【 ORIGINAL ARTICLE 】

The Efficacy of Minodronate in the Treatment of Glucocorticoid-induced Osteoporosis

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Abstract:
Objective   To investigate the efficacy of minodronate in the treatment of glucocorticoid-induced osteoporosis (GIO).
Methods   The study population included patients in whom the administration of minodronate (50 mg, once every 4 weeks) had been newly started for the treatment of GIO in Niigata Rheumatic Center from 2012 to 2015. Patients who were bisphosphonate-naïve and those who switched from other bisphosphonates were classified into the naïve and switch groups, respectively. The changes in the bone mineral density (BMD) and bone metabolic markers after one year of minodronate treatment were retrospectively evaluated. We also compared the BMD and bone turnover marker changes of minodronate-naïve patients with those in whom alendronate or risedronate had been prescribed as a first bisphosphonate (control group).
Results   Minodronate was prescribed to 142 patients, and data were successfully obtained from 120 patients. New vertebral fractures were observed in 5 of the 142 patients; 1 fracture occurred during the cessation of minodronate for dental treatment, and 3 patients already had multiple vertebral fractures before the initiation of minodronate. The patients' tartrate-resistant acid phosphatase 5b (TRACP-5b) (-27.0%, p<0.001) and bone alkaline phosphatase (BAP) (-15.7%, p<0.01) levels were decreased, but no patients showed a decrease to below the normal range. One year of treatment with minodronate significantly increased the lumbar BMD in the naïve (+3.9%, p<0.001) and switch (+2.3%, p<0.001) groups. Although the femoral BMD did not change to a significant extent overall, the patients with a low young adult mean (YAM) (<80%) at baseline showed a significant increase in their femoral BMD (+2.1%, p=0.034) values. Compared with the control group, the minodronate-naïve group showed a significant decrease in the TRACP-5b levels and a significant increase in the lumbar BMD.
Conclusion   The administration of minodronate appears to be an effective treatment for GIO.

Key words: glucocorticoid-induced osteoporosis, bisphosphonate, minodronate, minodronic acid, bone mineral density, bone turnover marker

Introduction

Glucocorticoids are frequently used as immunosuppressive agents in the treatment of rheumatic diseases, including rheumatoid arthritis (RA), polymyalgia rheumatica (PMR) and systemic lupus erythematosus (SLE). Glucocorticoids increase bone resorption and reduce bone formation (1); thus, osteoporosis is one of the major side effects of glucocorticoid treatment. The administration of oral glucocorticoids that use more than 5 mg of prednisolone (or equivalent) leads to a reduction in the bone mineral density

(BMD) and increases the risk of fracture within 3 to 6 months after the initiation of therapy (2). Thus, the early implementation of preventive measures against glucocorticoid-induced osteoporosis (GIO) is strongly recommended.

In the 2017 American College of Rheumatology guideline for the prevention and treatment of GIO, oral bisphosphonates are recommended as the preferred first-line therapy in most clinical situations (3). The antifracture benefit and safety of oral bisphosphonates were closely evaluated in the guideline (3). The efficacy of alendronate and risedronate in patients receiving glucocorticoids was previously reported (4, 5). Minodronate is a third-generation nitrogen-containing bisphosphonate that was originally developed in Japan. Some studies have demonstrated the positive effect of minodronate on the BMD and the risk of fracture in the treatment of primary osteoporosis. (6, 7).

The effects of minodronate-in relation to the BMD elevation in the treatment of patients with primary osteoporosis-are reported to be comparable to those of alendronate. However, only a few reports have described the effect of minodronate on GIO. Kitamura et al. showed that daily minodronate increased the BMD and decreased levels of bone turnover markers in a total of 25 patients with GIO (8). Ebina et al. reported the effects of switching weekly alendronate (n= 44) or risedronate (n=40) to once-every-4-weeks minodronate on the BMD and bone turnover markers in rheumatoid arthritis patients, approximately 70% of whom were using glucocorticoids (9). After 12 months, the lumbar and total hip BMD and bone turnover markers were significantly ameliorated in patients who had switched to minodronate compared with those who had continued alendronate or riesedronate.

The purpose of this study was to investigate the effects of minodronate on bone turnover markers and the BMD among patients treated with glucocorticoids.

Materials and Methods

Study population

We retrospectively investigated the patients in whom the administration of minodronate had been initiated for the prevention or treatment of GIO in Niigata Rheumatic Center between December 2012 and June 2015. The data of patients who started oral bisphosphonate other than minodronate for the treatment of GIO between 2013 and 2014 were also obtained as a control group.

The decision to start bisphosphonates was made according to the guidelines on the management and treatment of glucocorticoid-induced osteoporosis published by the Japanese Society for Bone and Mineral Research (10). In our institution, we started prescribing minodronate once every four weeks as an external prescription from October 2011 and as an internal prescription from June 2013. The patients-including bisphosphonate-naïve patients and those who had been treated with bisphosphonate-were asked to indicate their preferred oral bisphosphonate dosing interval; minodronate was initiated for the patients who preferred a four-week interval. After minodronate, risedronate (monthly) was approved as an external prescription from April 2013. After the approval of monthly risedronate, the patients who had used risedronate daily or weekly could choose whether they wished to use minodronate (once every four weeks) or risedronate (monthly).

The present study was a retrospective observational study, and the examinations and treatments were performed within the context of routine care. We did not obtain an agreement document from the patients. The publication of this study was approved by the ethics committee of Niigata Rheumatic Center (approval number: 2017-004). The study was conducted in accordance with the Declaration of Helsinki.

