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Pharmacist-initiated interventions to test quantitative bone mineral density and prescribe osteoporosis medications to prevent steroid-induced osteoporosis

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Fragility fractures associated with glucocorticoid-induced osteoporosis (GIO) can markedly impair quality of life. However, only 20% of patients are treated in compliance with the relevant management guidelines, and bone mineral density analysis with dual-energy X-ray absorptiometry (DXA) is only rarely performed. We report the intervention methods suggested by pharmacists and describe their efficacy. Patients who visited the outpatient clinic of the General Medicine Department of Ogaki Municipal Hospital and received steroids were enrolled. The rates of DXA implementation and compliance with GIO pharmacotherapy guidelines before and after pharmacist to physician-suggested interventions were compared. Guideline compliance was defined as prescription of osteoporosis drugs to patients with a score of ≥3. Administered prophylaxes and bone mineral density were subsequently assessed. The before and after intervention DXA rates were 1% (1/100 patients) and 96.0% (96/100 patients; P<0.01), respectively. Overall, 96.9% (93/96) of the patients met the GIO criteria for pharmacotherapy initiation (score ≥3), and the guideline compliance rates before and after the intervention were 39.8% (37/93) and 93.5% (87/93; P<0.01), respectively. Of the 56 patients who did not receive prophylaxis, 52 were recommended treatment, yielding an acceptance rate of 82.7% (43/52). Among the 37 patients receiving prophylaxis, 20 (54.1%) had a DXA-related young adult mean of ≤70%, of whom 11 (55.0%) agreed to drug therapy. The acceptance rate of pharmacotherapy recommendations for patients not receiving prophylaxis was higher than that for those receiving prophylaxis (P=0.03). Pharmacist-initiated interventions for GIO facilitates the administration of appropriate pharmacotherapy.

1. Introduction

Corticosteroids exert potent anti-inflammatory and immunosuppressive effects and may be used to treat many diseases, including connective tissue diseases, rheumatoid arthritis, blood disorders, respiratory diseases, skin diseases, and renal diseases. However, 30–50% of patients treated with steroids develop glucocorticoid-induced osteoporosis (GIO) (Weinstein 2011; van Staa et al. 2002). Steroid use, even at low doses, is associated with rapid bone loss and increased fracture risk (Mazziotti et al. 2010; De Vries et al. 2007). GIO generally presents as secondary osteoporosis, resulting in fragility fractures even when bone density is maintained (Weinstein 2011; van Staa et al. 2002). The development of fragility fractures due to osteoporosis markedly impairs the quality of life of patients. As such, GIO requires precise management.

The management and treatment guidelines for GIO by the Japanese Society of Bone Metabolism (Suzuki et al. 2014) outline treatment decisions based on existing fractures, age, steroid dosage, and lumbar spine bone density and recommend medication to prevent osteoporosis according to the assigned scores. However, compliance with these guidelines has been reported to be only 20% (Kirigaya et al. 2011), and GIO management remains inadequate. In particular, there were a few isolated cases in which GIO prophylaxis was administered. However, bone mineral density (BMD) testing using dual-energy X-ray absorptiometry (DXA) testing is not frequently performed, although it has been established that DXA is an important scoring factor (Suzuki et al. 2014).

In the fields of infectious diseases and supportive care for cancer chemotherapy, physicians often prioritize treatment within their areas of expertise. However, it is important to acknowledge that there may be areas where this expertise is limited. As such, accumulating evidence (Ohashi et al. 2019; Chun et al. 2020) has supported pharmacist-initiated interventions in infectious diseases and cancer chemotherapy, which has led to the promotion of pharmacist-initiated interventions in the treatment of GIO. However, no studies have yet reported satisfactory results for hospital pharmacists intervening in GIO management. To address this knowledge gap, in the present study, we conducted a pharmacist-initiated intervention to suggest DXA and prescribe osteoporosis medications for patients receiving steroids.

