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Very high frequency of fragility fractures associated with high-dose glucocorticoids in postmenopausal women: A retrospective study☆

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ABSTRACT

Purpose
To evaluate the incidence of fragility fractures associated with high-dose glucocorticoid therapy in patients with systemic rheumatic disease.
Methods: A retrospective study of patients who were treated with high-dose prednisolone (>0.8 mg/kg) for systemic rheumatic disease at Kobe University Hospital from April 1988 to March 2012. The primary outcome was a major osteoporotic fracture (defined as a clinical vertebral, hip, forearm, or proximal humerus fracture) after high-dose glucocorticoid therapy. For postmenopausal women and men over 40 of age, the patient's fracture risk at the beginning of high-dose glucocorticoid therapy was assessed by the World Health Organization's Fracture Risk Assessment Tool (FRAX®).
Results
Of 229 patients (median age: 49 years), 57 suffered a fragility fracture during the observation period (median observation period: 1558 days). Of 84 premenopausal patients, 5 suffered a fracture. In contrast, of 86 postmenopausal female, 36 suffered a fracture. Fragility fractures were far more frequent than predicted by the FRAX® score. Patients with FRAX® scores over 8.3% had a particularly high risk of fracture.
Conclusions
Fragility fractures associated with high-dose glucocorticoid therapy are common among postmenopausal women. Extreme care should be taken especially for postmenopausal women when high-dose glucocorticoid therapy is required.

1. Introduction

Glucocorticoid (GC) therapy is the primary treatment option for patients with systemic rheumatic disease. Osteoporosis, which is a common complication of high-dose GC therapy, is associated with significant morbidity and mortality. Although awareness of GC-induced osteoporosis (GIO) has increased in recent years, GIO remains underdiagnosed and undertreated. GIO's distinctive characteristics include rapid bone loss and an increase in fracture risk shortly after beginning GC therapy; therefore, the primary prevention of fractures in high-risk individuals is critical (Compston, 2010).

The American College of Rheumatology (ACR) published Recommendations for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis in 1996 (American College of Rheumatology Task Force, 1996), and various guidelines have since been published for other countries (American College of Rheumatology Ad Hoc Committee, 2001) (Bone and Tooth Society of Great Britain, National Osteoporosis Society, Royal College of Physicians, Glucocorticoid-induced-osteoporosis guidelines for prevention and treatment, 2002) (Devogelaer et al., 2006) (Watts et al., 2008) (Grossman et al., 2010) (Suzuki et al., 2014). Some of these guidelines use the World Health Organization's Fracture Risk Assessment Tool (FRAX®), which uses a computer-based algorithm (http://www.shef.ac.uk/FRAX) to calculate the 10-year probability of a major osteoporotic fracture (defined as a clinical vertebral, hip, forearm, or proximal humerus fracture) and the 10-year probability of a hip fracture (Watts et al., 2008) (Grossman et al., 2010). FRAX® integrates seven clinical risk factors—a prior fragility fracture, a parental history of hip fracture, smoking, use of systemic corticosteroids, rheumatoid arthritis, secondary osteoporosis,

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and excessive alcohol intake—which, in addition to age and sex, contribute to fracture risk independently of bone mineral density (BMD) (Kanis et al., 2008).

Although FRAX® is a valuable tool, it can underestimate risks because it does not include dose-response effects from contributing factors. For instance, there is strong evidence that the risks associated with excessive alcohol consumption (Berg et al., 2008), smoking (Hollenbach et al., 1993), and GC use (van Staa et al., 2000) are dose-responsive, and that the risk of fracture increases progressively with the number of prior fractures (Lindsay et al., 2001). However, FRAX® scores do not reflect these graded risks. Kanis et al. proposed adjusting FRAX® scores according to GC dosage, using these simple rules: for low-dose exposure, defined as <2.5 mg/day prednisolone or the equivalent, the probability of a major fracture is about 20% less than predicted by the FRAX® score (although this result also depends on the patient's age). For a dosage of 2.5–7.5 mg/day prednisolone, the unadjusted FRAX® score can be used. For a dosage >7.5 mg/day prednisolone, the probability is revised upward by about 15% (Kanis et al., 2011). However, these guidelines do not adequately assess the risks associated with high-dose GC therapy (prednisolone 0.8 mg/kg/day or more, equal to 40 mg prednisolone/day for a 50-kg patient), which is often used for patients who are severely affected by a rheumatic disease. The adjusted relative fracture rate increases drastically for daily GC doses above 20 mg prednisolone (van Staa et al., 2000). Despite this dramatic increase in the risk of fractures, the incidence rate of fragility fractures after high-dose GC therapy has not been reported.

Bisphosphonates, a family of anti-osteoporosis drugs that strongly inhibit osteoclasts, are reported to treat GIO effectively (Saag et al., 1998) (Cohen et al., 1999) (Reid et al., 2000) (Wallach et al., 2000) (Adachi et al., 2001) (de Nijs et al., 2006) (Reid et al., 2009) (Stoch et al., 2009) (Fahrleitner-Pammer et al., 2009) and are listed as a first-line pharmacologic intervention in several GIO-treatment guidelines (Bone and Tooth Society of Great Britain, National Osteoporosis Society, Royal College of Physicians, Glucocorticoid-induced-osteoporosis guidelines for prevention and treatment, 2002) (Devogelaer et al., 2006) (Watts et al., 2008) (Grossman et al., 2010) (Suzuki et al., 2014). Thus, many patients undergoing high-dose GC therapy also take bisphosphonates. However, bisphosphonate therapy for GIO has been studied only in patients receiving 20 mg/day prednisolone or less, and its efficacy for preventing fragility fractures associated with high-dose GC therapy has not been studied. Although newer, more effective GIO-prevention drugs have become available recently or are in development, it is not clear which patients on high-dose GC therapy should be given the newer drugs.