The treatment and evaluation

The patients received minodronate (50 mg, once every 4 weeks) for up to 12 months. The effectiveness of minodronate was assessed by measuring the BMD and the serum bone turnover marker levels at baseline and after 1 year of treatment. The lumbar spine BMD data of patients with vertebral fracture were excluded, as compression can lead to the overestimation of the lumbar BMD. The bone formation marker bone alkaline phosphatase (BAP) and the bone resorption marker tartrate-resistant acid phosphatase 5b (TRACP-5b) were both measured as bone turnover markers. However, due to changes in the medical insurance policy of Japan, we were unable to measure the TRACP-5b level in the one-year follow-up examinations that were performed after January 2016. The BMD of the L1-L4 lumbar vertebrae and the femoral neck was measured. In order to report the new fracture occurrence during treatment, X-ray images of the thoracic and lumbar vertebrae and the femoral neck were obtained at baseline and at the one-year follow-up examination, as well as any time the patients had noticeable symptoms, or when new fractures were reported.

Statistical analyses

The BMD and serum bone turnover marker levels at baseline and at the one-year follow-up examination were compared using Wilcoxon's signed rank test. Differences between each groups were compared using a nonparametric Wilcoxon's rank sum test for continuous variables and Fisher's exact test for categorical variables. Multiple regression analyses were performed to determine the predictive factors for the lumbar BMD after one year. We selected seven candidate factors: the BMD at baseline, age, gender, smoking history, serum creatinine, dose of prednisolone, and the usage of biologics previously reported to affect the BMD; we also added the usage of minodronate. All of the statistical analyses were performed using the SPSS software program (ver. 19; SPSS, Chicago, USA). p values of <0.05 were considered to indicate statistical significance.

Table 1.   The Baseline Characteristics of the Patients.

	over all n=120	naïve n=52	switch n=68
Age (years)	64.0±14.0	65.7±12.6	62.8±14.9
Sex, male/female	37/83	18/34	19/49
Previous treatment (number)	Risedronate (50), Alendronate (17), Etidronate (1), naïve (52)	naïve (52)	Risedronate (50), Alendronate (17), Etidronate (1)
Basal disease (number)	RA (82), PMR (8), SLE (11), Vasculitis (4), BD (3), SSc (3), PM (2), SS (3), MCTD (1), AOSD (1), SNSA (1), DM (1)	RA (43), PMR (4), SLE (1), Vasculitis (2), BD (1), SSc (1)	RA (39), PMR (4), SLE (10), Vasculitis (2), BD (2), SSc (2), PM (2), SS (3), MCTD (1), AoSD (1), SNSA (1), DM (1)
Smoking, past/current	34/8	15/3	19/5
Serum creatinine (mg/dL)	0.72±0.28	0.76±0.29	0.70±0.28
eGFR (mL/min)	76.0±21.7	71.8±20.0	79.3±22.4
Dose of prednisolone (g/day)	6.5±6.8	6.9±5.1	6.2±8.0
Biologics usage, n (%)	33 (27.5)	15 (28.8)	18 (26.4)
Immunosuppresive agents usage (number)	ETN (12),ADA (6), IFX (5), TCZ (3), GLM (3), ABT (3), CZP (1) MTX (51), MZR (33), SASP (31), BUC (28), TAC (17), IGU (8), CyA (6), AZP (2)	ETN (5), ADA (2), IFX (3), TCZ (2), GLM (2), ABT (0), CZP (1) MTX (24), MZR (16), SASP (15), BUC (16), TAC (8), IGU (4), CyA (2), AZP (0)	ETN (7), ADA (4), IFX (2), TCZ (1), GLM (1), ABT (3), CZP (0) MTX (27), MZR (17), SASP (16), BUC (12), TAC (9), IGU (4), CyA (4), AZP (2)
Existing vertebral fractures, n (%)	15 (12.5)	6 (11.5)	9 (13.2)
Lumber BMD (g/cm^2)	0.995±0.216	0.937±0.196	1.044±0.222
Lumber BMD (YAM %)	87.5±17.7	82.3±16.0	91.7±18.1
Lumber BMD (T-score)	-1.233±1.761	-1.343±1.026	-0.870±1.878
Total hip BMD (g/cm^2)	0.768±0.149	0.754±0.135	0.779±0.159
Total hip BMD (YAM%)	83.7±15.5	82.0±13.9	85.1±16.6
Total hip BMD (T-score)	-1.215±1.155	-1.343±1.026	-1.115±1.244
Serum BAP (U/L)	14.0±7.7	16.3±8.3	12.4±6.9
Serum TRACP5b (mU/dL)	412.5±230.0	517.7±235.3	338.6±196.4

RA: rheumatoid arthritis, PMR: polymyalgia rheumatica, SLE: systemic lupus erythematosus, BD: Beçhet disease, SSc : systemic scleroderma, PM : polymyositis, SS : Sjögren's syndrome, MCTD : mixed connective tissue disease, AOSD : adult-onset Still's disease, SNSA : seronegative spondyarthritides, DM : dermatomyositis, eGFR : estimated glomerular filtration rate, ETN : etanercept, ADA : adalimumab, IFX : infliximab, TCZ : tocilizumab, GLM : golimumab, ABT : abatacept, CZP : certolizumab pegol, MTX: methotrexate, MZR: mixoribine, SASP: salazosulfapyridine, BCL: bucillamine, TAC: tacrolimus, IGU: iguratimod, CyA: cyclosporine A, AZP: azathioprine, BMD: bone mineral density, BAP : bone alkaline phosphatase, TRACP-5b : tetrate-resistant acid phosphotase 5b

Results

Patient characteristics

Clinical data were successfully obtained at the baseline and 1 year later from 120 of 142 patients who had started treatment with minodronate (once every 4 weeks). Fifty-two patients were bisphosphonate-naïve (naïve group), and 68 had switched from other bisphosphonates (switch group). Twenty-two patients could not be followed up for the following reasons: changing hospital (n=7), discontinuance due to dental treatment (n=4), discontinuance due to side effects (n=7, for gastrointestinal symptoms, n=2; bone pain, n=4; itching sensation, n=1), discontinuance due to new fracture (n=3), and switching to teriparatide at the patient's request (n=1). All three patients who developed new fracture were switched to teriparatide. All seven patients who had side effects recovered from their symptoms after the cessation of minodronate.

