were computed at each measurement point, using the FAS; the one-sample Wilcoxon test was applied for the within-group difference from baseline, and the two-sample Wilcoxon test was applied for the between-group difference. The incidence of adverse events was compared using the χ^2 test for 2×2 cross-table. For the between-group differences in the incidences of adverse events, two-sided 95% CI was constructed.

Results

Patient allocation and baseline characteristics

A total of 496 eligible patients were randomized to receive either once-weekly treatment with 17.5 mg risedronate (n = 249) or once-daily treatment with 2.5 mg risedronate (n = 247). In the once-weekly treatment group, 23 (9.2%) patients were prematurely withdrawn, and 226 patients completed the study. In the once-daily treatment group, 2 (0.8%) patients received no study drug; 40 (16.2%) patients were prematurely withdrawn, and 205 patients completed the study (Fig. 1). The most common reason for premature withdrawal was "occurrence of an adverse event", accounting for 13 (5.2%) patients in the once-weekly group and 25 (10.1%) patients in the once-daily group. In the PEP; the numbers of patients in the once-weekly and once-daily treatment groups were 214 and 195, respectively; in the PPS, 211 and 193, respectively; and in the FAS, 245 and 243, respectively. The demographic and baseline characteristics of patients in the PEP are shown in Table 1. As is common practice in Japanese studies, the regulatory guidelines for the evaluation of new therapeutics for the treatment of osteoporosis require the inclusion of involutional osteoporosis. Therefore, male patients were enrolled in the trial; however, they were few in number (2.9%). The two treatment groups were well matched with regard to demographic and other baseline characteristics, although a slight imbalance between the groups was found in age and in years since menopause in the females. These results were similar for the FAS and PPS populations.

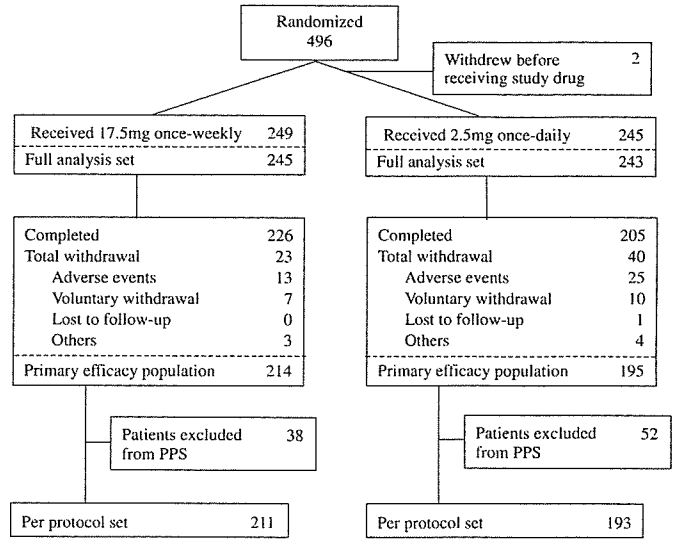

Fig. 1. Study profile and subject disposition. The primary efficacy population (PEP) was used for the analysis of the primary efficacy endpoint (percent changes from baseline in L2-L4 bone mineral density [BMD]). The per protocol set (*PPS*) was used for the analysis of the primary endpoint to confirm the robustness of the result obtained in the primary analysis. The full analysis set (FAS) was used for the analyses of other efficacy endpoints. FAS comprised all the subjects who received at least one dose of the investigational product and underwent observation of any kind after administration. Of the subjects in the FAS, the population of those who were evaluable for the main assessment parameter (i.e., L2-L4 BMD at both baseline and week 48) was defined as the PEP. Of the subjects in the FAS, the population of those who had no serious protocol deviation and were evaluable for the main assessment parameter was defined as the PPS

Bone mineral density

The mean percent increases in L2-L4 BMD from baseline to week 48 in the once-weekly and once-daily treatment groups were 5.36 ± 4.27% (mean ± SD) and 5.87 ± 4.47%, respectively, and the between-group difference (once-weekly minus once-daily) was –0.5% (two-sided 95% CI; –1.35%, 0.35%). The 95% CI fell entirely on the positive side of the range of the predefined noninferiority margin (>–1.5% Δ), demonstrating the noninferiority of once-weekly treatment with 17.5 mg risedronate compared with once-daily treatment with 2.5 mg risedronate (Table 2). Similarly, no between-group difference was observed in the subgroups of female subjects alone, (L2-L4 BMD, 5.38 ± 4.30% in the once-weekly group [n = 211] vs 5.86 ± 4.46% in the once-daily group [n = 186]; between-group difference, –0.48% [two-sided 95% CI, –1.35%, 0.38%]). Time-course profiles of the increase in BMD were similar for the once-weekly and once-daily treatments (Fig. 2).

Vertebral fracture incidence

The incidence of new vertebral fractures, including the worsening of prevalent fractures, was 5 in 227 evaluable patients (2.2%; 95% CI, 0.7%, 5.1%) in the once-weekly treatment group, and 6 in 222 evaluable patients (2.7%; 95% CI, 1.0%, 5.8%) in the once-daily treatment group.

Table 1. Demographic and baseline characteristics of patients[a]

Characteristics	Treatment group	
	Once-weekly (n = 214)	Once-daily (n = 195)
Age (years)	66.3 ± 7.8	68.5 ± 7.9
Height (cm)	149.7 ± 6.4	149.0 ± 6.4
Weight (kg)	49.1 ± 6.9	48.9 ± 7.0
Body mass index (kg/(height in m)^2)	21.9 ± 2.8	22.0 ± 2.9
Time since menopause (years)[b]	17.2 ± 9.3 (n = 199)	19.1 ± 9.0 (n = 171)
Lumbar spine bone mineral density (g/cm^2)		
Hologic (QDR type)	0.64 ± 0.06 (n = 138)	0.63 ± 0.07 (n = 130)
Lunar (DPX type)	0.73 ± 0.08 (n = 56)	0.75 ± 0.09 (n = 49)
Norland (XR type)	0.64 ± 0.06 (n = 20)	0.67 ± 0.06 (n = 16)
T-score of lumbar spine bone mineral density	−3.08 ± 0.51	−3.11 ± 0.58
Bone turnover markers		
Serum bone-specific alkaline phosphatase (U/l)	30.6 ± 9.9	30.7 ± 10.6
Serum 1α,25-dihydroxyvitamin D (ng/ml)	21.0 ± 6.6	20.8 ± 5.7
Urinary deoxypyridinoline (pmol/mmol CRN)	8.95 ± 3.27	9.07 ± 3.31
Urinary NTX (nmol BCE/mmol CRN)	54.1 ± 24.2	52.0 ± 22.1
Urinary CTX (μg/mmol CRN)	259.8 ± 137.9	260.7 ± 120.7
Patients with prevalent vertebral fractures[c]	50 (23.4%)	56 (28.7%)

Data values are shown as means ± SD unless otherwise specified
NTX, N-terminal telopeptide of type I collagen; CTX, C-terminal telopeptide of type I collagen; BCE, bone collagen equivalent; CRN, creatinine
[a] Primary efficacy population
[b] Male patients (three in the once-weekly group and nine in the once-daily group) and women for whom the time since menopause was unknown were excluded
[c] Number (percentage) of patients

Table 2. Mean changes in lumbar spine BMD from baseline to week 48

Groups	Once weekly (17.5 mg)	Once daily (2.5 mg)
Number of patients[a]	214	195
Rate of change (mean ± SD; %)[b]	5.36 ± 4.27	5.87 ± 4.47
Median (minimum, maximum)	5.00 (−4.5, 22.2)	5.90 (−4.7, 19.2)
Noninferiority analysis (delta limit, 1.5%); PEP	t = 2.304; P = 0.0109	
Difference in mean percent change (weekly − daily)	−0.50	
Two-sided 95% confidence interval of difference	Lower, −1.35; upper, 0.35	

[a] Primary efficacy population
[b] Mean percent changes in L2-L4 BMD from baseline to week 48

The between-group difference in the fracture incidence was −0.5% (95% CI, −3.4%, 2.4%), and it was not significant. A single fracture occurred in 4 patients in the once-weekly group and in 4 patients in the once-daily group, and two fractures occurred in 1 patient in the once-weekly group and in 2 patients in the once-daily group. None of the patients in either group had three or more fractures.

