Guidelines on the Management and Treatment of Glucocorticoid - induced Osteoporosis : from the Japanese Society for Bone and Mineral Research

Yoshiya Tanaka[1,2,3], Yasuo Suzuki[1,2], Satoshi Soen[1,2], Saeko Fujiwara[1,2], Hisanori Nakayama[1,2], Ikuko Tanaka[1,2], Keiichi Ozono[1], Akira Sagawa[1], Ryoichi Takayanagi[1], Hiroyuki Tanaka[1], Takami Miki[1], Naomi Masunari[2], Hajime Nawata[1]

[1] Committee for the Revision of Guideline on the Management and Treatment of Glucocorticoid-induced Osteoporosis of the Japanese Society for Bone and Mineral Research

[2]Working group for the Revision of Guideline on the Management and Treatment of Glucocorticoid-Induced Osteoporosis of the Japanese Society for Bone and Mineral Research

[3]President, Japanese Society for Bone and Mineral Research

Y. Tanaka: The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan

Abstruct/Conclusion

Glucocorticoid (GC)-induced Osteoporosis (GIO) is the most common secondary osteoporosis and fractures occur in 30 to 50 % of patients receiving GC therapy. Although it is important to prevent bone loss and fragility fracture by the early intervention, adherence to guidelines on the management of GIO is about 20% in Japan. We, therefore, revised the guideline based on accumulated references and collected data from 5 Japanese cohorts of GIO. By the analysis of 903 patients from 3 cohorts, age, GC dose, lumbar BMD and prior fragility fracture were identified as factors that predicted future fractures. When the hazard ratio for age was calculated versus <50 years, the fracture risk was 1.446 times higher at age 50≤ <65 and 2.108 times higher at age ≥65. Similarly, hazard ratio of fracture risk was as followings; GC dose 5≤ <7.5: 1.149, ≥7.5: 2.166 vs. < 5mg/day; %YAM of lumber BMD 70≤ <80: 1.373, <70: 1.863 vs. ≥80; with prior fragility fracture: 3.485 vs. w/o it; with bisphosphonate 0.481 vs. w/o it. The parameter estimates for each risk factor were converted to tentative scores by the formula. The optimal cut-off score for setting the intervention threshold was validated by the data of 144 patients from 2 cohorts on primary prevention and determined by the careful discussion in the committee. It covers patients ≥18 years who use or are planning to use GC for ≥3 months and the intervention is based on achievement of a total score of ≥3 from each score in 4 domains: prior fragility yes: 7, age 50≤ <65: 2 and ≥65: 4, GC 5≤ <7.5: 1 and ≥7.5: 4, %YAM of lumber BMD 70≤ <80: 2 and <70: 4. Thus, it will aid the physician in easy and adequate decision-making for initiation of intervention to prevent fragility fracture due to GIO.

Introduction

Glucocorticoids (GCs) are widely used to treat various inflammatory, immunologic, and allergic disorders that cause rheumatic, respiratory, bowel, hepatic, neurological, renal, and skin diseases. An early rapid loss of bone mineral density (8 ~ 12%) occurs within the first several months of starting GC therapy, although bone mineral density decreases more slowly thereafter, with the annual loss being approximately 2 ~ 4%. It is important to prevent early bone loss and to decrease in fracture risk as early as possible after the start of GC therapy. Based on the concept of early prevention and treatment of GIO, the American College of Rheumatology (ACR) developed recommendations for the prevention and treatment of GIO in 1996. Based on such new evidence regarding GIO, the ACR recommendations was updated to incorporate FRAX® as an assessment tool for fracture risk in the 2010 revision. The Joint GIO Guidelines Working Group of the International Osteoporosis Foundation and the European Calcified Tissue Society has also published a framework for the development of guidelines for the management of GIO.

In response to these international changes related to GIO, the Japanese Society for Bone and Mineral Research (JSBMR) set up a Committee for the Revision of Guidelines on the Management and Treatment of Glucocorticoid-induced Osteoporosis.

Subjects and Methods

1. Subjects

In order to determine risk factors for fractures, the committee requested data on the following Japanese GIO cohorts; patients in a Japanese multicenter randomized controlled trial (RCT) on the primary and secondary prevention of GIO with alendronate plus alfacalcidol: The GOJAS study (Cohort E and A), the longitudinal GIO cohort of the National Hospital Organization National Sagamihara Hospital (Cohort B), the longitudinal GIO cohort of Fujita Health University Hospital (Cohort C), and patients in an RCT of the University of Occupational and Environmental Health investigating primary prevention of GIO (Cohort D). Cohort A, D, and E were in randomized controlled studies, while cohort B and C were in longitudinal studies. A total of 1047 patients were recruited from these 5 Japanese cohorts.