The baseline characteristics of the patients are summarized in Table 1. Overall, the average age was 62.81±14.9 years (range 22-84 years), 69.2% of the patients were women, and the average dose of prednisolone was 6.2±7.96 mg. The basal diseases included RA (n=82), SLE (n=11), PMR (n=8), vasculitis [n=4 (microscopic polyangiitis, n=1; granulomatosis, n=1; Takayasu arteritis, n=1; unclassifiable vasculitis, n=1)], Behçet's disease (n=3), and polymyositis (n=2). Pre-existing vertebral fractures were observed in 15 patients (naïve group, n=6; switch group, n=9). The bisphosphonates that had previously been used by the patients in the switch group included risedronate (n=50), alendronate (n=17), and etidronate (n=1). No patients in t naïve group and six patients in the switch group used activated vitamin D3 in combination.

Response to minodronate

Among the 120 patients, new vertebral fractures occurred in 2 patients (naïve group, n=1; switch group, n=1). One of these fractures occurred while the administration of mino-

Table 2.   The Characteristics of the Patients who Suffered New Vertebral Fractures.

Age	Sex	Dose of prednisolone (mg)	Previous treatment	Basal disease	Femoral YAM(%) at baseline	Existing vertebral fracture	Duration of usage of minodronic acid before the new fracture (months)	Treatment after the fracture
77	female	5.0	naïve	RA	69	multiple	10(during drug holidays)	minodronate
58	female	4.5	alendronate	RA	56	multiple	12	minodronate
86	female	5.0	naïve	RA	84	multiple	2	teriparatide
63	female	10.0	risedronate	DM	68	(-)	7	teriparatide
68	female	2.0	risedronate	RA	88	(-)	11	teriparatide

YAM: young adult mean, RA: rheumatoid arthritis, DM: dermatomyositis

Table 3.   The Characteristics of the Patients at after One Year of Minodronate Treatment.

After 1-year of treatment	over all n=120	naïve n=52	switch n=68
Dose of prednisolone (mg/day)	4.8±3.3	5.1±3.7	4.5±2.9
New vertebral fractures, n (%)	2 (1.7)	1 (1.9)	1 (1.5)
Lumber BMD (g/cm^2)	1.027±0.225	0.970±0.200	1.070±0.234
Lumber BMD (YAM%)	90.5±18.7	85.4±16.5	94.4±19.4
Lumber BmD (T-score)	-0.756±1.832	-1.080±1.788	-0.509±1.840
Total hip BMD (g/cm^2)	0.776±0.148	0.753±0.132	0.792±0.158
Total hip BMD (YAM%)	84.3±15.4	81.9±13.5	86.1±16.5
Total hip BMD (T-score)	-1.168±1.150	-1.342±1.020	-1.037±1.230
Serum BAP (U/L)	10.9±4.8	11.4±6.1	10.5±3.5
Serum TRACP5b (mU/dL)	264.5±131.2	299.5±161.9	248.6±125.3

BMD: bone mineral density, BAP: bone alkaline phosphatase, TRACP-5b: tetrate-resistant acid phosphatase 5b

dronate had been stopped for dental treatment. Both patients had already had multiple vertebral fractures at the baseline examination, with baseline femoral young adult mean (YAM) values of 69% in one and 56% in the other. The clinical characteristics of the patients who suffered new fractures during treatment with minodronate are summarized in Table 2; these included three patients who switched to teriparatide after the fracture. There were no significant differences in the age, dose of prednisolone, or femoral YAM at baseline between the patients with and without the occurrence of new fracture. However, the rate of existing vertebral fracture was significantly higher in patients with new fracture than in those without new fracture (p=0.0105).

The clinical data obtained after one year of treatment with minodronate are summarized in Table 3.

The level of TRCP-5b (reference range 120-420 mU/dL)- a bone resorption marker-was significantly reduced after 1 year of minodronate treatment (n=106, -27.0% in total, p< 0.001). This reduction was observed in both the naïve group (-35.5%, p<0.01) and the switch group (-22.3%, p<0.01), and exceeded the minimum significant change (MSC) for TRACP-5b (12.4% change) (Fig. 1a). On comparing the patients based on their baseline TRACP-5b levels (high-level group, >420 mU/dL, normal group; <420 mU/dL; baseline characteristics summarized in Table 4a), a larger change was observed in the high-level group than in the normal group

(-39.7% vs. 19.4%) (Fig. 1b). The TRACP-5b level did not fall below the reference range in any of the patients.

The levels of BAP (reference range: 3.7-20.9 U/L in males, 2.9-14.5 in premenopausal females, 3.8-22.6 in post-menopausal females)-a bone formation marker-were also significantly reduced after 1 year of treatment with minodronate (-15.7% in total, p<0.01). Although both the naïve group (-25.3%, p<0.001) and the switch group (-7.5%, p< 0.001) showed statistically significant changes, only the naïve group reached the MSC of BAP (23.1% change) (Fig. 2a). However, among the patients high baseline levels of BAP (above the reference range of BAP), the BAP value was reduced significantly beyond the MSC (45.1% in total, 50.8% in the switch group; baseline characteristics summarized in Table 4b). The BAP level did not fall below the reference range in any of the patients (Fig. 2b).