Biochemical markers of bone turnover

Urinary NTX and CTX decreased significantly after 4 weeks of treatment in both the once-weekly and once-daily dosing groups, and low levels were maintained over the 48-week treatment period (Fig. 3a,b). The percent decreases in NTX at week 48 in the once-weekly and once-daily dosing groups were 36.4 ± 29.2% (mean ± SD) and 39.0 ± 27.8%, respectively, and those in CTX were 51.4 ± 37.5% and 55.1 ± 33.7%, respectively. Urinary deoxypyridinoline showed a pattern similar to that of NTX (data not shown). Significant, but small, between-group differences were found in CTX;

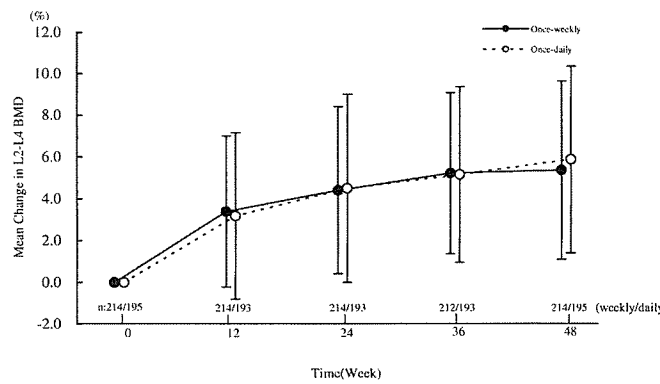

Fig. 2. Time course of mean (±SD) percent changes from baseline in L2-L4 bone mineral density (*BMD*) as measured by dual-energy X-ray absorptiometry during 48-week treatment with a once-weekly dose of 17.5 mg risedronate (*solid line*), and once-daily dose of 2.5 mg risedronate (*broken line*)

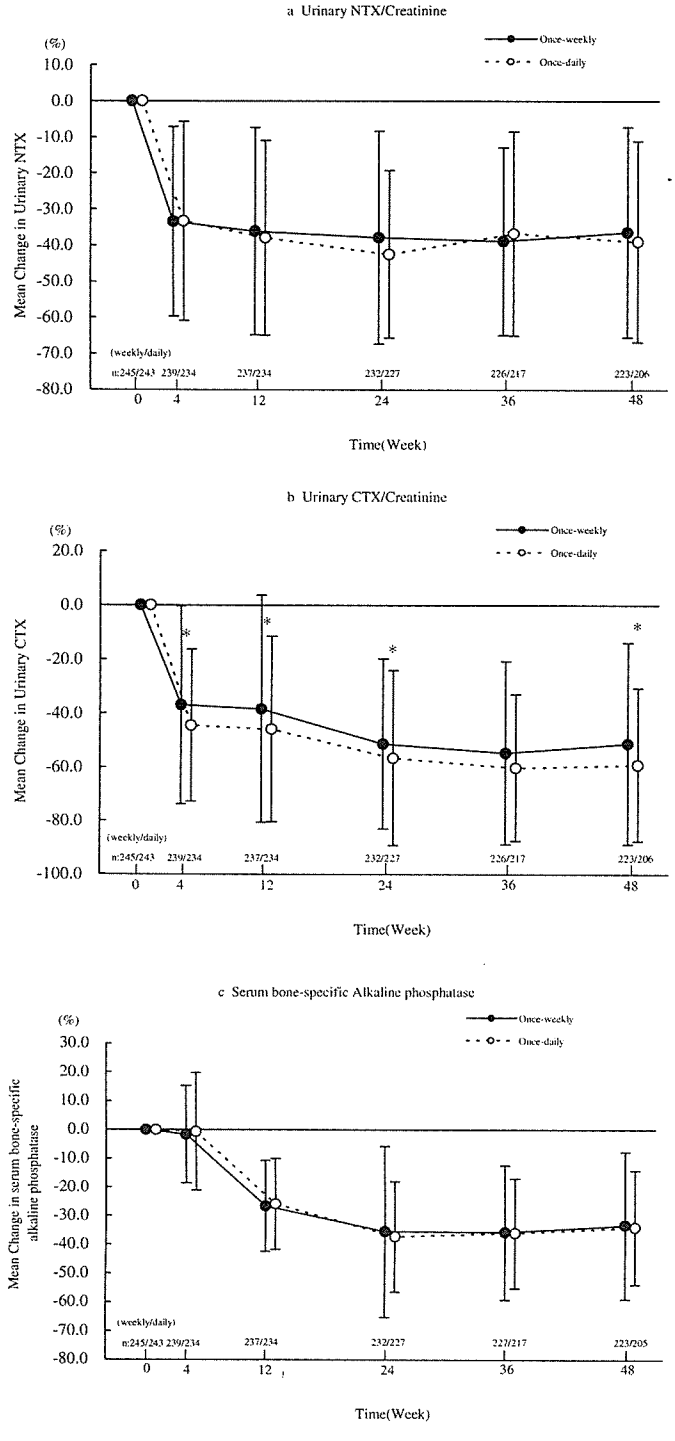

Fig. 3. Time course of mean (±SD) percent changes from baseline in bone resorption markers (**a** Urinary N-terminal telopeptide of type I collagen (*NTX*) creatinine; **b** urinary C-terminal telopeptide of type I collagen [*CTX*] creatinine) and a bone formation marker (**c** serum bone-specific alkaline phosphatase) during 48-week treatment with a once-weekly dose of 17.5 mg risedronate (*solid lines*) and a once-daily dose of 2.5 mg risedronate (*broken lines*). * $P < 0.05$: Two-sample Wilcoxon test for between-group differences

however, no significant differences in NTX decreases were observed between the once-weekly and once-daily dosing groups. BAP also decreased after 12 weeks of treatment, and low levels were maintained over the 48-week treatment period (Fig. 3c). The percent decreases in BAP at week 48 in the once-weekly and once-daily dosing groups were 33.3 ± 19.9% and 34.0 ± 21.5%, respectively, and no significant difference was found between the groups.

Safety assessment

The overall safety profiles of the once-weekly and once-daily treatments showed no distinct differences. The incidence of any adverse event was similar in both treatment groups, but the incidence of adverse events assessed by the investigator to be drug-related tended to be lower with the once-weekly treatment compared with the once-daily treatment (24.9% vs 32.2%; Table 3). Most of the drug-related gastrointestinal adverse events were mild; 8 of moderate severity were reported out of 245 (3.3%) patients in the once-daily treatment group, whereas, in the once-weekly treatment group, only 1 patient (0.4%) experienced an event of severity moderate ($P = 0.0173$). No severe gastrointestinal adverse events were reported. The incidence of abnormal changes in laboratory parameters assessed by the investigator to be drug-related was significantly lower in the once-weekly regimen than in the once-daily regimen. Laboratory parameters that contributed to this imbalance included alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, and urinary occult blood.