	Populations studied to determine the cut-off score for intervention (N=903[117*])			Populations studied to verify the cut off score for intervention (N=144[1*])	
	Cohort A	Cohort B	Cohort C	Cohort D	Cohort E
Number of subjects	108 [18*]	617 [64*]	178 [35*]	108 [1*]	36 [0*]
Age (years)	54.4 ± 14.6	59.7 ± 11.1	50.1 ± 14.9	48.1 ±15.6	49.3 ± 15.9
GC dose (mg/day)**	11.5 ± 13.6	5.7 ± 4.6	11.1 ± 13.6	45.7±13.4	41.7±26.4
Duration of GC therapy (year)	7.9 ± 8.8	4.8 ± 6.1	Data not available	0	0.07 ±0.19
Lumbar BMD (%YAM)	88.2 ± 16.9	80.0 ± 15.6	78.7	95.9 ±15.6	91.4 ±16.5
Prior fragility fracture	17 (15.7%)	146(23.7%)	48(27.0%)	6 (6%)	4 (11.1%)
New fracture	8 (7.4%)	96(15.6%)	52(29.2%)	10 (11.4%	6 (16.7%)
Underlying disease					
RA	26(24.1%)	467(75.7%)	83 (46.6%)	1(0.9%)	3(8.3%)
SLE	36(33.3%)	36(5.8%)	44(24.7%)	37(34.3%)	11(30.6%)
PM/DM	12(11.1%)	12(1.9%)	13(7.3%)	30(27.8%)	7(19.4%)
Vasculitis syndrome	4(3.7%)	4(0.6%)	0	13(12.0%)	4(11.1%)
PMR	2(1.9%)	12(1.9%)	1(0.6%)	0	1(2.8%)
Miscellaneous	23(21.3%)	41(6.6%)	37(20.8%)	23(21.3%)	8(22.2%)
Overlap syndrome					
RA+SLE	0	0	0	0	2
RA+PM/DM	1	0	0	0	0
RA+ miscellaneous	1	36	0	0	0
SLE+PM/DM	1	0	0	1	0
SLE+ miscellaneous	2	6	0	0	0
PM/DM+ miscellaneous	0	2	0	0	0
RA+PM/DM+ miscellaneous	0	1	0	0	0

*number of male patients

**prednisolone equivalent mg /day. In patients receiving methylprednisolone pulse therapy, 50mg/day (1mg/kg body weight) was set as the usual dose following pulse therapy for analytical convenience.

2.Process of updating guidelines

- Phase 1: Analysis of patients from three Japanese GIO cohorts (N=903) → Identification of factors predicting fractures by Cox proportional hazard analysis and categorization of factors → Determination of relative weights of each factor for calculation of scores (tentative scores obtained by conversion of parameter estimates into integers) → Identification of the cut-off score that efficiently separates fracture and non-fracture cases by receiver operating characteristics (ROC) analysis
- Phase 2: Analysis of patients (N=144) treated with high-dose GC from two primary prevention RCTs for GIO → Verification of cut-off score that efficiently separates fracture and non-fracture cases by ROC analysis
- Phase 3: Integrate and refine the results of phases 1 and 2, review GIO data from overseas and Japan, and determine the optimal cut-off score applicable to an intervention threshold for physicians to initiate drug therapy in clinical practice.
- Phase 4: Review systematically the data from randomized or controlled clinical trials to determine the recommendation grades of drug therapy by comprehensively assessing the efficacy for BMD and fractures.