Minodronate treatment produced a significant increase in the lumbar spine BMD (3.0% from baseline, p<0.001). Both the naïve group (3.9%, p<0.001) and the switch group (2.3%, p<0.001) showed significant increases in their lumbar spine BMD values (Fig. 3). No significant differences were observed in the total femoral neck BMD among the total population (0.8% from baseline, p=0.137), the naïve group (0.01%, p=0.781), or the switch group (1.5%, p=0.105) (Fig. 4a). However, among the patients with a low baseline YAM value (<80%), the BMD of the femoral neck
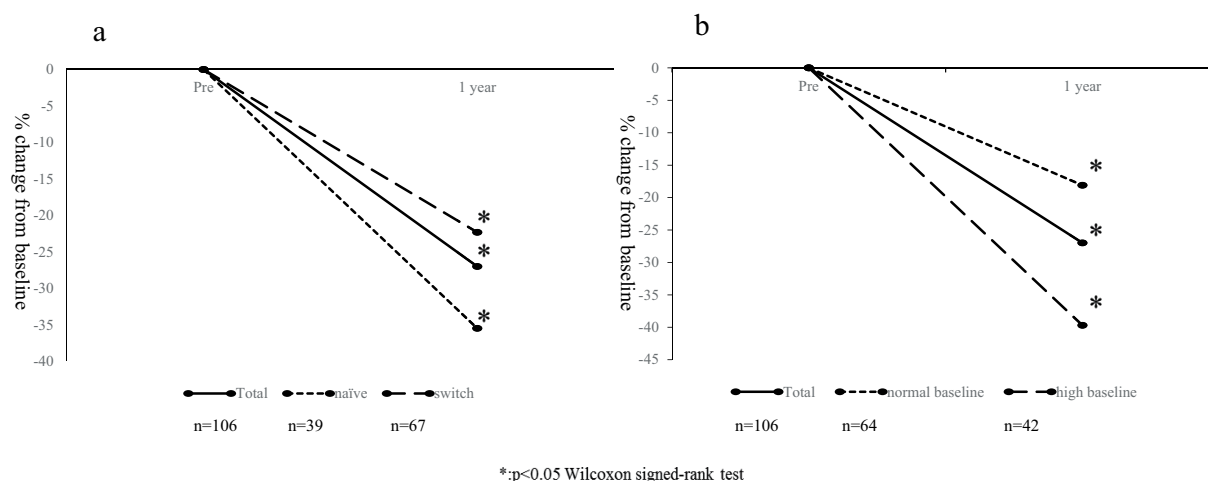
Figure 1. a: The changes in the TRACP-5b levels of the naïve and switch groups. b: The changes in the TRACP-5b levels of the high-baseline and normal-baseline patients.

was significantly increased (2.1% from baseline, p=0.034) after 1 year of treatment with minodronate (Fig. 4b). The baseline characteristics of patients with high and low YAM are summarized in Table 4c and 4d. The cut-off of YAM at 80% was determined because YAM <80% is regarded as a risk factor of GIO in the guidelines for the management and treatment of GIO of the Japanese Society of Bone and Mineral Research 2014 (10).

Among the 82 patients with RA, 33 were using biological disease-modifying antirheumatic-drugs (bDMARDs). Patients with bDMARDs tended to be younger (63.4±10.3 vs. 67.9±13.1, p=0.021) and the dose of prednisolone smaller (4.1±1.9 vs. 5.6±4.7, p=0.031) than those not taking these agents. There were no significant differences in other baseline characteristics (estimated glomerular filtration rate, lumbar BMD, total hip BMD, TRACP-5b level, BAP level) between patients taking or not taking bDMARDs. The change in the TRACP-5b level (-33.1%±20.9% vs. -25.4%±31.0%, p=0.379), BAP level (-16.1%±23.0% vs. -6.5%±852%, p=0.975), lumbar BMD (3.3%±3.2% vs. 3.2%±3.3%, p=0.871), and total hip BMD (1.2±4.2% vs. 0.0±3.8, p=0.639) were not significantly different based on the use of bDMARDs. There were also no significant differences in the change in the BMD or bone turnover markers based on the use of csDMARDs (methotrexate, mixoribine, salazosulfapyridine, bucillamine, and tacrolimus).

The total dose of prednisolone decreased during 1 year of treatment with minodronate (6.5±6.8 mg vs. 4.8±3.3 mg, p< 0.001).

A comparison to treatment with other oral bisphosphonates

Clinical data were successfully obtained from 55 of 63 patients who started alendronate or risedronate for the treatment of GIO as a first-line therapy (control group). Eight patients could not be followed up for the following reasons: changing hospital (n=1), discontinuance due to dental treatment (n=1), discontinuance due to side effects (n=3, for gas-

trointestinal symptoms, n=2; cramp in leg, n=1), discontinuance due to new fracture (n=3). Their clinical characteristics are summarized in Table 5.

Thirteen alendronate-using patients and 41 risedronate-using patients were included. There was no significant differences in the age, sex, or dose of prednisolone compared with the minodronate-naïve group (minodronate group). However, the TRACP-5b level at baseline was higher in the minodronate group than in the control group. After 1-year treatment, both groups showed significant increases in the lumbar BMD from baseline. The change in the lumber BMD was significantly larger in the minodronate group than in the control group (+3.0%±3.3% vs. +1.4%±4.9%, p= 0.019) (Fig. 5a).

The results of the multiple regression analysis are shown in Table 6. The usage of minodronate and the lumbar BMD at baseline were determined to be important variables for improving the lumbar BMD after one year. The TRACP-5b level was decreased after 1-year treatment of minodronic acid but not in the control group (-35.5%±28.4% vs.+1.6%± 53.1%, p=0.001) (Fig. 5c). The change rate of total hip BMD and the BAP level were not markedly different between the two groups (Fig. 5b and d). During the one-year treatment period, the control group experienced three new vertebral fractures, and the minodronate group experienced two vertebral fractures. There were no statistically significant differences in the fracture rate between the control group and minodronate group.

Discussion

The present study showed that minodronic acid reduced the bone turnover marker levels and ameliorated the changes in the lumbar and femoral BMD in patients using glucocorticoids. Minodronate appears to be effective for treating GIO.