Discussion

The clinical noninferiority of once-weekly treatment with 35 mg risedronate compared with once-daily treatment with 5 mg risedronate has been well established [15,16], and a once-weekly 35-mg dosage regimen is being used widely in many countries outside Japan, as an alternative to a daily dosage regimen, to treat postmenopausal osteoporosis. However, this once-weekly dosage regimen could not be directly applied to Japanese patients, due to a difference in basal daily dose. In previous studies [7,8], we have demonstrated that treatment with a daily dose of 2.5 mg risedronate increased lumbar spine BMD and decreased the risk of vertebral fractures in Japanese osteoporotic patients. These results were comparable to results in Caucasian patients treated with a daily dose of 5 mg. A 2.5-mg once-daily dosage regimen has been approved for the treatment of involutional osteoporosis in Japan. Accordingly, in this study, we compared the effect of once-weekly treatment with 17.5 mg risedronate on lumbar spine BMD, with that of once-daily treatment with 2.5 mg, in Japanese patients with involutional osteoporosis, to prove the noninferiority of the once-weekly regimen compared with the once-daily regimen.

The mean increase in L2-L4 BMD from baseline to week 48 was 5.36% with the once-weekly regimen, and 5.87% with the once-daily regimen, and the between-group difference (once-daily vs once-weekly) was −0.5% (95% CI, −1.35%, 0.35%). The result showed that the 95% CI of the

Table 3. Summary of adverse events

	Once-weekly	Once-daily	χ^2-test[a]
Number of patients	249	245	
Any adverse events[b]	212 (85.1%)	215 (87.8%)	$P = 0.396$
Drug-related adverse events[b]	62 (24.9%)	79 (32.2%)	$P = 0.071$
Gastrointestinal adverse events[c]	30 (12.0%)	43 (17.6%)	$P = 0.085$
Abdominal distension	1 (0.4%)	4 (1.6%)	NT
Upper abdominal pain	4 (1.6%)	5 (2.0%)	NT
Constipation	6 (2.4%)	9 (3.7%)	NT
Dyspepsia	1 (0.4%)	3 (1.2%)	NT
Gastritis	2 (0.8%)	3 (1.2%)	NT
Stomach discomfort	15 (6.0%)	13 (5.3%)	NT
Abnormal laboratory parameters[b]	22 (8.8%)	37 (15.1%)	$P = 0.032$
Alanine aminotransferase increased	3 (1.2%)	5 (2.0%)	NT
Aspartate aminotransferase increased	4 (1.6%)	6 (2.5%)	NT
γ-Glutamyltransferase increased	6 (2.4%)	15 (6.1%)	NT
Urinary occult blood positive	4 (1.6%)	5 (2.1%)	NT

NT, not tested
[a] χ^2 test for 2 – 2 cross-table
[b] Patients who experienced one or more adverse events were counted only once
[c] Patients who experienced one or more gastrointestinal adverse events were counted once for each event

between-group difference fell entirely on the positive side of the range of the predefined noninferiority margin (>–1.5% Δ), indicating the noninferiority of the once-weekly regimen compared with the once-daily regimen. The primary analysis to demonstrate noninferiority was performed using the PEP ($n = 409$), and the additional analysis using the PPS ($n = 404$) showed consistent results. The once-weekly dosage regimen was as effective in Japanese patients as in Caucasians; the magnitude of the increase in L2-L4 BMD in the present study was comparable to or even greater than those obtained in Caucasian patients treated once weekly with 35 mg risedronate (3.94%) or once daily with 5 mg risedronate (4.00%) [15]. The increase in L2-L4 BMD in present once-daily 2.5-mg group was entirely consistent with data obtained in a previous study in Japanese patients (4.93%) [7]. Complying with the Japanese Guideline, we included male patients with involutional osteoporosis in our study: 3 in the once-weekly group and 9 in the once-daily group. Although the male patients in both groups showed a considerable increase in L2-L4 BMD (4.43 ± 2.14% in the once-weekly group, and 6.01 ± 4.91% in the once-daily group), the sample size was too small to show statistical noninferiority of the once-weekly treatment.

The biochemical bone resorption markers – urinary NTX and CTX – which are considered to be a sensitive endpoint to predict the reduction of risk of vertebral fractures [24], as well as long-term changes in vertebral BMD [25], decreased significantly after 4 weeks in both our dosage regimens, suggesting an early onset of action of risedronate. Decreases in NTX and deoxypyridinoline were similar and showed no significant difference between the once-weekly and once-daily dosing groups, whereas CTX decreased a little more with the once-daily treatment compared with the once-weekly treatment. The bone formation marker BAP also decreased after 12 weeks. This delay in the response of BAP suggests that inhibition of bone formation may occur secondarily in association with the inhibition of bone resorption induced by bisphosphonates [26]. The time-course profiles of these markers were similar for the once-weekly and once daily dosage regimens.

Both the 17.5-mg once-weekly and the 2.5-mg once-daily dosage regimens were well tolerated by Japanese patients and no delayed adverse events were shown. With the once-weekly treatment, the incidence of drug-related adverse events tended to be lower than that with the once-daily treatment. The incidence of drug-related abnormal changes in laboratory parameters with the once-weekly regimen was significantly lower than that with the once-daily regimen. Upper gastrointestinal disorders have been a well-known adverse effect of bisphosphonates and are considered to be dependent on the frequency of contact with the gastrointestinal mucosa, rather than the dose of bisphosphonate [27]. The incidence of drug-related gastrointestinal disorders, all of which were mild to moderate in severity, was lower in our patients with the once-weekly regimen than in those with the once-daily regimen; the numbers of patients who experienced moderate gastrointestinal disorders were significantly lower with the once-weekly compared with the once-daily regimen. Also, the numbers of patients who were withdrawn from the study due to the occurrence of adverse events were smaller with the once-weekly regimen. These results suggest that reducing the dosing frequency may reduce the risk of gastrointestinal adverse events, by reducing the occasions on which the upper gastrointestinal tract is exposed to the drug, even though a dose sevenfold larger than the daily dose is given at a time.

The efficacy and safety of long-term therapy with a once-daily dosage regimen of risedronate have been confirmed [5,6], but a longer observation period for therapy with a once-weekly dosage regimen of risedronate may be also important.

In conclusion, in Japanese patients with involutional osteoporosis, once-weekly treatment with 17.5 mg risedronate produced increases in lumbar spine BMD and decreases in

bone turnover markers similar to those seen with once-daily treatment with 2.5 mg risedronate. The once-weekly dosage regimen of risedronate was well tolerated, with favorable safety profiles compared with the once-daily dosage regimen. The once-weekly dosage regimen is expected to provide a more convenient therapeutic option as an alternative to the once-daily dosage regimen, and to enhance patient compliance in long-term therapy for osteoporosis.

