1. Subject recruitment

Many RCT s were performed in Futase Social Insurance Hospital, which served as a regional center for neurological diseases particularly among elderly patients. and Mitate Hospital. Futase Social Insurance Hospital is located in Chikuho Province of Fukuoka Prefecture, Japan, which has about 433,000 community dwellers. However, only 5 neurologists are practicing in the district, 2 in Futase Social Insurance Hospital and 3 in another hospital. The details of the reasons for the accumulation of elderly patients in Futase Social Insurance Hospital were described in the reply to a similar comments (*J Neurol Neurosurg Psychiatry* 2004;75:511).

We recruited a large number of neurologic patients during 15 years. The lead author (Y. Sato) took charge of patient follow-up with support by 2 additional physicians of Mitate Hospital. Mitate Hospital has 410 beds and is located in the same Chikuho Province. As described above, only five professional neurologists practiced in two hospitals—Mitate Hospital and another one—and physicians who could diagnose and treat elderly neurologic patients were very few in view of the population in Chikuho Province. For example, our hospital admits mild stroke patients without any impaired consciousness and patients with unconsciousness were transferred to other hospitals as we described elsewhere (*Neurology* 2005; 65:1513-4). Thus, many stroke patients in our hospital met the inclusion criteria of the studies.

In some studies on stroke and Alzheimer's disease (AD), we included patients from two collaborating hospitals and a nursing home in addition to the patients treated in Mitate Hospital. The nursing home is affiliated with Mitate Hospital and most of the institutionalized patients were treated as out-patients of the hospital. This fact was described as a correction for a paper in JAMA (*JAMA* 2006; 296: 396).

2. Randomization

It is pointed out that, in a RCT, comparisons of variables randomly extracted from the population at baseline produce an equal likelihood of p-value

occurrence that naturally defines a reference point of comparisons in deciles as “expected proportion 0.1”. I believe it is disputable if the comparisons of variables regardless of their types, either continuous or categorical, may result in an equal likelihood of p-values.

The distribution of the standardized sample means for 401 baseline continuous variables is summarized in Fig 1. (right panel, uppermost) of the manuscript recently submitted to JAMA. The SD (standard deviation) of the standardized sample mean differences is calculated and the equality of the SDs between the calculated and expected ones is examined using an F-test (SAS 9.2). The SD calculated is 0.59 and that of the expected distribution, N (0, 1), is 1. The result of F-test is a p value of 1.7 x 10-24. Similarly, a p value of 1.2 x 10-9 is presented for illness duration and of 5.5 x 10-5 for Study A13. I am concerned myself about the validity of using F-test with degree of freedom given to the variance of the expected distribution N (0, 1). Carlisle (Anesthesia 2012; 67: 521-537.) used sdtest (Intercooled STATA® 12) for this purpose

3. Positive results

The remarkable outcome of the effects of interventions ―administration of vitamin D and bone resorption inhibitors (A22) ― on fracture or bone density may be attributed to the fact that our study subjects were neurological patients, who may have higher risk of fracture without any intervention. Generally patients with Parkinson disease have higher levels of impaired movement as compared to postmenopausal women. This fact may explain the occurrence, in these patients, of immobilization-induced hypercalcemia due to enhanced bone resorption, which, in turn, may inhibit PTH secretion resulting in the suppression of vitamin D activation. These characteristics of bone and calcium metabolism in patients with Parkinson disease may have predisposed them to high effectiveness of the interventions.

4. Other inconsistencies

The two studies (A22, A30), with higher rates of hip fractures in control group, examined only female patients with Parkinson disease (PD). The relatively lower rate in control group in another study (A23) on PD may be due to the fact that the subjects were only male patients. Sunlight exposure to PD (A30) was carried out in both genders, while two studies (A22, A30)were performed in female PD patients. This may result in high incidence hip fracture in female PD patients.

In four studies with basal vitamin D supplementation (A18, A22, A23, A30), the control subjects were administered with ergocalciferol, while sunlight is known to bring about cutaneous production of cholecalciferol which is 1.6 times more effective than ergocalciferol. This may explain the BMD decrease in vitamin D supplemented group in view of increased BMD and extremely low rate of fracture in sunlight exposure group (A16, A31).

Stevenson et al. (Stevenson M et al. A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis. Health Technol Assess. 2005; 9:1-160) performed a systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis. Effect of alendronate on hip fracture in comparison with placebo or no treatment in postmenopausal women with osteoporosis or osteopenia (Cummings SR, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998;280:2077-82.Liberman UA et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med 1995;333: 1437-43). Postmenopausal women received a supplement containing 500 mg of calcium and 250 IU of cholecalciferol. Subjects were randomly assigned to either placebo or 5 mg/d of alendronate sodium for 2 years followed by 10 mg/d for the remainder of the trial. As a result, the relative risk (RR) of hip fracture was 0.79 (95% CI

0.44 to 1.44: Cummings SR, et al. (Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998;280:2077-82.) In another study, postmenopausal women were treated with placebo or alendronate (5 or 10 mg daily for three years, or 20 mg for two years followed by 5 mg for one year); all the women received 500 mg of calcium daily. The RR of hip fracture was 0.22 (95% CI 0.02 to 2.12: Liberman UA, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med 1995;333: 1437-43.). In our study (A22) of postmenopausal PD patients were randomly assigned to daily treatment with 5 mg of alendronate (n=144) or a placebo combined with 1000 IU of vitamin D2 (n=144), and followed for 2 years. The RR for hip fractures in the alendronate group as compared with the placebo group was 0.29 (95% CI, 0.10 to 0.85). Comparing the two studies (Cummings SR, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998;280:2077-82. Liberman UA, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med 1995;333:1437-43), value of the RR of PD patients who may have lower 25-OHD and high incidence of fall is relatively low A22). It is possible, combined therapy of alendronate and vitamin D2 may be a cause of low RR. In addition, alendronate inhibited bone resorption as evidenced by normalization of immobilization-induced hypercalcemia and increasing metacarpal BMD at 3.1% during 2 years study period. (A22). Percent change of BMD of femoral neck during the 3 years treated by 5mg/day alendronate in postmenopausal women was between 2 and 3% (Liberman UA, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med 1995;333: 1437-43).

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