We showed that treatment with minodronate was associated with a significant decrease in bone turnover markers

Table 4.

a. The baseline characteristics in the patients with TRACP-5b levels of the high baseline and normal baseline

	normal TRACP-5b level at baseline n=64	high TRACP-5b level at baseline n=42	p
Age (years)	62.4±16.0	66.5±9.9	0.479
Sex, male/female	23/41	10/32	0.205
Previous treatment (number)	Alendronate(11), Risedronate(34), Etidronate(1)	Alendronate(5), Risedronate(12)	
Basal disease (number)	RA(37), SLE(10), PMR(5), Vasculitis(4), SSc(3), BD(2), PM(1), AOSD(1), SNSA(1)	RA (33), SLE(1), PMR(2), SSc(2), Vasculitis(1), SS(1), PM(1), MCTD(1)	
Dose of prednisolone (g/day)	6.1±5.7	7.2±8.4	0.365

RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, PMR: polymyalgia rheumatica, SSc: systemic scleroderma, BD: Beçhet disease, PM: polymyositis, AOSD: adult-onset Still's disease, SNSA: seronegative spondyarthritides, SS: Sjögren's syndrome, PM: polymyositis, MCTD: mixed connective tissue disease

b. The baseline characteristics in the patients with BAP levels of the high baseline and normal baseline

	normal BAP level at baseline n=74	high BAP level at baseline n=46	p
Age (years)	63.4±15.6	64.7±11.2	0.711
Sex, male/female	27/47	10/36	0.106
Previous treatment (number)	Alendronate(12), Risedronate(38), Etidronate(1)	Alendronate(5), Risedronate(12)	
Basal disease (number)	RA(47), SLE(10), PMR(7), SSc(3), Vasculitis(3), PM(1), SS(1), AOSD(1), SNSA(1)	RA (35), SLE(1), PMR(1), Vasculitis(1), SS(2), BD(3), PM(1), MCTD(1), DM(1)	
Dose of prednisolone (g/day)	7.4±8.3	4.9±2.6	0.362

RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, PMR: polymyalgia rheumatica, SSc: systemic scleroderma, BD: Beçhet disease, PM: polymyositis, AOSD: adult-onset Still's disease, SNSA: seronegative spondyarthritides, SS: Sjögren's syndrome, PM: polymyositis, MCTD: mixed connective tissue disease, DM: dermatomyositis

c. The baseline characteristics in the patients with lumbar BMD values in the baseline YAM<80% and YAM≥80%

	lumber spine BMD<80 at baseline n=38	lumber spine BMD≥80 at baseline n=67	p
Age (years)	67.5±10.5	61.9±23.2	0.09
Sex, male/female	9/29	23/44	0.279
Previous treatment (number)	Alendronate(1), Risedronate(14)	Alendronate(13), Risedronate(30)	
Basal disease (number)	RA(31), Vasculitis(1), SLE(1), PMR(1), BD(1)	RA (40), SLE(8), PMR(4), SLE(8), SSc(2), Vasculitis(4), BD(1), MCTD(1)	
Dose of prednisolone (g/day)	4.4±4.0	7.2±8.0	0.089

BMD: bone mineral density, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, PMR: polymyalgia rheumatica, BD: Beçhet disease, SSc: systemic scleroderma, MCTD: mixed connective tissue disease

d. The baseline characteristics in the patients with total hip BMD values in the baseline YAM<80% and YAM≥80%

	total hip BMD<80 at baseline n=45	total hip BMD≥80 at baseline n=75	p
Age (years)	67.0±10.3	61.9±23.2	0.352
Sex, male/female	8/37	29/46	0.024
Previous treatment (number)	Alendronate(8), Risedronate(19)	Alendronate(9), Risedronate(30), Etidronate(1)	
Basal disease (number)	RA(32), PMR(5), SLE(3), Vasculitis(2), SS(1), PM(1), SSc(1)	RA (50), SLE(8), PMR(3), BD(3), SSc(2), Vasculitis(2), SS(2), PM(1), DM(1), AOSD(1), MCTD(1), SNSA(1)	
Dose of prednisolone (g/day)	5.5±5.9	7.0±7.4	0.024