Appendix. Other members of the Risedronate Phase III Research Group

Institution	Department	Investigators
Asahikawa Rehabilitation Hospital	Internal Medicine / Orthopedic Surgery	J. Maruyama, S. Nakamura, J. Nakagawa
Wada Obstetrician Hospital	Obstetrics and Gynecology	H. Wada
Ohta Orthopaedic Clinic	Orthopedics	T. Ohta
Shin-Sapporo Orthopaedic Hospital	Orthopedics	K. Kasai, K. Susuda
Sapporo Kiyota Orthopaedic Hospital	Orthopedics	G. Katahira, M. Tsuji, H. Matsui
Sapporo Tokushukai Medical Center	Orthopedics	T. Mori, T. Kawakami
Kusanagi Ladies Clinic	Obstetrics and Gynecology	T. Kusanagi
Fushimi Keimei Orthopedic Clinic	Orthopedics	H. Hashimoto
Teine Keijinkai Hospital	Orthopedics / Obstetrics and Gynecology	I. Sasaki, K. Ohno, C, Sato, J. Tsujino, H. Otsubo, T. Fujino, Y. Fukushi, S. Wada, K. Kakuta
Bibai Rousai Hospital	Orthopedics	H. Taneichi, K. Kaneda, T. Kasashima, K. Suda, T. Kajino, H. Kukita, H. Ebihara, H. Moridaira
Cardiovascular Hospital of Central Japan	Internal Medicine	S. Ichikawa, Y. Takayama, H. Kumakura
Toyooka Daiichi Hospital	Orthopedics	H. Yamane, S. Yamane
Saitama Medical School Hospital	Orthopedics	K. Takahashi, T. Miyajima
Saitama Medical School Hospital	Central Clinical Laboratory	A. Itabashi, K. Nemoto
Kubojima Clinic	Internal Medicine	J. Oshima, A. Itabashi, K. Nemoto
Tsuruta Clinic	Surgery	Y. Tsuruta, M. Tanno
Tokyo Metropolitan Geriatric Medical Center	Endocrinology	T. Hosoi, T. Horiuchi
Shiratori Clinic	Internal Medicine	K. Fukuda, S. Sano
Oimachi Orthopaedic Clinic	Orthopedics	M. Omata, R. Omata
Kanto Medical Center NTT EC	Orthopedics	M. Shimode, T. Umeyama, S. Suzuki, S. Azuma, H. Koizumi, T. Saito, T. Shirahata
Kanto Medical Center NTT EC	Obstetrics and Gynecology	T. Yasumizu, K. Sakakibara, K. Tadauchi
Shirahigebashi Hospital	Internal Medicine	T. Ishihara, S. Touga, T. Furusawa, M. Kaneda, H. Osawa
Shin-Nihonbashi Ishii Clinic	Internal Medicine	H. Ishii, K. Fujii, K. Marumo, M. Tsuji
New Medical Research System Clinic	Internal Medicine	M. Karube, K. Nemoto, A. Itabashi, M. Hamada, N. Nakamichi, Y. Murata, T. Kishino, M. Maruyama
Nishi-Niigata Chuo National Hospital	Rehabilitation	Y. Takahashi
Hokushin General Hospital	Orthopedics	S. Kumaki, K. Yumoto
Aobadai Fukuchi Orthopedic and Gastroenterology Clinic	Orthopedics	M. Fukuchi
Denda Orthopedic Hospital	Orthopedics	M. Denda
National Center for Geriatrics and Gerontology	Department of Functional Restoration	A. Harada, Y. Matsui, M. Mizuno, H. Tokuda, M. Takemura, Z. Ito, N. Wakao
Meitetsu Hospital	Obstetrics and Gynecology	N. Hosoi, S. Hori, R. Adachi, K. Higuchi, T. Shikata
Higashinagoya National Hospital	Orthopedics	Y. Sasaki, T. Fujibayashi, H. Makino
Osaka City University Medical School Hospital	Orthopedics	T. Koike
Chibune General Hospital	Internal Medicine	T. Kita, D. Nakaoka, T. Takahashi, S. Tai
Baba Memorial Hospital	Orthopedics	Y. Honda, M. Kamano, S. Shinozuka, T. Yoshimura, R. Tanigake, I. Tatsumi, S. Miya, R. Tamuram M. Toyama
Gracia Hospital	Orthopedics	M. Fujii, J. Hashimoto, S. Oka
National Hyogo-Chuo Hospital	Internal Medicine	A. Miyauchi, Y. Yoshimoto, Y. Takagi
Kitade Hospital	Internal Medicine	M. Ozaki, Y. Katae, T. Sakata
San-in Rousai Hospital	Orthopedics	H. Kishimoto, M. Murata, K. Nawata
Tottori University	Orthopedics	T. Okano, H. Hagino, H. Katagiri, Y. Yamashita, T. Kikkawa
Ueno Orthopedic Clinic	Orthopedics	T. Ueno
Tanaka Orthopaedic Clinic	Orthopedics	M. Tanaka
Hidaka Orthopedics Hospital	Orthopedics	S. Hidaka
Fukuoka University	Orthopedics	S. Hida, Y. Morishita, K. Kubo, A. Nakamura, S. Sasaki, K. Noda
Fukuoka University	Obstetrics and Gynecology	Y. Inoue, R. Tamura, S. Sukimoto, K. Noda
Mitsuyasu Orthopaedic Hospital	Orthopedics	M. Mitsuyasu
Munakata Suikokai General Hospital	Orthopedics	K. Minamitani, T. Miyazaki, T. Matsugaki
Isahaya Soyokaze Clinic	Internal Medicine	T. Kiriyama
KS Okamoto Clinic	Internal Medicine	S. Okamoto, S. Okamoto
Sanyo Osteoporosis Research Foundation	Internal Medicine	S. Okamoto, T. Nakamura, K. Fukagawa, K. Kuwatani, K. Kubota, F. Anan, N. Yamashita, T. Anai
Sakamoto Medical Clinic	Internal Medicine	H. Sakamoto

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骨の再生医療

ティッシュエンジニアリング　2006

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Regenerative medicine of the bone tissues

再生医学技術の基礎研究はめざましい進歩を遂げ，一部が先端的医療として臨床応用されはじめている．骨組織における再生医療も同様な傾向にある．一般に，分化組織再生という生物現象には3要素が必須であるとされる．

① 多分化能を有する未分化細胞，② 細胞の増殖・分化を制御する成長因子/サイトカイン，③ 細胞が増殖・分化する足場(scaffold) である．

未分化間葉系細胞を特異的に軟骨細胞または骨芽細胞へ分化誘導し，骨誘導活性を発揮するbone morphogenetic protein(BMP)が種々の動物で骨組織再生を可能にすることが確かめられている．BMP familyの一分子が単一で，間葉系細胞に作用して*in vivo*で骨新生を可能にすることは骨再生においてはきわめて重要であるが，ヒトでの臨床利用に広く用いるには，いまだ解決すべき問題点が残されている．それらの主要な問題点は，有効で安全性の高いDDSの開発，ヒトでのBMPに対する低い応答性などである．これらの問題解決によって汎用性が高い画期的な骨再生・骨修復技術となることが期待できる．

*Yuuki Imai · Kunio Takaoka**

Key words：骨組織再生，骨形成，bone morphogenetic protein(BMP)，drug delivery system(DDS)，生体吸収性ポリマー

骨再生研究の背景の概要

近年，さまざまな生体組織の再生促進技術が研究され，その成果を再生医学に応用する努力が行われ，一部が先端的医療として実際に，諸外国ならびに本邦においても臨床応用されはじめている．骨組織における再生医療も同様な傾向にある．