This retrospective study was conducted to research the incidence rate of fragility fractures in patients treated with high-dose GC therapy in a real-world clinical setting, and to investigate the discrepancy between the FRAX 10-year probability of a major osteoporotic fracture and the actual fracture rate.

2. Methods

This study was reviewed and approved by the ethics board of Kobe University Hospital prior to enrolling the subjects.

We retrospectively reviewed medical records for all patients treated for systemic rheumatic disease at Kobe University Hospital from April 1998 to March 2012. In total, 2094 medical records were reviewed. The patients treated with prednisolone at a dose >0.8 mg/kg/day were eligible for the study if they were followed continuously for at least 1 year after beginning treatment, and were not treated with teriparatide or denosumab. Based on these inclusion and exclusion criteria, 1865 records were discarded. We included 229 patients in the analysis.

The primary outcome for this study was a major osteoporotic fracture (defined as a clinical symptomatic vertebral, hip, forearm, or proximal humerus fracture) after high-dose GC therapy. We identified major osteoporotic fracture by retrospective medical record review. The diagnosis of osteoporotic fracture had been made mainly by rheumatologists or local orthopedist.

For postmenopausal women and men over 40 years of age, we calculated the 10-year probability of a major osteoporotic fracture by using Japanese version of FRAX®, with or without femoral BMD, at the start of high-dose GC therapy. For patients who sustained a fragility fracture during the observation period for any given course of GC therapy, we used the data from the most recent admission and treatment period prior to the fracture.

We collected clinical information of each patient. For postmenopausal women and men over 40 years of age, we calculated the FRAX® 10-year probability of a major osteoporotic fracture, with or without femoral BMD, at the start of high-dose GC therapy. Patients were considered to have received bisphosphonate and/or active vitamin D treatment if they are prescribed those medicines for at least 80% of the observation period. Patients who are prescribed bisphosphonate and/or active vitamin D treatment for <80% of the observation period were used as comparison subjects; most of these patients are prescribed bisphosphonates or Vitamin D for <20% of the observation period.

To assess calibration (i.e., the degree of similarity between predicted and observed risks), we stratified the postmenopausal women and men over 40 years of age into 4 groups according to their FRAX® score and compared the 10-year probability of a major fragility fracture with the observed incidence of fractures in our real-world clinical setting.

The fracture incidence was calculated using the Kaplan-Meier method. We used the Cox proportional hazard model for multivariable analysis of the incidence of fragility fractures after high-dose GC therapy; the variables analysed included the FRAX® 10-year probability of a major

Table 1
Baseline subject characteristics.

Disease	Number	Female	Median Age [25%–75%]	Median Observation Period [25%–75%]	Median FRAX[a] [25%–75%]	Bisphosphonates prescription (%)	Prior high-dose GC (%)	Fragility Fracture (%)
SLE	76	66 (86.8)	30.5 [24–37]	2226 [1124–3085]	5.3 [3.7–10.9]	28 (36.8)	30 (39.5)	6 (7.8)
Vasculitis[b]	58	45 (75.9)	66 [47.8–70.8]	1166 [618.3–2087]	14 [6.8–24]	38(65.5)	9 (15.5)	18 (31)
PM/DM	51	34 (66.7)	58 [47–69]	1655 [676–2587]	9 [5.9–14]	34 (66.7)	5 (9.8)	18 (35.3)
AOSD	12	7 (58.3)	37.5 [26–56]	1613 [1215–2335]	7.2 [3.2–9.8]	7 (58.3)	1 (8.3)	2 (16.7)
MCTD	7	6 (75)	42 [35–54]	1975 [1768–2540]	5.7 [2.8–10]	6 (85.7)	2 (29)	1 (14.2)
Others[c]	25	12 (48)	63 [57.5–70]	833 [283–2650]	6.7 [4.9–13]	9 (36)	4 (16)	12 (48)
Total	229	170 (74.2)	49 [31–66]	1558 [803–2596]	9 [5.2–15]	122 (53.2)	51 (22.2)	57[c] (24.9)

AOSD = adult-onset Still's disease.

[a] FRAX is calculated for postmenopausal women and men over 40 of age.

[b] Vasculitis syndromes: Takayasu arteritis (11); giant-cell arteritis (11); microscopic polyangiitis (10); granulomatosis with polyangiitis (7); eosinophilic granulomatosis with polyangiitis (6); Behcet's disease (5); rheumatoid vasculitis (4); unclassified vasculitis (4). [b]Other diseases: IgG4-related disease (4); Castleman's disease (3); overlap syndrome (3); sarcoidosis (2); diffuse fasciitis (3); systemic sclerosis (2); relapsing polychondritis (2); idiopathic thrombocytopenia (1); autoimmune haemolytic anaemia (1); autoimmune hepatitis (1); eosinophilic pneumonia (1); and pachymeningitis (1).

[c] 52 clinical spinal, 3 hip, 1 humerus and 1 wrist fracture.