Transitional changes in the incidence of osteonecrosis in systemic lupus erythematosus patients: focus on immunosuppressant agents and glucocorticoids

（SLE 患者における骨壊死発生頻度の推移:免疫抑制剤とステロイドに着目して）

千葉大学大学院医学薬学府

先端医学薬学専攻

（主任：大鳥　精司 教授）

縄田　健斗

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Abstract

Objective: The purpose of this study was to investigate transitional changes in the incidence of glucocorticoid-associated osteonecrosis in SLE patients, with a focus on immunosuppressive agent and glucocorticoid consumption.

Methods: We retrospectively registered 185 SLE patients with 740 joints, who were newly diagnosed and hospitalized for initial high-dose glucocorticoid therapy from 1986 to 2015. Immunosuppressive agent, glucocorticoid dose, age, sex, organ lesion at hospitalization, complement (C3, C4, CH50) and anti-DNA antibody before initial glucocorticoid therapy, the frequency of use of anticoagulant and antilipidemic drugs, and incidence of osteonecrosis were documented.

Results: Based on trends in immunosuppressive agent use, 116 patients treated from 1986 to 1999, before calcineurin inhibitors were introduced, comprised the past group, and 69 patients treated from 2000 to 2015 comprised the recent group. Patient characteristics (age, sex and organ lesion at hospitalization, complement, anti-DNA antibody, the frequency of use of anticoagulant and antilipidemic drugs) were similar between groups. Glucocorticoid doses were significantly lower in the recent group than in the past group (highest daily glucocorticoid dose, 45.7 vs 59.0 mg/day, respectively; dose per weight, 0.88 vs 1.16mg/day/kg, respectively; and cumulative dose at 3 months, 3118 vs 3985mg). The incidence of osteonecrosis was significantly lower in the recent group than in the past group (26.4 vs 41.0%, respectively), particularly in the knee (25.4 vs 46.6%, respectively).

Conclusion: The incidence of glucocorticoid-associated osteonecrosis in SLE patients decreased in association with a decrease in glucocorticoid administration after introduction of

immunosuppressant agents.

Keywords: systemic lupus erythematosus, osteonecrosis, glucocorticoids, MRI, immunosuppressant, calcineurin inhibitors

Introduction

Multifocal osteonecrosis is a well-known complication in patients who undergo systemic glucocorticoid therapy. This glucocorticoid-associated osteonecrosis is presumed to arise from circulatory impairment to the epiphysis [1], osteocyte apoptosis and death [2], although the exact pathogenesis is currently unclear. Among patients with a history of systemic glucocorticoid administration, SLE was reported most frequently [3]. Oinuma et al. [4] reported a 44% incidence of osteonecrosis in adult patients with SLE.

MRI is a non-invasive diagnostic tool that enables osteonecrosis to be detected much earlier and with greater sensitivity and specificity than simple X-ray and bone scintigraphy [5]. Although it is asymptomatic at the time of osteonecrosis development, MRI can visualize the osteonecrosis with low intensity band in the T1 image during the early phase of up to 3 months after glucocorticoids start [6]. Gradually, the necrotic area becomes mechanically vulnerable, and when it collapses, it causes pain. In other words, there is a time lag from development of osteonecrosis to symptomatic onset by collapse of the femoral head. At the time of collapse, MRI shows diffuse bone marrow edema with low intensity in the T1 image and high intensity in the short tau inversion recovery sequence (or STIR) image [7]. MRI screening of osteonecrosis is important because incidence of osteonecrosis is frequent after high-dose glucocorticoids therapy and surgical treatment is often required [8]. Sakamoto [9] revealed that the incidence of osteonecrosis was highest in the hip (63%), followed by the knee (51%), ankle (16%) and shoulder joints (16%), while the incidence of osteonecrosis in the ankle and shoulder was 0% in a patient without osteonecrosis in the hips or knees. Nakamura et al. [10] observed no new lesions in the first year following initiation of glucocorticoid administration in SLE patients who received low-dose glucocorticoids for more than a decade; delayed osteonecrosis occurred in only one patient, who experienced an SLE recurrence. These results suggest that MRI of bilateral hip and knee joints is a sufficient

screening method for osteonecrosis during the first year of glucocorticoid therapy.

Recently, immunosuppressive regimens for renal allografts have improved, resulting in a decreased incidence of osteonecrosis, presumably due to reduced glucocorticoid doses [11, 12]. However, it is unclear whether these improved immunosuppressive regimens would lead to a similar decrease in the incidence of osteonecrosis in patients with autoimmune diseases. The purpose of this study was to clarify temporal trends in the incidence of osteonecrosis in SLE patients, with a focus on immuno- suppressant agent and glucocorticoid consumption.

Material and Methods

The research protocol of this retrospective observational cohort study was approved by the Research Ethics Committees of the Graduate School of Medicine, Chiba University Board in compliance with the Helsinki Declaration. The participants were informed by bulletin board.