骨組織には元来再生能力が潜在しており，その再生能力を利用して，骨折をはじめとした骨損傷修復を試みてきた．臨床的経験から骨の潜在的再生能力は幼児期には旺盛であるが加齢とともに低下することが知られている．したがって，成人では再生能が低下しており骨損傷の再生修復は必ずしも容易ではなく，また相当の期間を要するのが現状である．骨の再生医学の主要な目的は，局所的骨形成を人為的に促進して，損傷した骨の修復

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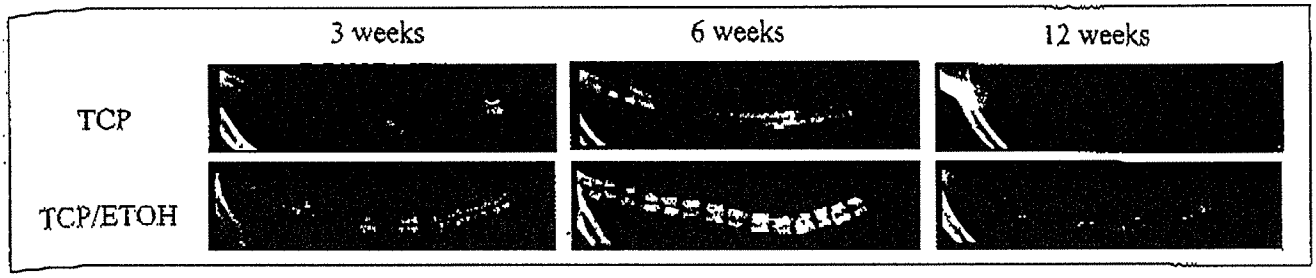

図1 シリンダー状β-TCPを用いたイヌ肋骨再建
骨膜を温存した状態では，骨伝能のみを有するTCPの移植により骨形成を認める(上段)が，骨膜をエタノール処理することにより局所の蛋白を不活化した状態では，骨形成を認めない(下段)．骨誘導能を持たない生体材料のみでは，骨組織再生は限局した条件でのみ可能である．(Hoshino M et al.[5] より引用改変)

を能率化することであろう．

再生目的組織の種類にかかわらず，組織再生という生物現象には3要素が必須であるとされる．

① 多分化能を有する未分化細胞
② 細胞の増殖・分化を刺激する成長因子/サイトカイン
③ その細胞が増殖・分化する足場(caffold)

骨形成能(骨基質産生能)を持った分化細胞は骨芽細胞(osteoblast)であり，その前駆細胞(増殖能を有する)は骨形成細胞(osteoprogenitor)と称される．この細胞は主として骨膜の骨表面に接する細胞層(cambium layer)や骨髄間質細胞群(bone marrow stromal cells)に局在することも知られている．骨損傷の修復反応過程でこれらの細胞が増殖・分化し骨再生を行うことが知られている．局所的骨形成を促進する手段として従来から整形外科領域で汎用されてきた自家骨移植は，それらの細胞移植とみなすことが出来る．また，これらの細胞を*ex vivo*で選択的に増殖させて骨再生が必要な部位に移植することで再生を促進することも理論的には可能であり，その試みも行われている[1]．

骨組織に潜在する再生能を担う分子の同定は，骨の生理学での古くからの課題であった．骨組織に骨形成を促進する活性分子が存在することは1960年代に明らかにされ，骨形成蛋白(bone morphogenetic protein：BMP)と称され[2]，その同定を目指した研究が長い期間整形外科領域で行われていた[3]．

1988年にWozneyらによってその分子のcDNAが同定され[4]，遺伝子組換え技術で合成が行われるに至った．現在，BMP-2, BMP-7が工業的に生産され，欧米で限定された対象(脊椎固定，遷延治癒骨折治療)に使われている[5]．BMPの標的

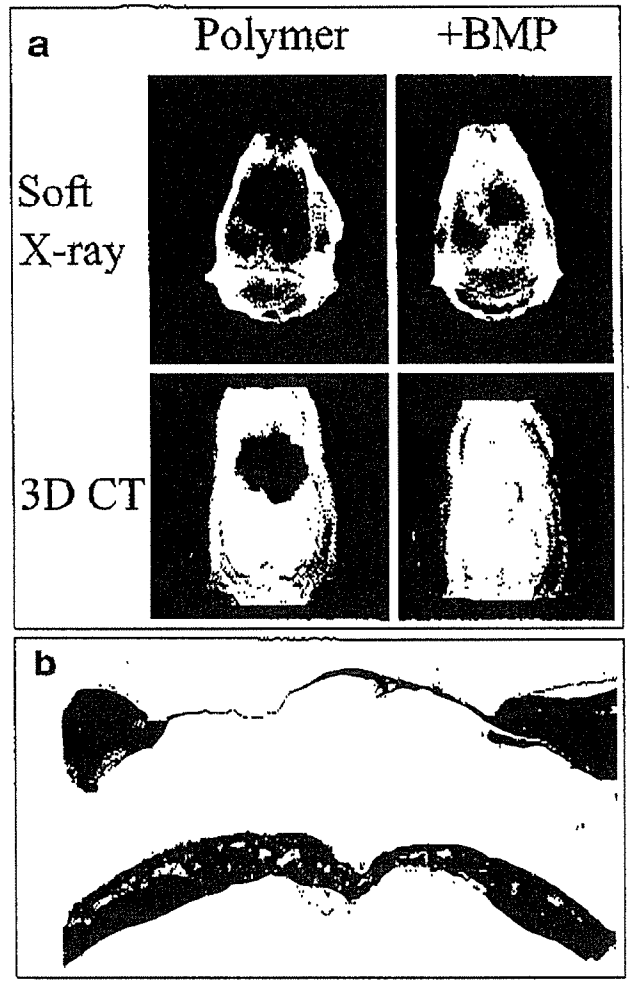

図2 ラット頭蓋冠 critical 骨欠損の再建
a：BMPを含有しない場合(左列)，骨形成を軟X線(上段)でも3DCT(下段)においても認めないが，rhBMP-2を5μg含有したポリマーを埋殖した場合(右列)，術後3週で良好な骨形成を認める．
b：組織像．上段：BMP非含有群，下段：BMP含有群
(Suzuki A et al.[10]より引用改変)

