Original Article

The Effect of Atorvastatin on the Incidence of Steroid-associated Osteonecrosis of the Femoral Head in Patients with Systemic Lupus Erythematosus: A Randomized Controlled Trial

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Abstract: Statins have been shown to prevent the occurrence of steroid-associated osteonecrosis in animal experiments. However, it is unknown whether statins have preventive effects on the occurrence of osteonecrosis of the femoral head (ONFH) because of the lack of well-controlled clinical studies. The present study was designed to determine whether atorvastatin would prevent steroid-associated ONFH in a randomized controlled trial. Forty-seven patients with systemic lupus erythematosus (SLE) who were scheduled to receive steroid treatment for the first time were randomly assigned to either the atorvastatin treatment group (23 patients) or the control group (24 patients). In the treatment group, the administration of atorvastatin and steroids was simultaneously initiated. Magnetic resonance imaging was performed before and 6 months after the start of steroid treatment, and blinded radiologists assessed the presence of ONFH. ONFH occurred in 6 patients in each group. Both on-treatment or intention-to-treat analysis showed no evidence that atorvastatin prevents the development of ONFH. Even though multivariate analyses were performed, they showed no preventive effects of atorvastatin on the development of ONFH. In the present randomized clinical trial, atorvastatin did not reduce the incidence of ONFH in SLE patients treated with steroids.

Key Words: Osteonecrosis of the femoral head, Randomized controlled trial, Statin.

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Introduction

Osteonecrosis of the femoral head (ONFH) is known to frequently occur after the administration of large doses of steroids[1]. Steroids are essential drugs for the treatment of various diseases, including systemic lupus erythematosus (SLE). For ONFH occurring after steroid treatment, there are no established preventive measures or conservative therapies[2)3)]. When the necrotic area is large, the femoral head collapses; the function of the hip joint is abolished, and the patients' activities of daily living are markedly impaired, thus necessitating surgical intervention. Surgical invasiveness and long-term outcomes are still challenging issues, although surgical outcomes have improved. Because the period during which steroid-associated ONFH occurs can be limited to some extent[4], the establishment of preventive measures against ONFH would benefit many patients.

The incidence of steroid-associated ONFH is considered to be associated with multiple factors, such as dyslipidemia[5] and oxidative stress[6]. The 3-hydroxyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, known as statins, have pleiotropic effects that include not only lipid-lowering effects but also antioxidant effects[7]. Statins have been reported to prevent steroid-associated osteonecrosis in animal models[8)9)]. Moreover, a retrospective study also suggested that statins may prevent steroid-associated ONFH in humans[10]. However, there have been no well-controlled clinical studies that have examined the preventive effect of statins on steroid-associated ONFH. The present study aimed to determine whether statins prevent steroid-associated ONFH in a randomized controlled trial. Moreover, the association of serum total cholesterol (T-chol) levels with atorvastatin and ONFH was examined as secondary outcomes.

Materials and methods

Patients: The subjects were patients with SLE, the most common disease underlying steroid-associated ONFH, accounting for approximately 30% of all cases[11]. The diagnosis of SLE was established according to the diagnostic criteria developed by the American College of Rheumatology in 1997[12]. The study enrolled patients newly diagnosed with SLE who had no history of treatment with steroids or lipid-lowering drugs and who would start steroid treatment at a dose equivalent to 0.5 mg/kg/day of prednisolone; written informed consent was obtained from all patients prior to their participation in this study. The following patients were excluded from the study: (i) female patients who wished to become pregnant, (ii) patients with serious hepatic dysfunction, renal dysfunction, or heart disease, and (iii) patients who were determined to be ineligible for the study by attending physicians. The patients who visited the Departments of Rheumatology and Internal Medicine at the participating institutions (Kyoto Prefectural University of Medicine, Juntendo University, the University of Occupational and Environmental Health, Kyoto University, Saitama Medical University, and Niigata University) during a 5-year period from 2004 to 2008 and who satisfied the above inclusion criteria were assigned to either the atorvastatin treatment (AS) group or the control without atorvastatin (CTR) group via blocked randomization by an author (M. I.) who was blinded to patient data. In the AS group, administration of atorvastatin at 10 mg/day was simultaneously initiated with steroid treatment. No placebo was administered.