→ Guidelines on the Management and Treatment for Glucocorticoid-induced Osteoporosis of the Japanese Society for Bone and Mineral Research: 2014 update

1. Phase 1 analysis

◆Identification of fracture predictors

Factor		Hazard ratio	95% confidence interval	P value
Age	1 year old increase	1.024	1.008 - 1.040	0.025
GC dose*	1mg/day increase	1.038	1.024 - 1.051	<0.0001
Lumbar bone mineral density (%YAM)	1% increase	0.979	0.968 - 0.991	0.006
Prior fragility fracture	+	3.412	2.409 - 4.832	<0.0001
Bisphosphonate therapy	+	0.472	0.302 - 0.738	0.001

*prednisolone equivalent

◆Categorization of factors predicting fractures

Factors		Reference	Hazard ratio	95% confidence interval	P value
Age (years)	50≤ <65	< 50	1.446	0.86-2.427	0.16
	65≤		2.108	1.214-3.660	0.08
GC dose (mg/day)*	5≤ <7.5	< 5	1.149	0.754-1.756	0.5186
	7.5 ≤		2.166	1.405-3.338	0.0005
Lumbar bone mineral density (%YAM)	70≤ <80	80 ≤	1.373	0.896-2.104	0.1452
	< 70		1.863	1.244-2.790	0.0025
Prior fragility fracture	+	-	3.485	2.457-4.943	<0.0001
Bisphosphonate therapy	+	-	0.481	0.307-0.753	0.061

*prednisolone equivalent

◆Tentative scores obtained by conversion of parameter estimates

Predictor		Parameter estimates by logistic regression	Tentative score*	Final score**
Age (years old)	< 50			0
	50≤ < 65	0.36890	4	2
	65 ≤	0.74589	8	4
GC dose (mg/day)***	< 5			0
	5 ≤ < 7.5	0.13867	2	1
	7.5 ≤	0.77294	8	4
Lumbar bone mineral density (%YAM)	80≤			0
	70 ≤ < 80	0.31724	4	2
	< 70	0.62218	7	4
Prior fragility fractures	-			0
	+	1.24846	13	7
Bisphosphonate therapy	-			0
	+	-0.73190	-8	-4

* Calculated 10 times for each parameter estimate, decimals rounded off, and rounded up to the next integer.

** Tentative score divided by 2, decimals rounded off, and rounded to an integer <10.

*** Prednisolone equivalent

2. Phase 2 analysis

◆Verification of the phase 1 results

		Male	Female
Number of subjects		1	143
Age /years (range)		57.0	48.3 ± 15.7(18-84)
Percentage of menopause (%)		-	49.0%
GC dose (mg/day)*		40	44.7 ± 17.7 (0-160)
	< 5	0	0
	5≤ <7.5	0	1 (0.7%)
	≥ 7.5	1	137 (99.3%)
Methylprednisolone pulse therapy		0	6 (4.1%)
Lumbar bone mineral density(%YAM)		86.8	94.8 ± 15.9
Prior fragility fracture		0	10 (7.0%)
New fracture		0	16 (11.2%)
Underlying disease			
RA		0	4 (2.8%)
SLE		0	48 (33.6%)
PM/DM		1	36 (25.2%)
Vasculitis syndrome		0	17 (11.9%)
PMR		0	1 (0.7%)
Miscellaneous		0	31 (21.7%)
Overlap	RA+SLE	0	2
	SLE＋PM/DM	0	1
Medications for osteoporosis			
None		0	1
Aminobisphosphonates		0	50
Non-aminobisphosphonates		0	34
SERM		0	0
Active vitamin D3		1	54
Vitamin K2		0	0
Miscellaneous		0	1

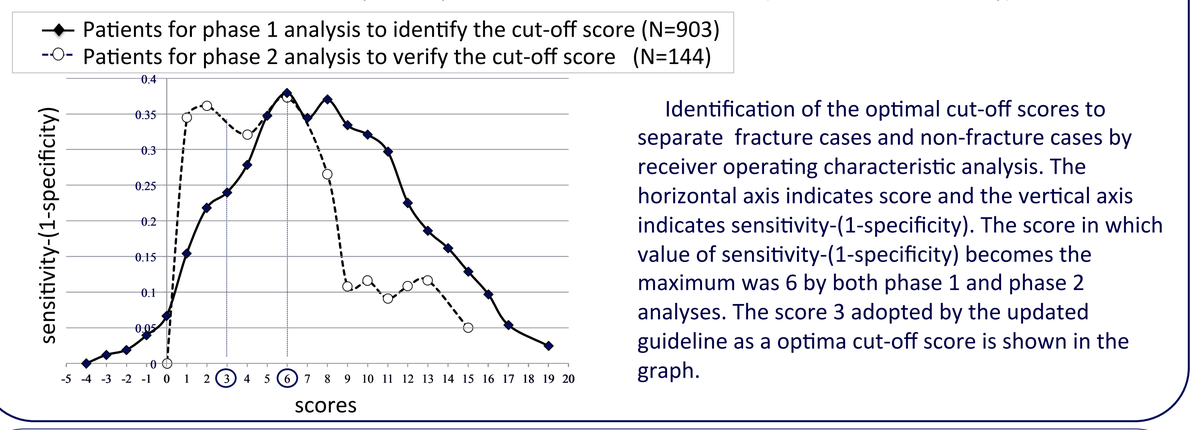
❖ Phase 1 and 2 analysis

◆Determining the optimal score for discrimination between fracture and non-fracture patients