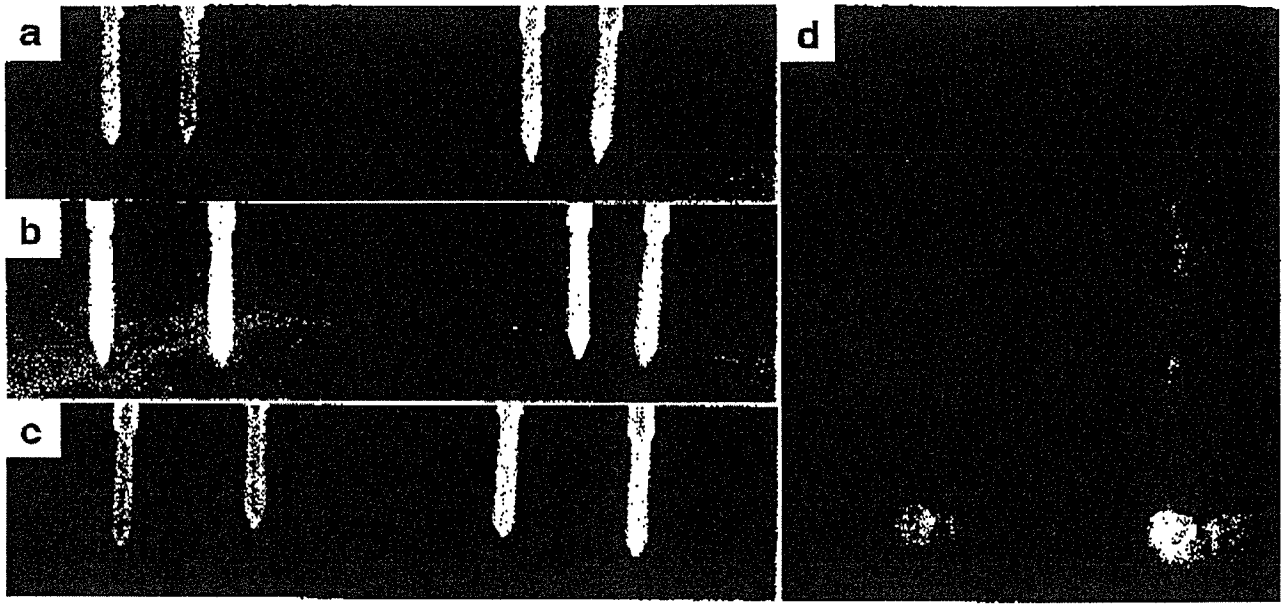

図3　日本白色家兎大腿骨巨大骨欠損モデルにおけるrhBMP-2，β-TCP，生体吸収性ポリマーによる骨欠損修復

a：欠損後8週．骨欠損部に変化を認めない．
b：欠損部に生体吸収性ポリマー，β-TCP移植後8週．骨形成を認めない．
c：欠損部にrhBMP-2，生体吸収性ポリマー，β-TCP移植後8週．良好な骨形成を認め，完全に骨欠損は修復されている．
d：同24週(右)．非処理骨(左)とほぼ同等の径の骨修復を認める．
(Yoneda M et al., 2005[17]より引用改変)

細胞は体内に広く分布する未分化間葉系細胞であり，BMPの作用によってこれらの細胞の骨芽細胞または軟骨細胞への分化が誘導できる．したがって，BMPによって元来骨がない部位にでも骨形成を誘導できる(BMPの骨誘導能による異所性骨形成)．BMP受容体，細胞内シグナル伝達系に関する研究も進んでおり，骨形成反応での中心的分子とされている．

BMPのcDNAを用いた動物での遺伝子治療も試みられている[6,7]．しかし，vectorの安全性，形成される骨の量の形態制御の困難さなどが解決されていないために，実用化には至っていない．

細胞分化の足場となる生体材料の研究は進んでいる．すなわち，その材料表面で種々の段階の骨芽細胞系細胞の増殖分化が可能な材料(骨伝導能を有する材料)として，チタン，チタン合金，アルミナセラミックス，ジルコニアセラミックス，ハイドロキシアパタイト，β-TCP[8]などがすでに臨床の場で使われている(図1)．特に多孔性(pore size 100～400 μm)構造が骨形成に有利であるとされる．

このように骨の再生技術の創生のための材料はそろっており，実用化については，いかに安全性，経済性，利便性にすぐれたものとするかが問題となっている．

BMPによる骨再生技術

上述のように骨再生の技術としては骨芽細胞系細胞の*ex vivo*での培養と移植，BMP遺伝子導入による方法などが提唱され研究が行われてきたが，経済性，安全性，利便性などに問題があり，汎用には至っていない．これらの問題点を克服できる方法としてBMPの遺伝子産物(ヒト型リコンビナントBMP：rhBMP)を用いて骨再生を行うのが現時点で適当であろうと考えられる．

筆者らはすでに工業的に合成されているrhBMP-2を有効かつ，より安全に利用して骨再生を達成する技術の開発をこれまでに行ってきた．ここではその概略と現状，さらに残された問題点について述べる．

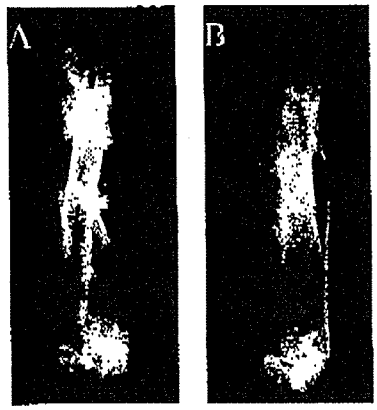

図4 ウサギ大腿骨骨幹部autoclave処理骨による骨再建後4週の軟X線像
A：Autoclave処理骨のみのControl群．再建部の骨形成を認めない．B：rhBMP-2 5 μg/β-TCP 15mg/polymer 15mgのインプラントをautoclave処理骨周囲に塗り込んだ群．処理骨周囲に旺盛な骨形成を認め，大腿骨全体の再建がなされている．

1．BMPの生物化学的特徴

BMPは，正常骨芽細胞系細胞によって産生分泌されるホモ2量体の若干の糖鎖を有する活性蛋白(サイトカイン)である．その成熟領域の分子構造の特性としては，2量体の分子量は30kDa前後で疎水性の強い中性蛋白分子である．また，アミノ酸配列ではC末端からみて7個のシステイン残基の位置がtransforming growth factor-β (TGF-β)と同一である．したがって，BMPはTGF-β superfamily に属する一群のfamilyをなしている[9]．アミノ酸配列の種特異性は低く，たとえばヒトBMP-4ではマウスBMP-4のアミノ酸配列と比較してN末端近くに2カ所の変換がみられるのみである．それゆえヒトBMPは，マウス，ラット，ウサギ，イヌ，霊長類などでも骨誘導活性が発現される．

現在ではBMP-2～BMP-15の14種類の分子が同定されている(BMP-1はのちにサイトカインとしてよりもむしろプロコラーゲンⅠ・Ⅱ・Ⅲに対するコラゲナーゼとして作用するためBMP familyから除外された)が，このうち骨形成促進活性を有して*in vivo*において異所性に骨形成を誘導する活性が確認されているのはBMP-2，BMP-4，BMP-6，BMP-7(OP-1)，BMP-9である[6,7]．それぞれのBMPの詳細な生理学的役割の違いは明らかではないが，発生過程[10]や骨折治癒過程[11,12]でみられる骨形成にはBMPおよびBMP受容体の発現が重要な役割を担っているとされている．

BMPの三次元分子構造にはcystine knotと称する安定化構造があり，きわめて安定な蛋白である．したがって，変性しにくく，実際に90℃30分程度の熱処理でも生物活性は保たれる[13]．すなわち，生物製剤としての保存・搬送に関する問題はほとんどないと考えられる．

2．BMPによる骨組織再生のための薬物伝達系(DDS)

rhBMPの生体内埋植による局所的骨形成促進効果はこれまで多くの実験で示されている．

目的とする局所にBMPを作用させて適切な形，大きさの骨組織を誘導するためには，BMPを局所に留め持続的に徐放する系，すなわちBMPに適したdrug delivery system(DDS)(または担体)が必要である．BMPの担体に求められる特性としては，生体に対して毒性がないこと，免疫原性を有しないこと，生体吸収性であること，生理的環境で不溶性であること，成形が容易であることなどが求められる．これらの要件を満たすものとして従来から動物由来コラーゲンが用いられてきた．欧米では脊椎前方固定や骨折後偽関節治療のためのBMPの担体としてコラーゲンが用いられている[14]．