Herein, we present the pharmacist-initiated intervention methods recently applied in our department and assess the usefulness of these interventions. We further investigated the BMD in patients receiving prophylactic administration to clarify the adverse effects of injudicious prophylactic administration.

2. Investigations and results

2.1. Patient background

Overall, 100 patients were included in this study. The baseline characteristics of the participants are summarized in Table 1. Most patients were diagnosed with Polymyalgia rheumatica.

2.2. Suggestions for DXA

DXA was suggested for 99 patients, and 1 was excluded as DXA was performed at another hospital in the previous 6 months. The approval rate of this proposal was 96.0% (95/99), as four patients did not undergo DXA.

Table 1: Baseline characteristics of the study participants

Characteristics	No. (%) or mean [SD]	
No. of patients	100	
Age, years	74.5	[9.29]
<50	1	(1.0)
50–65	8	(8.0)
≥65	91	(91.0)
Sex		
Male	41	(41.0)
Female	59	(59.0)
Baseline, mean (SD)		
Height, cm	157.8	[8.1]
Weight, kg	54.2	[9.83]
Body mass index, kg/m^2	22.2	[3.2]
History of fractures	2	(2.0)
Previous oral bisphosphonate use	41	(41.0)
DM	12	(12.0)
Prednisolone dosage, mg	6.0	[4.79]
Diseases treated with prednisolone		
PMR	84	(84.0)
RS3PE	3	(3.0)
SLE	4	(4.0)
AIH	1	(1.0)
Erythema nodosum	1	(1.0)
Adult-onset Still's disease	1	(1.0)
Giant cell arteritis	1	(1.0)
IgG4-related diseases	1	(1.0)
Some seronegative rheumatoid disease	3	(3.0)
Disease name unknown	1	(1.0)

AIH, autoimmune hepatitis; DM, diabetes mellitus; PMR, polymyalgia rheumatica; RS3PE, remitting seronegative symmetrical synovitis with pitting edema; SLE, systemic lupus erythematosus; SD, standard deviation

2.3. DXA implementation rate

The DXA implementation rate increased from 1% (1/100) before intervention to 96.0% (96/100) after intervention (P<0.0001). A graph of the DXA implementation rates before and after the intervention is shown in Fig. 1.

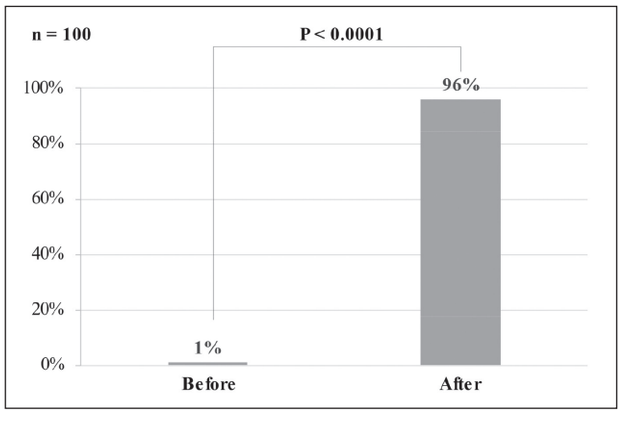

Fig. 1: DXA implementation rates before and after the pharmacist-initiated intervention. DXA: dual-energy X-ray absorptiometry.

2.4. Drug therapy suggestions based on DXA results

The number of patients who met the GIO criteria for the initiation of pharmacotherapy after DXA, YAM%, and the acceptance rate of drug therapy suggestions are shown in Fig. 2. According to the