Methods: The following parameters, which are reportedly associated with the occurrence of ONFH, were selected as the analyzed factors pertaining to patient background: sex[13], age[14], initial steroid dose[13], steroid pulse therapy[15], concomitant use of anticoagulant drugs[16], antiphospholipid antibody[17], and history of alcohol consumption[18]. The diagnosis of ONFH was defined as the presence of a peripheral convex

band-like low-signal intensity area in the femoral head on plain T1-weighted magnetic resonance images (MRI) of the hip joint, excluding tumors, tumor-like disease, epiphyseal dysplasia, and secondary ONFH[19]. Diagnostic images were assessed by a radiologist blinded to patient assignment. Before the start of steroid treatment, the presence or absence of pre-existing ONFH was determined by plain MRI of both hip joints. In patients for whom MRI were difficult to obtain before the start of steroid treatment due to serious underlying disease, MRI obtained within 4 weeks after the start of steroid treatment were considered the "pretreatment" assessment. Six to 12 months after the start of steroid treatment, MRI of the hip joints were obtained again to determine the presence or absence of ONFH. Moreover, biochemical tests were performed immediately before steroid treatment as a baseline and then again each month afterwards to determine the presence or absence of adverse reactions and to measure T-chol levels as an index of dyslipidemia. T-chol levels were measured in each institute using cholesterol dehydrogenase ultraviolet method.

Outcomes: The primary outcome was the presence or absence of ONFH as determined by the MRI conducted 6 to 12 months after the start of steroid treatment. The ability of atorvastatin to reduce the incidence of steroid-associated ONFH was determined. For the secondary outcomes, assessments were made of fluctuations in T-chol levels according to the presence or absence of atorvastatin treatment and the presence or absence of ONFH development as well as differences in patient background factors according to the presence or absence of ONFH.

Statistical analysis

A study using MRI reported the incidence of ONFH to be 30% or higher among SLE patients[13]. In a retrospective clinical study mainly including patients undergoing organ transplantation, Pritchett reported that the incidence of steroid-associated ONFH was 1% in patients concomitantly treated with statins[10]. Under the assumption that the incidence of ONFH among SLE patients would be reduced from 30% to approximately 1% by the use of statins, the required sample size was 23 patients per group for a power of 0.8 and a significance level of 0.05. To assess statistical significance in the univariate analysis, Fisher's exact probability test, Student's t-test, Welch's t-test, the Mann-Whitney U test, and the Wilcoxon signed-rank test were used, and a value of $p < 0.05$ indicated statistical significance. Missing data for T-chol levels were substituted by the last observation carried forward procedure, and Bonferroni adjustment was used for multiple comparisons. Multivariate analysis was performed using the logistic regression model, and a value of $p < 0.05$ indicated statistical significance. Adjusted odds ratios of developing osteonecrosis while taking atorvastatin were calculated using age, sex, initial steroid dose, or T-chol levels before steroid treatment as potential confounders. The statistical analyses were performed using SAS software ver. 6.12 (SAS Institute Inc., Cary, NC, USA).

Ethical consideration

The study design was approved by the Kyoto Prefectural University of Medicine Review Board (MCHS-462). The study was sufficiently explained to patients, and written informed consent was obtained. Withdrawal from the study was allowed at any time when the following conditions occurred: serious adverse reactions developed, patients or their families requested the discontinuation of the medication, or the attending physicians determined that the patients were unfit to continue the study. Moreover, if patients in the CTR group presented with severe hyperlipidemia, appropriate treatment was started. This study was funded by The Practical Research Project for Rare/Intractable Diseases of the Japan Agency for Medical Research.

Results

Patient backgrounds and clinical courses: There were 23 patients (3 males and 20 females) in the AS group and 24 patients (2 males and 22 females) in the CTR group. No significant differences were observed

Table 1 Characters of patients

	CTR group n=24 (%)	AS group n=23 (%)	p	analysis
female/male	22/2(8.3)	20/3(13)	0.48	*
age(years)	37±15	36±8.4	0.8	**
initial dose of PSL(mg)	46±22	48±11	0.91	**
steroid pulse therapy	6(25)	5(22)	0.53	*
anticoagulant/ antiplatelet drug	8(33)	6(26)	0.41	*
anticardiolipin IgG	2(8.3)	2(8.7)	0.48	*
alcohol consumption	2(8.3)	0(0)	0.26	*

CTR: control; AS: atorvastatin; PSL: predonisolone; *Fisher's exact probability test; **Welch's t test. Values are numbers (%) or means ± standard deviation.