しかし，コラーゲンはBMPのDDSとして理想的担体とはいい切れない．なぜなら，臨床応用のためには，まだ改良を加え解決しなければならないいくつかの問題が残されているからである．すなわち，コラーゲンは比較的免疫原性が低いことは知られているものの異種由来蛋白であることから，大量または繰り返し使用することによる免疫反応のリスクが危惧されること，さらに，近年問題となっている狂牛病などの感染症のリスクが潜在していることなどである．しかし，欧米では，脊椎前方固定術に関してリコンビナントBMPと担体(ウシ由来コラーゲンスポンジ)を一体化した生体材料としてすでに商品化されている．将来改良を加えるべきであろう．

rhBMPと新しい合成ポリマー担体による骨再生

この問題の解決のために筆者らはBMPの担体として充分機能する生体吸収性合成ポリマーの開発を行ってきた．安全で安価な生体吸収性合成ポリマーである．筆者らはこのような特性を有する担体として数種類の合成ポリマーを開発した(polylactic acid-polyethylenglycol block copolymer：PLA-PEG)[15]．このpolymerに少量のBMPを混和して生体に埋植すると異所性にも同所性にも骨新生が起こり，埋植したpolymerと置き換わる．このpolymerの詳細はすでに報告しているため文献を参照していただきたい[15]．

動物実験では，このBMP/polymer 複合材料を用いると比較的大きな骨欠損でも修復可能である．たとえば，ラット頭蓋冠にcriticalな骨欠損を作製し，5 μgのrhBM-2を含有したpolymer pelletを埋植後3週間で旺盛な骨形成および骨欠損部位の再建が可能である(図2)[16]．また，多孔性生体材料の孔内にBMP/polymerを封入することで立体的構造を持ったインプラントを構成し骨欠損再生も可能である．ウサギ大腿骨に1.5cmのcritical defect 作製した際の骨組織再生例を図3に示す[17]．この例のように多孔性β-TCPのような生体吸収性材料を用いれば生体材料を残さずに骨再生が可能である．ほかにもこのインプラントを用いれば，イヌの8 cmにも及ぶ肋骨欠損の再生も比較的短時間で可能である．

しかし，このpolymerの欠点として，常温では粘着性が強いために，扱いにくく成形も困難な点がある．この点を改良するために，このBMP/polymer複合体の生体吸収性β-tricalcium phosphate(β-TCP)粉末をpolymerと等量混和することで軟粘土状にし，扱いやすさを改善した．これによってインプラント材料の容積がほぼ倍加し，形成される骨量もほぼ倍加するため，結果としてBMPによる骨形成効率を上げることにも有効である．また粘着性を減ずることで任意の形態に成形可能であり利便性が向上する．このBMP/polymer/β-TCP powder 複合材料を用いた場合，ウサギでの脊椎後側方固定に要したBMPの量は，すでに報告されている他のグループからの実験結果における必要最少量の約1/6となる15 μg/sideであり，大幅なBMPの低用量化を可能にすることができた[18]．また，粘土状rhBMP-2/β-TCP/ polymer複合体を骨表面や固形生体材料表面に塗り込むことによって骨形成を誘発することも可能である(図4)．その他，この骨再生活性を持った複合材料は臨床上の必要性に応じて多くの用途に使える可能性があると考えている．

このような実験結果はrhBMP，合成ポリマー，合成生体材料などのすべて人工合成物の複合によって骨再生が可能であることを示しており，従来骨再生促進の目的で行われてきた外科的侵襲を伴う自家骨移植を行うことなく骨再生が可能となることが期待できる．

現在の問題点

1．BMPの応答性：動物種間差

BMPを用いた骨再生技術開発研究成果を臨床応用し，かつ汎用化させるために克服すべき問題がいくつか存在している．第1にBMPに対する応答性に種差があり，より進化した動物種では応答性が低いことが知られている．したがって，ヒトではBMPに対する応答性が低く，マウスの1/15～1/30と推定されている．すなわち一定量の骨組織を誘導するのに要するBMP量がマウスに比して15～30倍の高用量が必要ということになる．その結果，安全性に対する危惧や高価になるとの問題点が提起される．

たとえば現在，コラーゲンを担体とした場合，ヒトでは1 cm^3の新生骨を形成するためには約1mgのBMPが必要である．この問題の解決には先に述べたようなBMPのDDSの有効性の改良，BMPに対する応答性を高める薬剤のスクリーニング，BMPの生理的拮抗物質の発現抑制などが考えられえる．特にBMPの生物活性を増幅する方法として，細胞内cAMP(cyclic adenosine monophosphate)の分解酵素であるphosphodiesterase inhibitorsがBMPの活性を増強することを

報告した[19-21].

また筆者らはprostagrandin E_2(PGE_2)の受容体EP4アゴニスト(ONO4819)が，全身投与[22]のみならず局所投与[23]によってもBMPの生物活性を増幅する作用があることを明らかにしている．すなわち，polymerにBMPに加えてこれらの物質を共投与することで，BMPによる骨形成活性がおよそ2倍程度増強されることを見いだしている．これらのBMP作用を増強させる物質は，いずれも細胞内cAMP濃度を上昇させることが明らかになっている．

筆者らは，細胞内cAMP濃度上昇によって，BMPシグナルの細胞内シグナル伝達が促進されること，またBMPシグナル伝達阻害因子であるSmad6の遺伝子発現が抑制されることにより，結果的にBMP活性が部分的に促進されていることも明らかにしている[24]．さらに強力なBMP活性の増幅物質が開発できればなお一層BMP用量を減少できる可能性がある．

2．経済性の改善

最近の研究報告ではsulfated polysaccharides[25]，人工的に作製されたペプチドであるB2A2[26]やTGFβ受容体選択的阻害剤[27,28]などがBMPの効果を増強させるなど多くの研究が進んでおり，*in vivo*でのBMP効果の増強が期待される．これらの薬剤をBMPによる骨組織再生に応用することにより，より効果的・効率的な骨組織の再生が可能になり，骨組織再生は汎用化される可能性がある．BMPの生産コスト低下による経済性の改善も課題である．2量体BMPの生合成には大腸菌ではなく動物細胞(chinese hamster ovary：CHO細胞)が用いられる．しかし，最新の報告では，CHO細胞によって産生されたリコンビナントBMPとほぼ同等の生物活性を有したBMPを大腸菌でも合成できるとのことであり，コストの低減化も図る試みも報告されつつある[29,30]．これらの報告により，BMPを用いた骨再生医療の汎用化につながる糸口となりうる可能性が高まり，近い未来に実現可能な技術となることが期待できる．

その他の骨再生医療技術

BMP以外のサイトカインや増殖因子で，骨再生促進を図る研究も進みつつある．

Kawaguchiらは，塩基性線維芽細胞増殖因子(basic fibroblast growth factor：bFGF, FGF-2)をDDSにハイドロゲルを用いて，non-human primatesの骨折治癒の促進を確認したと報告している[31]．また，bFGFを実際に用いた骨折治癒促進および歯槽骨欠損再生は，現在臨床治療試験を進行させている段階に入っている．

筆者らは骨組織再生におけるBMPのDDSとして，生体吸収性ポリマーおよびβ-TCPを用いて良好な骨組織再生を実験結果として得ているが，そのほかにも数多くの種類の異なるDDSとしての担体が報告されている．たとえばα-TCPを主成分としたリン酸カルシウム骨セメント[32]や連通多孔体を有したハイドロキシアパタイト[33]やハイドロキシアパタイト・ポリ乳酸複合多孔体[34]，多孔質ハイドロキシアパタイト・コラーゲン複合体[35]などである．それらの有効性については，各研究者が考察・報告しているが，さまざまな担体を比較し，骨組織再生に最も適切な担体を同定することも今後の重要な問題点である．