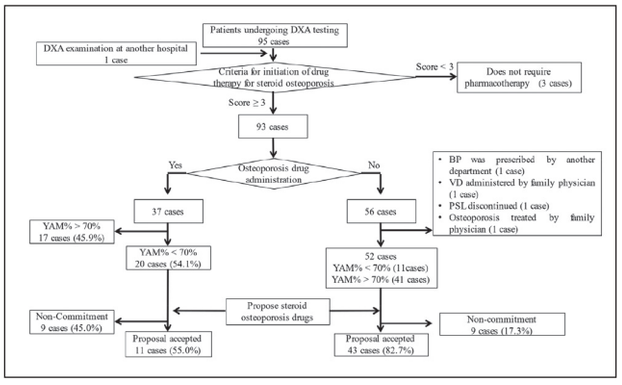

Fig. 2: Number of patients who met the criteria for the initiation of drug therapy for steroid-induced osteoporosis after DXA, YAM%, and drug therapy suggestion commission rate. BP, bisphosphonate; DXA, dual-energy X-ray absorptiometry; PSL, prednisolone; VD, vitamin D; YAM%, young adult mean (%).

2014 revision of the Guidelines for the Management and Treatment of GIO, 96.9% (93/96) of the patients met the GIO criteria for the initiation of pharmacotherapy. Of the 93 individuals who met the GIO criteria for the initiation of pharmacotherapy, 56 did not receive prophylactic dosing and 37 did. Furthermore, 77.4% (72/93) required suggestions for drug therapy.

Of the 56 patients not on prophylaxis, 52 were proposed a drug therapy (excluding one patient who was prescribed BPs by another department, one who was receiving VD prescribed by the family physician, one who discontinued prednisolone, and one who was being followed up for osteoporosis with DXA by another doctor). The approval rate for drug therapy proposals was 82.7% (43/52). BPs and VD were proposed for all patients. Furthermore, pharmacists recommended denosumab for 20 patients with significantly low YAM%, although the physicians did not approve this choice.

For the 37 participants receiving prophylaxis, the drugs prescribed were VD for 31 patients and BPs for 6. Overall, 54.1% (20/37) had a YAM% of ≤70% and the suggestion of drug therapy was accepted by the physician for 55.0% (11/20) of patients. Moreover, denosumab was recommended to 11 patients, although this change was not implemented as their physicians did not agree with this recommendation. The acceptance rate for drug therapy recommendations for patients who did not receive GIO prophylaxis was higher than that for those who received GIO prophylaxis (P=0.0305).

2.5. Guideline adherence rate

The before intervention guideline compliance rate for pharmacotherapy was 39.8% (37/93), whereas the after intervention guideline compliance rate significantly increased to 93.5% (87/93),

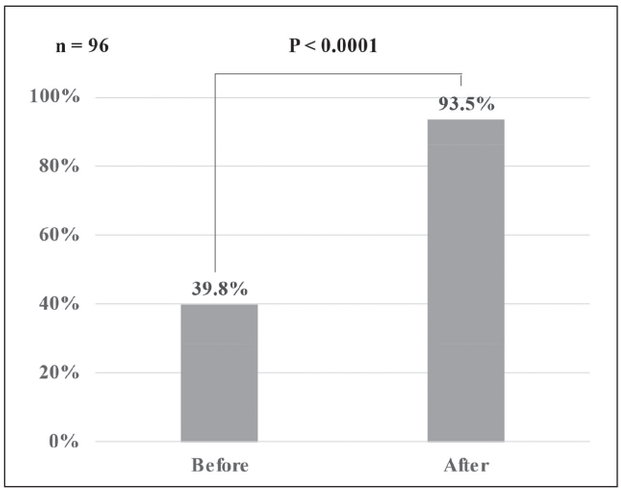

Fig. 3: Comparison of the guideline adherence rates before and after the pharmacist-initiated intervention.

demonstrating a substantial increase in guideline compliance after the intervention compared with that before (P<0.0001). The trend in guideline compliance rates is shown in Fig. 3. Among the six patients for whom treatment did not adhere to the guidelines, one died and two discontinued prednisone therapy. Overall, three patients had a YAM% of >80%.