RA: rheumatoid arthritis, PMR: polymyalgia rheumatica, SLE: systemic lupus erythematosus, SS: Sjögren's syndrome, PM: polymyositis, SSc: systemic scleroderma, BD: Beçhet disease, PM: polymyositis, DM: dermatomyositis, AOSD: adult-onset Still's disease, MCTD: mixed connective tissue disease, SNSA: seronegative spondyarthritides
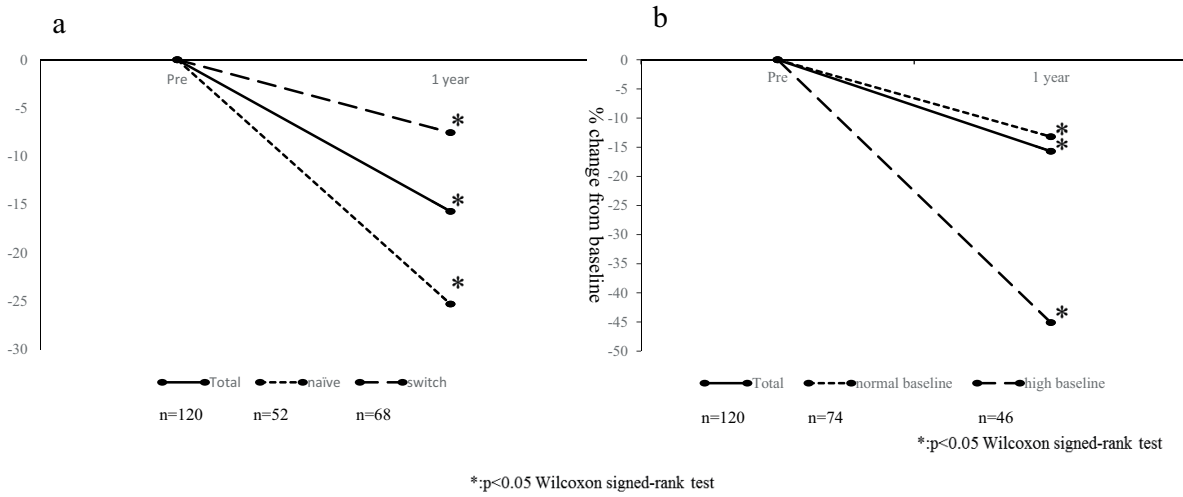
Figure 2.   a: The changes in the BAP levels of the naïve and switch groups. b: The changes in the BAP levels of the high-baseline and normal-baseline patients.
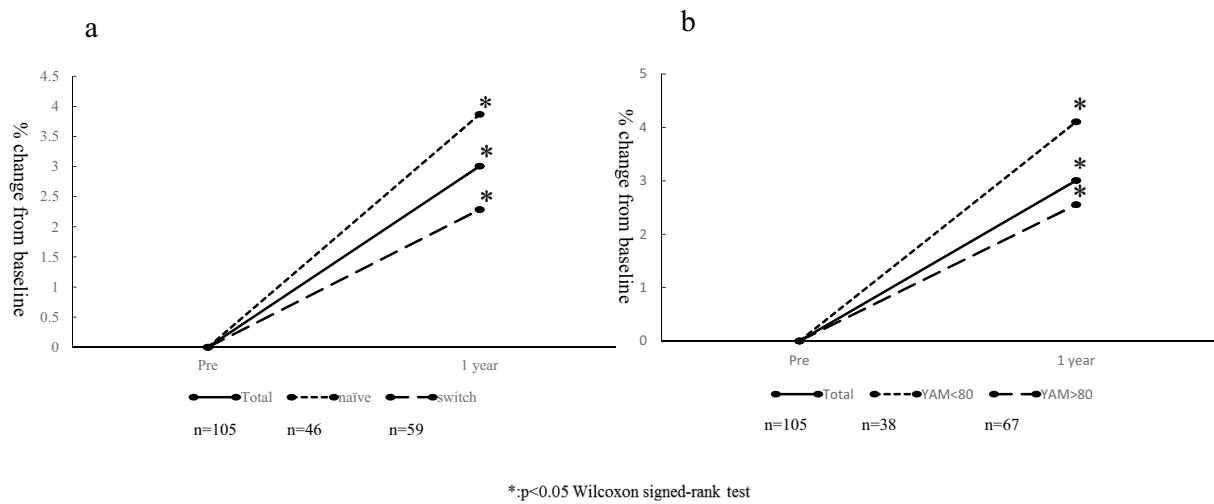

Figure 3.   a: The changes in the lumbar BMD values of the naïve and switch groups. b: The changes in the lumbar BMD values of the baseline YAM<80% and baseline YAM≥80% patients.
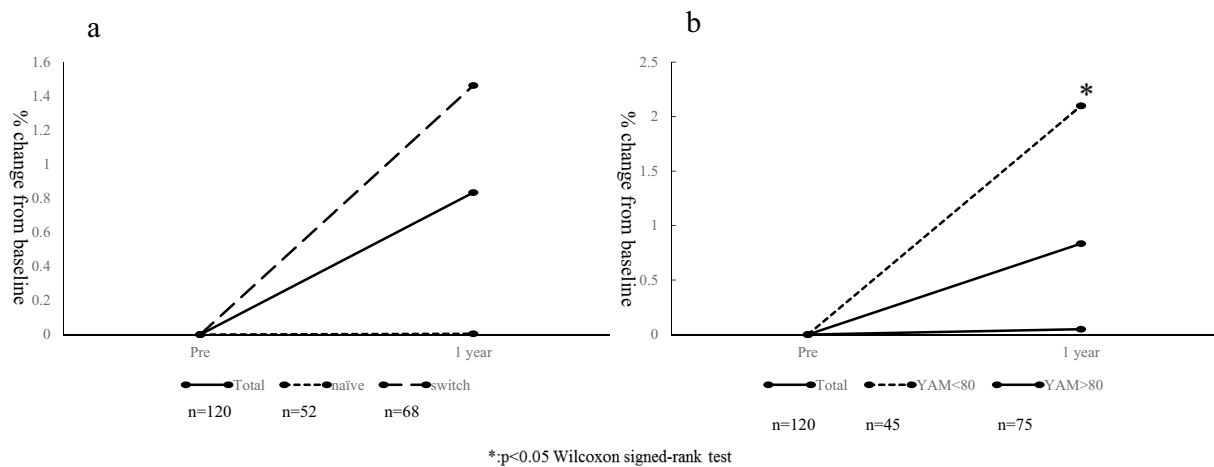

Figure 4.   a: The changes in the femoral BMD values of the naïve and switch groups. b: The changes in the femoral BMD values of the baseline YAM<80% and baseline YAM≥80% patients.

Table 5.   The Characteristics of the Patients in Control Group and Minodronate Group.

	control n=55	minodronate n=52	p
Age (years)	64.9±14.9	65.7±12.6	0.362
Sex, male/female	17/38	18/34	0.837
Bisphosphonate usage (number)	Alendronate (14), Risedronate (41)	Minodronate (52)	
Basal disease (number)	RA (42), Vasculitis (4), SLE (3), Gout (2), BD (1), PM (1), DM (1), SSc (1)	RA (43), PMR (4), SLE (1), Vasculitis (2), BD (1), SSc (1)	
Smoking, past/current	17/6	15/3	0.837/0.490
Serum creatinine (mg/dL)	0.75±0.28	0.76±0.29	0.310
eGFR (mL/min)	68.3±27.5	71.8±20.0	0.209
Dose of prednisolone (g/day)	7.1±7.5	6.9±5.1	0.752
Biologics usage, n (%)	12 (21.8)	15 (28.8)	0.505
Immunosuppresive agents usage (number)	ETN (3), ADA (3), IFX (1), TCZ (1), GLM (2), ABT (2), CZP (0) MTX (19), MZR (4), SASP (10), BUC (15), TAC (12), IGU (9), CyA (2), AZP (2)	ETN (5), ADA (2), IFX (3), TCZ (2), GLM (2), ABT (0), CZP (1) MTX (24), MZR (16), SASP (15), BUC (16), TAC (8), IGU (4), CyA (2), AZP (0)	
Existing vertebral fractures, n (%)	9 (16.4)	6 (11.5)	0.582
Lumber BMD (g/cm^2)	0.998±0.226	0.937±0.196	0.245
Lumber BMD (YAM %)	87.8±18.6	82.3±16.0	0.181
Total hip BMD (g/cm^2)	0.754±0.134	0.754±0.135	0.920
Total hip BMD (YAM%)	82.3±13.8	82.0±13.9	0.889
Serum BAP (U/L)	15.9±7.8	16.3±8.3	0.886
Serum TRACP5b (mU/dL)	403.4±148.8	517.7±235.3	0.049

RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, BD: Beçhet disease, PM: polymyositis, DM: dermatomyositis, SSc: systemic scleroderma, eGFR: estimated glomerular filtration rate, ETN: etanercept, ADA: adalimumab, IFX: infliximab, TCZ: tocilizumab, GLM: golimumab, ABT: abatacept, CZP: certolizumab pegol, MTX: methotrexate, MZR: mixoribine, SASP: salazosulfapyridine, BCL: bucillamine, TAC: tacrolimus, IGU: iguratimod, CyA: cyclosporine A, AZP: azathioprine, BMD: bone mineral density, BAP: bone alkaline phosphatase, TRACP-5b: tetrate-resistant acid phosphotase 5b

levels. Bisphosphonates are effective anti-resorptive agents, which suppress bone turnover by inhibiting osteoclast activity. Minodronate is a third-generation bisphosphonate that contains an amino group in the imidazole ring. Third-generation bisphosphonates, including minodronate and risedronic acid, strongly inhibit farnesyl diphosphate synthase and have very high anti-resorptive potency compared with other bisphosphonates (11). Minodronate was reported to be 10 times more effective than alendronate and 100 times more effective than pamidronate in inhibiting bone resorption in a rat model (12). In this study, minodronate significantly reduced the TRACP-5b level in both the naïve and switch groups, indicating the strong anti-resorptive effect of minodronate. The BAP level was also reduced during minodronate therapy, especially in patients with relatively high baseline BAP levels. These results were in line with the results of previous studies on minodronate (13). Despite the strong inhibition of bone resorption, minodronate did not excessively reduce the TRACP-5b and BAP levels, suggesting that minodronate is an efficient treatment for improving bone turnover. The TRACP-5b level was significantly lower in the minodronate group than in patients treated with other bisphosphonates. While the differences in the baseline characteristics should be considered in the interpretation of our findings, the minodronate group had a higher TRACP-5b level at baseline and a lower TRACP-5b level after one year of treatment, potentially suggesting a stronger inhibition ef-

fect on bone resorption with minodronate.

We also showed the effects of minodronate on the BMD. A previous study compared the effects of risedronate and minodronate in the treatment of primary osteoporosis in Japan and found that minodronate showed earlier efficacy, as measured by the BMD and bone turnover marker levels (14). Another study reported that primary osteoporosis patients who switched from alendronate and risedronate showed significantly elevated YAM values (13). In our study, treatment with minodronate significantly increased the lumbar BMD in both the naïve and switch groups. The femoral BMD values of the overall population did not change to a significant extent; this may be-in part-because our study included patients with relatively high baseline BMD values who were using minodronate for the prevention of osteoporosis. When the patients were divided according to their baseline BMD values, we confirmed that the patients with lower baseline BMD values showed a significant increase in their femoral BMD values. A multiple regression analysis showed that an elevated lumbar BMD was associated with choosing minodronate over other bisphosphonates. The long-term use of glucocorticoids increases the risk of vertebral fracture in particular, due to the greater effects of glucocorticoids on trabecular bone than on cortical bone (3). Higher efficacy of minodronate in elevating lumber BMD might be suitable for treating GIO.

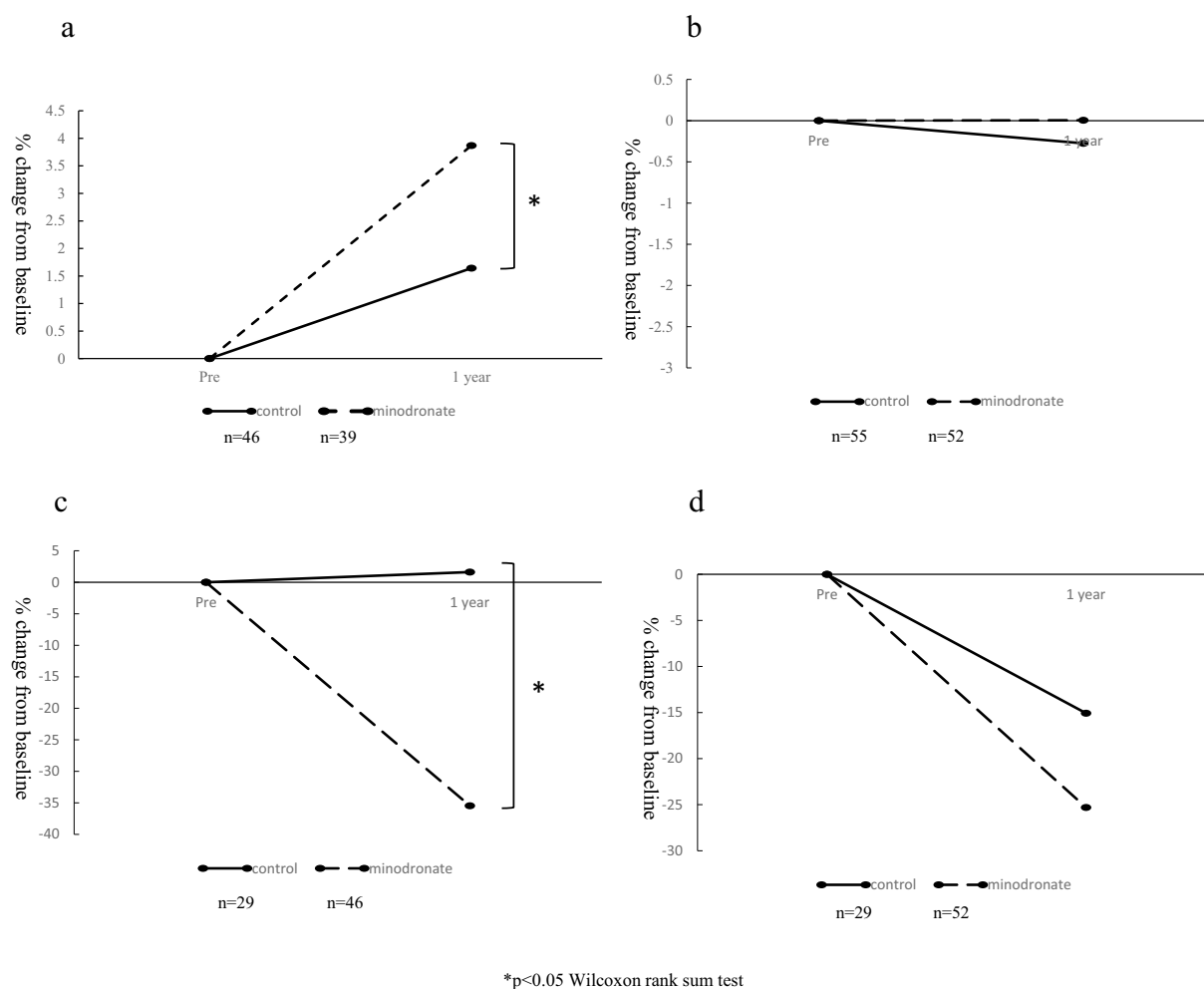In a previous study on GIO, the rate of vertebral fracture