まとめ

本邦の顕著な高齢化，さらには疾患および治療法の多様化に伴い，整形外科領域を中心に，有効かつ効率的な骨組織での再生医療の発展が急務となっている．本稿では，筆者らの研究結果ならびに諸家の先進的研究結果から，骨再生医療の現状および問題点を中心に述べた．現在は，世界保健機構によりBone and Joint Decadeと定められた2001～2010年までの10年間の中間点に当たり，世界的にさまざまな骨再生を目指した基礎的研究が進行中であるが，遺伝子組換え体サイトカインであるリコンビナントBMPを用いた骨再生医療は，骨組織再生の臨床的実用化の面からはより先行した技術であると考えられる．

近い将来には，普遍的な骨組織再生医療技術と

して，さまざまな分野で多くの疾患の治療に活用されると予想している．

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ラウンドテーブルディスカッション2 ● 転倒予防のハード面の課題

ヒッププロテクターによる大腿骨頸部骨折の予防
－Randomized Controlled Trial－

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【目　　的】

ヒッププロテクター（HP）による大腿骨頸部骨折予防に関する，これまでの randomized controlled trial（RCT）では，HPの装着率は50%以下と低い。われわれの行った第1，2次調査でも，施設スタッフに任せたままであったり，被験者にHPを渡しただけのことが多く，たちまち着用率が低下する結果となった。また，調査を依頼してから被験者の登録までに，3～6ヵ月もかかっていた。HPの有効性を調査するためには，製品特有の問題点もあるが，施設スタッフの「転倒・骨折予防」に対するモチベーションの低さと研究チームの介入のまずさも，RCTの結果に影響を与えていると考えた。そこで，今回，大規模RCTを実施するにあたり，施設スタッフへの介入を試み，コンプライアンス向上の可能性を探った。実際のRCTの結果は別に記載し（本誌p42を参照），ここでは施設スタッフへのアンケート（**付表**）の結果を中心に報告する。

【方　　法】

第1，2次調査で使用したプロトコールおよび記録物の見直しを行い，76参加施設の各担当者別に研究の目的，方法を説明し，被験者だけではなく，施設スタッフからもインフォームドコンセントが取得できるように努めた。また，「転倒・骨折予防」への動機付けを行い，モチベーションを高め，維持するために，6名で施設訪問チームを結成し，大阪府内へは月1回，他府県へは2～3ヵ月に1回訪問し，実施状況の確認や，被験者の情報収集を行った。施設スタッフや被験者とその家族への意識付けのために，HPについての絵本やポスターを作成し，研究の進行状況や他施設からの情報を協力施設全体に反映できるよう，毎月ニュースレター（三間森さん通信）の発行や，希望施設への教育講演を行った。これらの活動を行い，調査が1年を経過した時

表1　ヒッププロテクター着用継続の工夫

被験者選び	・転倒･骨折を起こしやすい人 ・ヒッププロテクター着用の必要性を理解できる人 ・歩行可能な人 ・認知症の人 ・家族が転倒・骨折を不安に思っている人 ・状態変化の少ない人 ・転倒を恐れて，外出をしない人 ・ケアワーカーのかかわりが多い人 ・着用希望の人
被験者の着用指導	・ヒッププロテクター着用が骨折予防になることを説明する ・着用状況をチェックし，指導，声かけを行う
スタッフ間の意識統一	・転倒・骨折予防，ヒッププロテクターについての学習会，ミーティング ・着用のチェックと記録忘れのないよう，業務内での引き継ぎ ・パンツ，シェルの置き場所を統一する

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表2 転倒・骨折予防とヒッププロテクターについての意識変化（ヒッププロテクター群）

調査前	現 在
・転倒・骨折はADL低下の原因となるため，利用者の活動を制限していた ・転倒はよくないが，仕方がないと思っていた ・観察，介助，環境整備など転倒予防に心がけていた	・転倒は避けられないことだから，骨折の予防が必要だと思った ・ヒッププロテクター着用により，骨折が予防できていると思う ・ヒッププロテクター着用により，スタッフに安心感ができ，利用者の活動制限が減った

表3 転倒・骨折予防とヒッププロテクターについての意識変化（コントロール群）

調査前	現 在
・転倒・骨折は仕方がないと思っていた ・ADLの低下，認知症につながるので転倒予防は必要だが，何をすればよいのかがわからなかった ・常に環境整備などを行い，転倒予防を心がけていた	・施設全体に転倒・骨折予防の意識が高まった（転倒・骨折は予防できると思った） ・被験者をあげることで，よく観察でき，転倒のリスクが理解できた ・骨密度，床の硬さなどさまざまな要因が骨折に関与していることを知った

点で，施設スタッフにアンケートを行い，「転倒・骨折予防」とHPについての意識変化を調査した。

【結　　果】

2004年1月より登録を開始し，2005年1月の時点で4ヵ月以上経過を観察できた614名（コントロール（C）群306名・HP群308名）に大腿骨頸部骨折はC群に17例，HP群に6例発生し，相対危険率は0.35であった。この期間のHP装着率は，87.5%と高い成績を得た。

施設スタッフへのアンケートは，88%の回収率で，回答したスタッフの平均年齢は35.3歳（1/3が20歳代），職種は，介護職員・生活相談員・ケアマネージャー・看護師・理学療法士等と多様であった。調査への参加理由は「大腿骨頸部骨折予防のために必要と考えた」が70%以上を占めたが，「上司の指示で仕方なく参加」も15%を超えていた。調査を進めるうえでは，「被験者選び」が最も困ったことであり，98%のスタッフが研究プロトコールを理解していた。絵本やニュースレター（三間森さん通信）は「役に立たなかった」とする回答が25%程度あり，配布物による教育効果は十分でなかった可能性がある。しかし，調査チームメンバーの訪問は「調査の手助けになった」が61%あり，月1回の訪問でも「少ない」と感じている回答が10.3%あった。施設スタッフが行った「ヒッププロテクター着用継続の工夫」を**表1**に示す。**表2**はHP群，**表3**はC群の「転倒・骨折予防とHPについての意識変化」で，両群ともに介入開始時よりも，転倒・骨折予防の発生機序の理解が深まり，転倒・骨折は予防可能であるという認識が広まっていた。

【考　　察】

HPは適切に使用すれば大腿骨頸部骨折を抑制できると考えられるが，施設スタッフのモチベーションがHPの着用率に大きく影響する。今回は，施設スタッフへの介入によりHPの高いコンプライアンスを得ることができた。施設の担当者は，調査を進めるにあたり，「被験者選び」に最も困っていたが，「スタッフ全員の理解と協力を得ること」にも困っていたという回答があった。担当者もまた，研究チームとスタッフの間に立ち，困惑していたことが，施設訪問時にも伺えた。大腿骨頸部骨折予防は，決して研究チームだけの成果ではない。施設利用者や家族あるいは施設にとっても，大腿骨頸部骨折予防が介護予防につながるという相互理解を深めるために，「上司の指示で仕方なく参加」した施設スタッフへの介入は重要だと考える。介護の現場を支えているスタッフの年齢は若く，職種も多様である。研究チームは調査を依頼するにあたり，高齢者施設に勤務するスタッフの特性も理解しなければならない。しかし，今回のよ