3. Discussion

GIO is a medical condition that develops as a side effect of treatment for a primary disease. Owing to its severity and potential negative influence on the quality of life, GIO requires careful management. However, in actual clinical practice, there are numerous cases in which GIO is treated prophylactically without performing DXA. To the best of our knowledge, this is the first pharmacist-led study to recommend DXA and drug therapy based on the test results. Of the patients receiving prophylactic treatment for GIO, 54.1% had a YAM% of <70%, suggesting that even when drugs are administered in a casual manner to prevent GIO, BMD loss may still occur. In such situations, pharmacists should assist physicians in managing patients with GIO. Furthermore, we suggest that pharmacist-initiated interventions for GIO could increase the implementation rate of DXA, thereby promoting the provision of appropriate drug therapies.

In a previous study, DXA was shown to be one of the most important elements of the management of GIO; however, the rate of its implementation was low before the intervention. The lack of DXA implementation for patients taking oral steroids could be partly due to a lack of awareness about GIO among physicians. Nevertheless, the approval rate for DXA in this study was high (96.0%), suggesting that the pharmacists' testing recommendations may promote appropriate treatment. The high approval rate for DXA was thought to be because the guidelines were explained directly to physicians, and therefore, their understanding was ensured. Regular DXA could lead to appropriate treatment, and pharmacist-initiated testing recommendations are practical as significant improvements in BMD based on DXA have been shown to be associated with significant reduction in fracture risk, particularly for vertebral and hip fractures (Bouxsein et al. 2019). Although DXA is minimally invasive, it cannot be performed in patients with dementia or those who cannot follow instructions. Therefore, the test consent rate was not 100% in the present study, as such patients were unable to undergo testing.

In the present study, treatment with BPs was the recommended drug therapy for patients who did not receive GIO prophylaxis, in accordance with the recommendations outlined in the 2014 revision of the Guidelines for the Management and Treatment of GIO.5) Furthermore, BPs have been shown to be the most effective drug for preventing GIO (Reid et al. 2000, 2009) and are recommended in several country-specific guidelines for GIO management (Pols and Wittenberg 2002; Geusens et al. 2004; Grossman et al. 2010). In the present study, the acceptance of drug therapy proposals was lower in patients who received prophylaxis for GIO than in those who did not. Two reasons may explain this phenomenon: First, drug suggestions were more likely to be accepted by physicians for patients who were not taking prophylactic medication, while they were less likely to be accepted for patients who were already on some form of prophylactic medication and adhered to the guidelines, as following the suggestion would involve a drug change or additional medications. Second, the proposed change from oral to injectable drugs for patients who were already taking some form of prophylactic medication and adhered to the guidelines primarily involved a change to denosumab, which requires injections, and is, therefore, less likely to be accepted by physicians.

The results of this study indicate that pharmacist-initiated interventions increase the rate of guideline compliance. Previous intervention trials aimed at reducing GIO were primarily conducted by trained physicians (general practitioners and rheumatologists) who also frequently educated patients deemed to be at risk of GIO. However, these trials have had only limited success (Naunton et al. 2004; Curtis et al. 2007; Solomon et al. 2004; Chitre and Hayes 2008). In addition, the only previous pharmacy-based randomized controlled trial of an intervention for GIO reported an increased rate of calcium prescriptions but not of BP prescriptions (McDonough et al. 2005). The increase in guideline compliance in the present study, in contrast to the lack of successful interventions in previous studies, was attributed to the fact that pharmacists within the same hospital took the lead in intervening with physicians. In the present study, our analysis showed that interventions by pharmacists in hospital settings yielded improved results that could not be obtained through physician or patient education alone. Together, these results indicate that the action of pharmacists may be a factor in increasing GIO treatment.

The strengths of this study include the ease of implementation and simplicity of the intervention setting. Compared with those included in previous studies, the patients and physicians investigated in the present study were relatively poorly educated regarding GIO, and pharmacists simply followed the latest guidelines without any additional training (McDonough et al. 2005; Yuksel et al. 2010). As such, the present study better reflects the real-world clinical situation and shows that identifying patients at risk of GIO can be easily integrated into pharmacists' practice, is less labor-intensive, and is cheaper to implement than interventions that include the education of physicians and patients (Laliberté et al. 2011).