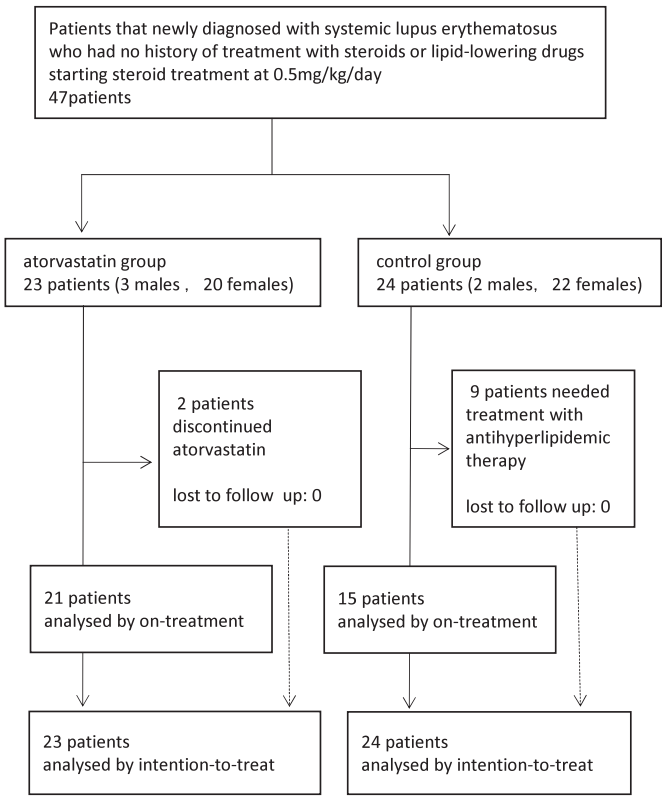

Fig. 1 Flow chart of patients

between the two groups in any of the following variables: mean age, initial steroid dose, the number of patients receiving steroid pulse therapy, the number of patients with concomitant use of anticoagulant or antiplatelet drugs, the number of patients positive for anticardiolipin antibody, and the number of patients who habitually consumed alcohol (Table 1). In the AS group, 2 patients discontinued atorvastatin treatment due to hypocholesterolemia or increased creatinine kinase levels. Moreover, 9 patients in the CTR group developed hyperlipidemia, thus necessitating treatment. The drugs used were probucol in 1 patient, simvastatin in 2, pravastatin in 5, and pitavastatin in 2. No other adverse events were observed, and there were no deaths during follow-up. The follow-up rate from the start of steroid treatment to the MRI acquired 6 to 12 months later was 100% (Fig. 1).

Incidence of ONFH

None of the patients had developed ONFH before the start of steroid treatment. Six to 12 months after the start of steroid treatment, ONFH was observed in 6 of the 24 patients in the CTR group. Three of them presented with hyperlipidemia, one at 2 weeks, one at 7 weeks, and one at 8 weeks after the start of steroid treatment, thus necessitating treatment. The drugs used were probucol in 1 patient and pravastatin in 2 patients. Of the 23 patients in the AS group, ONFH occurred in 6 patients, 1 of whom discontinued atorvastatin treatment due to an increased creatinine kinase level and hypocholesterolemia at 4 months after the start of steroid treatment. Both on-treatment and intention-to-treat analyses revealed that there was no difference in the incidence of ONFH between the two groups, confirming that atorvastatin did not have any preventive effects on steroid-associated ONFH (Table 2).