a

b

c

d

*p<0.05 Wilcoxon rank sum test

Figure 5. **The changes in the lumbar BMD value of the control and minodronate groups. a: The changes in the femoral BMD value of the control and minodronate groups. b: The changes in the TRACP-5b levels of the control and minodronate groups. c: The changes in the BAP levels of the control and minodronate groups.**

Table 6. **Multiple Logistic Regression Analysis for Lumber BMD after 1 Year.**

	lumber BMD after 1 year of treatment	
	PRC (95% CI)	p
lumber BMD at baseline	-0.2252 (-0.4774 to 0.0271)	0.0794
age	0.0675 (-0.1811 to 0.3160)	0.5904
male sex	0.4972 (-0.1602 to 1.1546)	0.1362
smoking history	-0.0598 (-0.6574 to 0.5381)	0.8427
serum creatinine	-0.1646 (-0.4441 to 0.1148)	0.1403
treatment with minodronate	0.4554 (0.0141 to 0.8966)	0.0433
dose of predonisolone	-0.2161 (-0.4623 to 0.0301)	0.0845
usage of biologics	0.1593 (-0.3397 to 0.6583)	0.5269

BMD: bone mineral density

in the placebo group (without bisphosphonates) was reported to be 3.7% (mean age: 54±15 years, mean dose of predniso-lone: 11 mg; 27% of patients had RA) (4). In our study, new vertebral fracture was observed in 5 out of 142 patients (3.5%) treated with minodronate. However, the patients were older and the dose of prednisolone lower in our study than in the previous one, and the underlying disease was differ-ent, so it is difficult to compare the results. The incidence of new fracture was observed at a similar frequency in minodronate-naïve patients and the control group (alendro-nate or risedronate group) in our study, although the num-bers of fractures were too small to compare. Many studies have shown that a low BMD is an effective predictor of os-teoporotic fracture (15-17). Although we were unable to

evaluate the rate of fracture sufficiently, our results suggest that minodronate is a promising therapy for the prevention of lumbar and hip fracture.

New fracture was more frequently observed in patients with existing vertebral fracture at baseline. Although the comparison was performed in a relatively small number of patients, we may need to practice particular caution when treating patients with existing vertebral fracture.

Recently, anti-inflammatory treatments including bDMARDs have been reported to reduce the rate of bone loss in RA patients (18). In our study, the use of bDMARDs did not have a significant effect on the BMD or levels of bone turnover makers. However, our study did not take into consideration the disease activity of RA. Further studies are needed to assess the effects of bDMARDs and conventional synthetic DMARDs with bisphosphonates.

A strong correlation is reported to exist between the cumulative prednisolone dose and reductions in the lumbar and hip BMD (2). In the across-study evaluation, no statistically significant relationship was noted between the daily prednisolone dose and the lumbar and hip BMD (2). Although the dose of daily prednisolone was decreased over the one-year course of our study, the cumulative dose of prednisolone was increased. Continuing prednisolone throughout the study period was considered to have a negative effect on the lumbar and hip BMD.

At present, minodronate remains a grade C recommendation in the guidelines on the management and treatment of GIO published by the Japanese Society for Bone and Mineral Research (10). However, according to our results, minodronate showed satisfactory results in the treatment of GIO in both the naïve and switch groups.

The present study is associated with some limitations. It was a single-center, retrospective study with a relatively small number of patients and a short observation period. Among many kinds of bone turnover markers have been reported, we were only able to assess two of those markers. Furthermore, we were unable to assess the anti-fracture efficacy of minodronate directly. Instead, we measured the bone turnover marker levels and BMD, which are widely accepted as surrogate endpoints in the evaluation of anti-fracture treatments. However, to our knowledge, the present study includes the largest number of patients among studies reporting the effects of minodronate on GIO.

The administration of minodroniate (once every four weeks) improved the bone turnover marker levels and BMD values of rheumatic disease patients using glucocorticoids who received minodronate as a first bisphosphonate and those who switched from conventional bisphosphonates. Minodronate is considered to be highly effective for the treatment of GIO. Further studies are needed to clarify the efficacy of minodronate in comparison to other bisphosphonates.

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