Compared with treatment with BP, that with denosumab has been shown to increase BMD (Ohashi et al. 2019; Meier et al. 2017). In the present cohort, denosumab therapy was recommended in patients in whom YAM% was low despite already taking BPs or in those who were not already taking osteoporosis medications and who had a significantly low YAM%; however, despite recommendations by the pharmacist, the physician did not agree to prescribe this as a first-line treatment as it is an injectable drug that requires specialized experience for use. Nonetheless, the low YAM% cannot be overlooked, and for women with low BMD and no vertebral fractures, the combination of 500 mg calcium, 250 IU cholecalciferol, and alendronate reduces the risk of first vertebral deformity (Cummings et al. 1998); as such, we proposed the addition of VD to the treatment regimen of patients not previously receiving VD.

In the present study, we proposed DXA and suggested drug therapy based on DXA results; however, we were unable to determine the efficacy of the drug therapy after its proposal. As such, this remains a topic for future research.

The primary limitations of the present study were that eligible patients were predominantly treated by general internists specializing in collagen diseases. By contrast, respiratory physicians often prescribe steroids more frequently and are more accustomed to employing denosumab as they treat a larger patient population with cancer. Additionally, orthopedic surgeons, including various sub-specialists, may exhibit varying degrees of adherence to guidelines. Consequently, the data obtained may vary, and compliance with the guidelines could potentially fluctuate. In addition, the study was limited to the disease and departments of the patients, and the results may differ when different diseases and departments are included. Furthermore, it should be noted that this study was conducted with alternative endpoints, as the true endpoint could not be the outcome.

To the best of our knowledge, this is the first pharmacist-initiated study to recommend DXA and drug therapy based on test results. Overall, our results show that, in clinical situations, pharmacists should assist physicians while managing patients with GIO; this will enable the optimal provision of appropriate drug therapies. Finally, the results of this study suggest that pharmacist-initiated interventions increase adherence to GIO guidelines and could reduce the risk of GIO-associated fractures.

4. Experimental

4.1. Participants

We enrolled 108 patients who visited the outpatient clinic of Ogaki Municipal Hospital between May 13, 2019 and August 12, 2021. Patients who had received steroids were scheduled to continue receiving steroids for at least three months and had at least three outpatient visits each before and after the initiation of pharmacist-initiated intervention were included. Patient data were extracted from the electronic medical records. The analyzed data included age, sex, height, weight, diagnosis, medical

history, medications administered, and DXA-related young adult mean (YAM%). Patients who were referred to other hospitals or received treatment for osteoporosis (n=8) were excluded.

The start date of the pharmacist-initiated intervention was May 13, 2020. In accordance with the instructions from the appropriate ethics committee, the period from May 13, 2019 to May 12, 2020 was defined as the non-intervention period, and the period from May 13, 2020 to August 12, 2021 was defined as the intervention period.

4.2. Intervention methods

An overview of the pharmacist-initiated intervention methods for the management and treatment of GIO is shown in Fig. 4. Here, the criteria for the initiation of pharmacotherapy for GIO and suggestions for DXA and pharmacotherapy to the attending physicians were set in accordance with the 2014 revised Guidelines for the Management and Treatment of GIO; these were explained in the note function of the electronic medical record after the end of the outpatient management on the evening of May 12, 2020. The procedures described below were conducted at the end of the outpatient clinic visit on May 12, 2020.