Presence or absence of ONFH and patient background factors

There were no significant differences in patient sex, age, initial steroid dose, use of steroid pulse therapy, positivity for the antiphospholipid antibody, or history of alcohol consumption between the patients with and those without ONFH. Comparison within the AS and CTR groups according to the presence or absence of ONFH revealed no significant difference in these factors. Although ONFH tended to be more likely to occur in men, no significant difference was observed in the sample size of this study ($p = 0.06$). Meanwhile, ONFH did not occur in any of the 14 patients concomitantly using anticoagulant or antiplatelet drugs, which was statistically significant ($p = 0.007$) (Table 3). Excluding these patients using anticoagulant or antiplatelet drugs, 6 of 16 patients in the CTR group and 6 of 17 patients in the AS group developed ONFH, which was not statistically significant.

Levels of T-chol

Although the patients were randomly assigned to one of the two groups, the T-chol levels before steroid treatment were 178 ± 35 mg/dl in the AS group and 146 ± 45 mg/dl in the CTR group, which were significantly different ($p = 0.012$). After steroid treatment, the T-chol levels increased in both groups. Although the T-chol levels after steroid treatment in the AS group tended to be lower than those in the CTR group, there was no statistically significant difference between the groups (Fig. 2a). The degree of elevation of T-

Table 2 Incidence of osteonecrosis of the femoral head

	AS group, n (%)	CTR group, n (%)	p*
on-treatment	5/21 (24%)	3/15 (20%)	0.53
intention-to-treat	6/23 (26%)	6/24 (25%)	0.6

AS: atorvastatin; CTR: control; *Fisher's exact probability test

Table 3 Presence or absence of osteonecrosis of the femoral head and patient background

	total (n=47)		p	CTR group (n=24)		p	AS group (n=23)		p	analysis
	ONFH (+)	ONFH (-)		ONFH (+)	ONFH (-)		ONFH (+)	ONFH (-)		
number of patients	12	35		6	18		6	17		
female/ male	9/ 3(25%)	33/ 2(5.7%)	0.06	5/ 1(17%)	17/ 1(5.6%)	0.45	4/ 2(33%)	16/ 1(5.9%)	0.16	*
Age(years)	35±13	37±12	0.71	32±16	39±15	0.4	38±10	35±7.9	0.45	**
initial dose of PSL(mg)	61±35	45±12	0.16	56±37	42±12	0.44	53±5.8	45±12	0.22	***
steroid pulse therapy	1(8.3%)	10(29%)	0.15	0(0%)	6(33%)	0.14	1(17%)	4(24%)	0.67	*
anticoagulant/ antiplatelet drug	0(0%)	14(40%)	0.0068	0(0%)	8(44%)	0.059	0(0%)	6(35%)	0.12	*
anticardiolipin IgG	1(8.3%)	3(8.6%)	0.73	0(0%)	2(11%)	0.75	1(17%)	1(5.9%)	0.46	*
alcohol consumption	1(8.3%)	1(2.9%)	0.45	1(17%)	1(5.6%)	0.45	0(0%)	0(0%)	0.64	*

Values are expressed as number (%) or mean ± standard deviation. ONFH: osteonecrosis of the femoral head; *Fisher's exact probability test; **Student's t test; ***Mann-Whitney's U test