Using the final scores, receiver operating characteristic (ROC) analysis was performed to obtain the optimal cut-off score. The score with the highest value (0.380) for Sensitivity- (1-Specicificty) was shown to be a score of 6. At a score of 6, the sensitivity, 1- specificity, true positive rate (%), true negative rate (%), false positive rate (%), and false negative rate (%) were 0.712, 0.332, 71.2%, 66.8%, 33.1%, and 28.8%, respectively. The area under the ROC curve (a measure of how well the score distinguished fracture and non-fracture groups) was 0.741

◆Verification of the optimal cut-off score from Phase 1

ROC analysis indicated that the score with the highest value (0.373) for Sensitivity-(1-Specicificty) was score 6 and this finding corresponded to the result obtained in phase 1. At the score 6, the sensitivity, 1- specificity, true positive rate (%), true negative rate (%), false positive rate (%), and false negative rate (%) were 0.600, 0.227, 60.0%, 77.3%, 22.7%, and 40.0%, respectively. The area under the ROC curve (an indicator of accuracy) was 0.741.



Identification of the optimal cut-off scores to separate fracture cases and non-fracture cases by receiver operating characteristic analysis. The horizontal axis indicates score and the vertical axis indicates sensitivity-(1-specificity). The score in which value of sensitivity-(1-specificity) becomes the maximum was 6 by both phase 1 and phase 2 analyses. The score 3 adopted by the updated guideline as a optima cut-off score is shown in the graph.

3. Determining the optimal cut-off score for intervention and outline of the updated guideline (Phase 3)

Committed or exposed to ≥ 3 months of oral glucocorticoid (GC) therapy

→ **General guidance**

→ **Assess clinical risk factors and calculate individual patient's score** (prior fragility fracture, Age, GC dose, BMD)

- **score ≥3** → **Treatment**: First-line treatment: alendronate, risedronate; Alternative treatment: teriparatide, ibandronate, alfacalcidol, calcitriol
- **score <3** → **Follow-up**: Assess clinical risk factors by calculating score

Risk factors		Score
Prior fragility fractures	No	0
	Yes	7
Age (years)	< 50	0
	50 ≤ < 65	2
	≥ 65	4
GC dose (PSL equivalent mg/day)	< 5	0
	5 ≤ < 7.5	1
	≥ 7.5	4
Lumbar BMD (%YAM)	≥80	0
	70 ≤ <80	2
	<70	4

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4. Recommendation of pharmacotherapy of GIO (Phase 4)

Medications		Recommendation grade*	Dose and Administration
bisphosphonates	alendronate	A	5mg daily, 35mg weekly, oral 900μg every 4 weeks, iv infusion
	risedronate	A	2.5mg daily, 17.5mg weekly, 75mg monthly, oral
	etidronate	C	200mg, 400mg 2 weeks per 3months, oral
	minodronate	C	1mg daily, 50mg every 4 weeks, oral
	ibandronate	B	1mg monthly, iv
active vitamin D3 analog	alfacalcidol	B	0.25μg, 0.5μg, 1μg daily, oral
	calcitriol	B	0.25μg, 0.5μg daily, oral
	eldecalcitol	C	0.5μg, 0.75μg daily, oral
teriparatide [recombinant human parathyroid hormone (1-34)]	teriparatide (rDNA origin)	B	20μg daily, sc
	teriparatide acetate	C	56.5μg, weekly, sc
vitamin K2	menatetrenone	C	45mg daily, oral
Selective estrogen-receptor modulators (SERM)	raloxifene	C	60mg daily, oral
	bazedoxifene	C	20mg daily, oral
humanized monoclonal antibody against RANKL	denosumab	C	60mg every 6 months, sc

* Recommendation grade
A: Recommend as the first line treatment
B: Recommend as the alternative treatment in cases of contraindications or early intolerance in the first line treatment or inadequate response to the first line treatment
C: Insufficient or limited evidence for the treatment of GIO to recommend