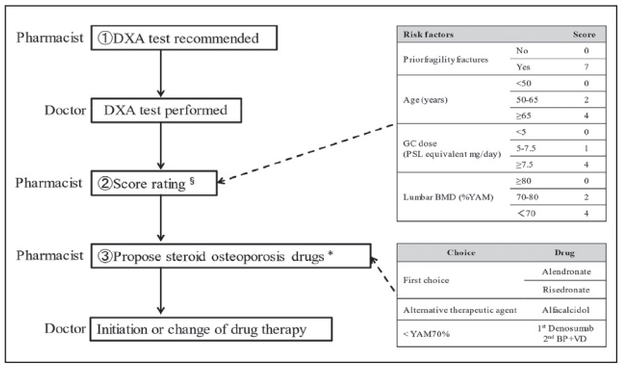

Fig. 4: Pharmacist-initiated interventions in the management and treatment of steroid-induced osteoporosis. § and * modified from reference 5. BP: bisphosphonate, BMD: bone mineral density, DXA: dual-energy X-ray absorptiometry, GC: glucocorticoid, PSL, prednisolone; VD: vitamin D; YAM%, young adult mean (%).

For eligible patients who had not undergone DXA within the prior six months, physicians were recommended to perform DXA with reference to the 2015 Guidelines for the Prevention and Treatment of Osteoporosis via the memo function of the electronic medical record. The DXA test results were subsequently used to calculate a score for fracture risk factors in accordance with the GIO Management and Treatment Guidelines. If the score was ≥3, oral alendronate 35 mg/week or oral risedronate 17.5 mg/week was recommended. If bisphosphonates (BPs) could not be prescribed, as in cases where dental procedures were required, alfacalcidol was considered as an alternative.

With regard to treatment for GIO, this was the same as that for primary osteoporosis; thus, we referred to the guidelines for primary osteoporosis and defined the criteria for requiring treatment as osteoporosis with a YAM% of ≤70%. If the YAM% was significantly low (≤70% for both the lumbar spine and femur), denosumab was recommended first (Saag et al. 2019), and BPs or vitamin D (VD) was additionally recommended.

4.3. Consent rate for proposed DXA

The consent rate for DXA was determined from the electronic medical records of eligible patients. The approval rate was defined as the number of cases in which the test was proposed by pharmacists and subsequently performed divided by the total number of cases in which the pharmacist proposed the test to the attending physician.

4.4. DXA implementation rate

The DXA implementation rate was determined from the electronic medical records of eligible patients and was compared before and after the intervention. The test implementation rate was defined as the number of patients who underwent DXA divided by the number of eligible patients. The dates were May 12, 2020 for before intervention evaluation and August 12, 2021 for after intervention evaluation.

4.5. Evaluation of DXA results in patients who had not received any osteoporosis

Pre-existing fractures, age, steroid dosage, and YAM% were all investigated in the electronic medical records of eligible patients who had not received osteoporosis medications before the intervention. The GIO Management and Treatment Guidelines 2014 revision score was calcd. to determine if any of the criteria for the initiation of drug therapy were met, and the % of patients who met the criteria for the initiation of drug therapy was subsequently calculated. The rate of compliance with the drug therapy proposal was further investigated.

4.6. Evaluation of DXA results in patients receiving osteoporosis treatment before intervention

In patients receiving osteoporosis treatment prior to the intervention, if the YAM% was <70%, we suggested changing the treatment to denosumab or adding a drug with a mechanism of action that differed from that of the previously administered osteoporosis drug. The drug acceptance rate was further assessed.

4.7. Guideline compliance rate

Compliance with the 2014 revision of the Guidelines for the Management and Treatment of GIO was investigated in eligible patients, and the compliance rate was compared before and after the intervention.

Compliance with the 2014 revised Guidelines for the Management and Treatment of GIO was defined as the prescription of alendronate, risedronate, teriparatide, ibandronate, alfacalcidol, or calcitriol to patients with a score of ≥3.

4.8. Statistical analyses

EZR version 1.26 (Kanda 2013) was used for statistical analyses. The Mann–Whitney *U* test was performed to compare median values between the two groups, and Fisher's exact probability test was performed to compare proportions between the two groups. The significance level was set at 5%.

4.9. Ethical considerations

This study was approved by the Ethics Committees of Ogaki Municipal Hospital (approval number: 20211223-13) and Gifu Pharmaceutical University (approval number: 3-48).

Data availability: The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of interest: None declared.

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