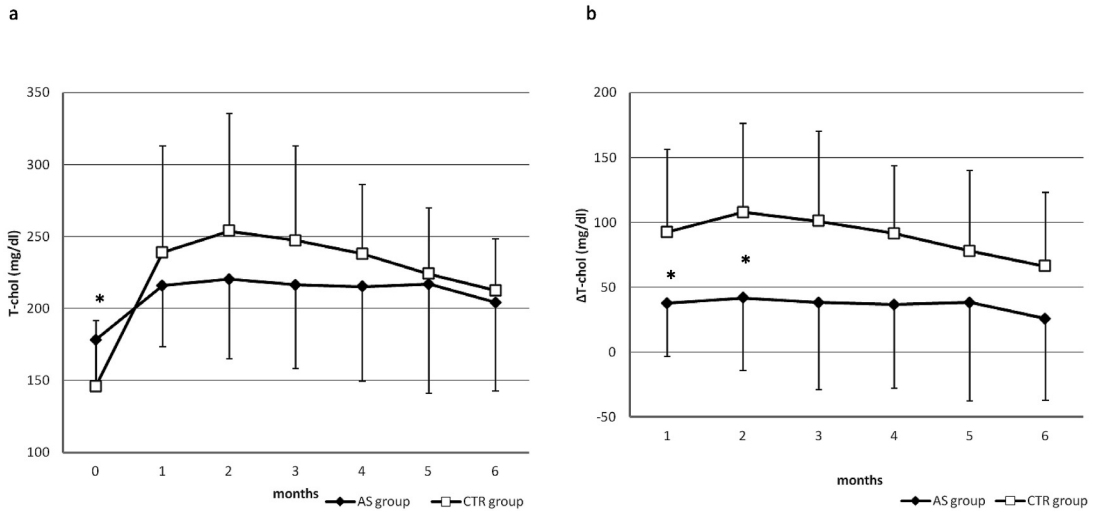

Fig. 2 Changes in total cholesterol levels after steroid treatment
a. Changes in total cholesterol levels after steroid treatment.
b. The degree of elevation of total cholesterol levels after steroid treatment.
95% confidence interval are displayed as the vertical lines. T-chol: total cholesterol; Δ T-chol: The degree of T-chol elevation from those before steroid treatment; AS group: patients who had administration of atorvastatin at 10 mg/day was simultaneously started with steroid treatment; CTR group: patients who had steroid treatment without atorvastatin. *p<0.05 student's t-test (after Bonferroni correction)

chol levels (Δ T-chol) above the levels before steroid treatment was significantly less for the first 2 months after steroid treatment in the AS group than in the CTR group (Fig. 2b). There was no significant difference in the T-chol levels before the start of steroid treatment between patients with and those without ONFH. The T-chol levels were significantly higher for the first 2 months in the patients with ONFH than

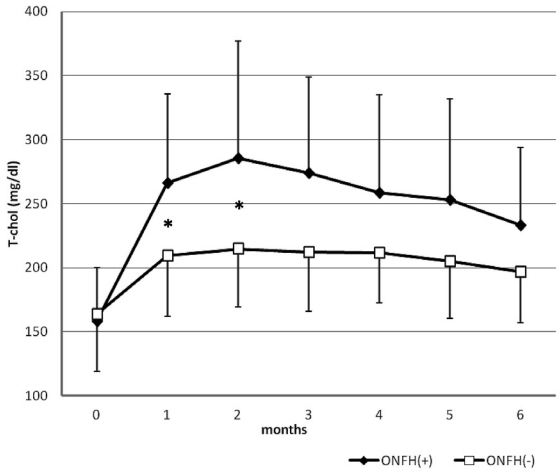

Fig. 3 Occurrence of osteonecrosis of the femoral head and total cholesterol levels
95% confidence interval are displayed as the vertical lines. ONFH: osteonecrosis of the femoral head; T-chol: total cholesterol. *p<0.05 student's t-test (after Bonferroni correction)

in the patients without ONFH (Fig. 3).

Multivariable analyses

Although the patients were randomly assigned to one of the two groups, the T-chol levels before atorvastatin treatment were significantly higher in the AS group than in the CTR group. Because differences in patient backgrounds might have affected the results of the univariate analysis, multivariate analysis adjusted for patient background variables, including T-chol levels, was performed using logistic regression. After adjusting for age, sex, initial steroid dose, and T-chol levels before steroid treatment, the odds ratios (95% confidence interval) of atorvastatin were 1.05 (0.28-3.92), 0.96 (0.24-3.77), 0.96 (0.21-4.38), and 1.17 (0.29-4.78), respectively, and no preventive effects of atorvastatin against ONFH were observed.

Discussion

Study design

Subject selection: The present study targeted patients with SLE, which is the most common disease underlying steroid-associated ONFH. Since SLE is a typical autoimmune disease requiring treatment with steroids, it is important to establish preventive measures against steroid-associated ONFH in patients with SLE. The background variables of the SLE patients enrolled in the present study, such as the male-to-female ratio, age distribution, and the number of patients positive for anticardiolipin antibody, were comparable to those reported in previous studies[20]. However, because the participating institutions were university hospitals, it cannot be denied that the present study might have included more patients with relatively severe SLE. Although the patients were assigned to one of two groups by an author who was blinded to patient data, there was a significant difference in the T-chol levels between the two groups before the start of steroid treatment.

Diagnosis of ONFH: MRI were used for the diagnosis of ONFH because the diagnostic sensitivity of

MRI is excellent for early ONFH[21]. Based on histology, MRI are reported to have a diagnostic sensitivity of 75% or more and a specificity of 100% before the femoral head collapses[19]. Because 4 weeks or more are required before signs of steroid-associated ONFH become apparent on MRI[4], the first 4 weeks after steroid treatment was defined as the "pretreatment" period. Moreover, the occurrence of ONFH is rare at 6 months or more after steroid treatment[4,15], and an accurate diagnosis is difficult to make once the femoral head collapses. Thus, the presence or absence of ONFH was determined using MRI between 6 and 12 months after steroid treatment.

Incidence of ONFH

The incidence of ONFH in the present study was roughly consistent with that reported in previous studies using MRI[13,22]. In the present study, the incidence of ONFH was 26% in the AS group and 25% in the CTR group, showing no difference between the two groups. Multivariate analysis revealed that none of the factors evaluated influenced the effect of atorvastatin on ONFH. No preventive effects of atorvastatin on steroid-associated ONFH were confirmed. Although the use of anticoagulant and antiplatelet drugs might have changed the incidence of ONFH, there was no difference in the number of patients concomitantly using those drugs between the AS and CTR groups, and the results of the analysis of the preventive effect of atorvastatin against ONFH were not affected. Nagasawa et al. administered warfarin together with the beginning of steroid therapy for SLE patients, but the preventative effect of warfarin for ONFH was not confirmed[23]. In our study, various anticoagulant/antiplatelet drugs were prescribed according to condition of each patients (warfarin, aspirin, dipyridamole etc.). ONFH did not occur in any of patients concomitantly using anticoagulant/antiplatelet drugs. Therefore, anticoagulant/antiplatelet drugs except warfarin, or combination of these drugs may have preventative effect of steroid-associated ONFH. Although no conclusions regarding whether anticoagulant/antiplatelet drugs have a preventive effect against ONFH can be drawn from the present study, another study has reported that the combination of statins and anticoagulant drugs can prevent steroid-associated osteonecrosis[16].Thus, additional studies are needed.

Levels of T-chol

Hyperlipidemia is known to occur after steroid treatment[16]. The present study also revealed a marked increase in T-chol levels after steroid treatment regardless of whether atorvastatin treatment was administered. In the AS group, the degree of T-chol elevation was moderate compared with that in the CTR group, and atorvastatin was effective at preventing hyperlipidemia in the early stage after steroid treatment. Kabata et al. reported that T-chol levels after steroid administration of osteonecrosis group were significantly higher than those without osteonecrosis in rabbit osteonecrosis model[24]. Kuroda et al. reported that T-chol level at 4 weeks after the start of steroid treatment tended to be higher in patients with ONFH than patients without ONFH in SLE patients[25]. The results of the present study support these findings. The possibility that there may be an association of dyslipidemia with the occurrence of ONFH cannot be disregarded. On the other hand, there are reports that the existence of hyperlipidemia before steroid treatment is not associated with the occurrence of ONFH[1,26]; in the present study, no association was observed between the presence of ONFH and T-chol levels before steroid treatment. Instead of hyperlipidemia itself, a marked increase in T-chol levels after steroid treatment may be associated with the occurrence of ONFH. Therefore, to suppress the marked increase in T-chol levels after steroid treatment by controlling statin doses may be effective to prevent steroid-associated ONFH.

Comparison between the present and previous results

Pritchett reported the incidence of steroid-associated ONFH to be 1% among patients receiving oral

statins, which is different from that observed in the present study[10]. This difference may be attributable to the following five factors. (i) Statins have no potentially preventive effects on steroid-associated ONFH. In a retrospective study without a control carried out by Pritchett, the preventive effects of statins were not fully assessed. In our present study, because atorvastatin did not prevent ONFH, statins may not have a preventive effect against ONFH. This observation is supported by a previous retrospective study involving 2881 patients with renal transplantation that reported that statins did not prevent symptomatic ONFH[27]. (ii) Unlike other types of statins, only atorvastatin has no potential effects on the prevention of ONFH. In the present study, atorvastatin was selected, which was the most frequently used statin at the start of the study. However, because both atorvastatin and steroids are metabolized by cytochrome P4503A, it cannot be denied that atorvastatin may delay the metabolism of steroids and enhance their pharmacological actions. Therefore, a preventive effect may be achieved if statins with different metabolic pathways are used[28]. (iii) Preventive effects of statins against steroid-associated ONFH may not be achieved after steroid treatment in patients with SLE as the underlying disease. Pritchett excluded SLE patients, who were regarded as a "high-risk group", from their study. Compared with patients with other connective tissue diseases, the incidence of ONFH is higher in those with SLE[13]. Preventing ONFH may be more difficult in SLE patients than in patients with other underlying diseases. (iv) The timing of the start of statin treatment may be late. In a study by Pritchett, and in experiments with animal models, statins were administered prior to steroid therapy[8]. After steroid treatment, intraosseous hemodynamics fluctuate for a few days[29]. When the time of statin administration is the same as that of steroid therapy, steroids may exhibit their pharmacological actions before the effects of statins are manifested. However, in case with severe SLE, which requires steroid therapy as soon as possible, it is difficult to administer statins before steroids, and it is preferable to establish preventive measures against ONFH even when the statin is simultaneously administered with steroid treatment. (v) The lipid-lowering drugs used in the CTR group during the present study may have influenced the therapeutic outcomes. Out of the 24 patients in the CTR group, 9 developed hyperlipidemia during the follow-up period and started treatment with lipid-lowering drugs. However, because ONFH occurred in 3 of the 9 patients treated with lipid-lowering drugs, we believe that the incidence of ONFH in the CTR group was not affected by the use of the lipid-lowering drugs.

Limitations

This study had several limitations. First, the number of study subjects was small, although our limited inclusion criteria allowed us to perform a strict evaluation for the first time. Since there was no tendency for atorvastatin to have a preventive effect against ONFH in the present 47 patients, continuing this study is ethically problematic. Thus, future studies should combine other methodologies by which preventive effects of different drugs and anticoagulant drugs[16] are shown, or procedures that are anticipated to be more effective for preventing ONFH (such as the implementation of a preventive measure as early as possible). Second, the present study was a single-blinded trial. Diagnoses were made according to MRI regardless of the presence of symptoms, and the follow-up rate was 100%. Thus, no bias was introduced by patient-related factors. Because diagnostic images were assessed by a radiologist who was blinded to the patient assignments, diagnostic bias was also avoided. Third, only the presence of ONFH was assessed. The follow-up period of the present study was as short as 6 months. Thus, the long-term effects of statins, including effects on the progression to symptomatic ONFH, remain unknown.

Conclusion

In this multicenter randomized controlled trial involving SLE patients receiving initial steroid treatment, the impact of atorvastatin on the incidence of steroid-associated ONFH was assessed. No preventive effects of atorvastatin against ONFH were confirmed. To establish preventive measures against ONFH, studies on different drugs, the concomitant use of other preventive measures, and the timing of the start of treatment are needed.

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〈和文抄録〉

全身性エリテマトーデス患者におけるステロイド関連大腿骨頭壊死症に対するアトルバスタチンの予防効果
―ランダム化比較試験―

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スタチンは動物実験においてステロイド関連骨壊死の発生を抑制することが報告されている．しかし，臨床例において大腿骨頭壊死症（osteonecrosis of the femoral head; ONFH）の発生を抑制できるかは明らかになっていない．本研究の目的はアトルバスタチンがステロイド関連ONFHの発生を抑制するかについてランダム化比較試験を行うことである．初回ステロイド投与を受ける全身性エリテマトーデス患者を対象とし，アトルバスタチン投与を行う治療群（23例）と投与を行わない対照群（24例）に無作為に振り分けた．ONFH発生の有無はステロイド投与から6か月後のMRIで判定した．ONFHは両群ともに6例に発生し，発生率に有意な差はなかった．多変量解析の結果，アトルバスタチンのONFHに対する抑制効果は明らかでなかった．本ランダム化比較試験において，アトルバスタチンは全身性エリテマトーデス患者におけるステロイド関連ONFHの発生を抑制しなかった．

キーワード：ステロイド関連大腿骨頭壊死症，ランダム化比較試験，スタチン．