We retrospectively studied 238 SLE patients who received glucocorticoid therapy from 1986 to 2015. The inclusion criteria were: fulfillment of the ACR 1982 revised criteria for the classification of SLE [13]; newly diagnosed SLE managed by hospitalization and administration of initial glucocorticoid therapy; and MRI screening of hips and knees during the first year following initial glucocorticoid administration. Eighteen patients who were previously diagnosed with SLE and were hospitalized for recurrence and 35 patients who did not undergo MRI screening were excluded. The remaining 185 patients with 740 joints comprised the study group for subsequent analyses.

Trends in immunosuppressive agent and glucocorticoid consumption were surveyed. Survey items concerned the use of intermittent pulse intravenous CYC therapy, calcineurin inhibitors (ciclosporin or tacrolimus) and glucocorticoid usage (steroid pulse therapy and highest daily glucocorticoid dose per oral dose) that were administered at the time of initial admission. Calcineurin inhibitors were introduced in 2000. As a policy of rheumatologists in our hospital, immunosuppressive drugs have been intention- ally prescribed to reduce the amount of steroid use. Therefore, patients were divided into two groups: the past group

(1986-99) and the recent group (2000-15). Our indication of hospitalization depends on the severity of organ lesions and the treatment strategy for SLE was consistent throughout the study period.

Incidence of osteonecrosis

The diagnosis of osteonecrosis was based on the 2001 revised criteria for classification of osteonecrosis of the femoral head from the Japanese Ministry of Health, Labor and Welfare [14]. Osteonecrosis of the knee was diagnosed in the same manner as the femoral head. The incidence of osteonecrosis and the extent of the necrotic area in the femoral head by using the type classification [14] was compared between the past and recent groups. Type classification is as follows; type A—lesion occupies the medial one-third or less of the weight-bearing portion; type B—lesion occupies the medial two-thirds or less of the weight-bearing portion; type C1—lesion occupies more than the medial two-thirds of the weight-bearing portion but does not extend laterally to the acetabular edge; and type C2—lesion extends laterally to the acetabular edge.

Risk factors for osteonecrosis

Age at initial glucocorticoid therapy, sex, complement (C3, C4, CH50) and anti-DNA antibody before initial glucocorticoid therapy, the organ lesion at hospitalization (be- cause each patient had a variety of symptoms, we counted them in duplicate) were compared between the past and recent groups. The highest daily glucocorticoid dose (mg/day) and the highest daily glucocorticoid dose per weight (mg/day/kg), and cumulative dose at 3 months (mg) were compared. Glucocorticoid doses were con- verted into equivalent prednisone doses based upon the method of Felson and Anderson [15]. Furthermore, anti- coagulants and antilipidemic drugs were compared during the first 3 months after glucocorticoid therapy.

Statistical analysis

JMP Pro 12.0 (SAS, Cary, NC, USA) was used for contingency table analysis with Pearson's Chi-square tests, and comparisons of unpaired groups with the Mann Whitney U test. Multivariate logistic regression analysis was calculated for osteonecrosis development as a dependent variable with treatment methods (intravenous CYC therapy, calcineurin inhibitors, steroid pulse and highest daily glucocorticoid dose) as independent variables. $P < 0.05$ was considered significant.

Results

Trends in immunosuppressive agent and glucocorticoid consumption are shown in Fig. 1. Characteristics of patients in the past and recent periods were similar in terms of clinical manifestations and disease activity (Table 1).

Glucocorticoid doses were significantly lower in the recent group than in the past group (highest daily glucocorticoid dose, 45.7 vs 59.0 mg/day; highest daily glucocorticoid dose per weight, 0.88 vs 1.16mg/day/kg; and cumulative dose at 3 months, 3118 vs 3985 mg).

The highest daily glucocorticoid dose was significantly lower in the recent period than in the past period (45.7 vs 59.0 mg/day, respectively). The highest daily glucocorticoid dose per weight was also significantly lower in the recent period than in the past period (0.88 vs 1.16mg/ day/kg, respectively).

The incidence of osteonecrosis was significantly lower in the recent period than in the past period (26.3 vs 41.0%, respectively). With respect to osteonecrosis of the knee joint, the incidence was also significantly lower in the recent period than in the past period (25.4 vs 46.6%, respectively). In hip joints, the incidence of osteonecrosis also tended to be lower in the recent period than in the past period (27.1 vs 35.3%, respectively), without statistical

significance. The extent of osteonecrosis of the fem- oral head showed almost similar distribution of the type classification between two groups.

In the past period, glucocorticoid doses were significantly lower in the group without osteonecrosis than in the group with osteonecrosis (highest daily glucocorticoid dose, 57.2 vs 60.9 mg/day, P = 0.006; highest daily glucocorticoid dose per weight, 1.12 vs 1.22mg/day/kg, P = 0.001), except cumulative dose at 3 months (3928 vs 4031 mg, P = 0.90). However, in the recent period, glucocorticoid doses were similar between the groups without osteonecrosis and with osteonecrosis (highest daily glucocorticoid dose, 47.5 vs 46.9 mg/day, P = 0.65; highest daily glucocorticoid dose per weight, 0.90 vs 0.91 mg/ day/kg, P = 0.93; and cumulative dose at 3 months, 3081 vs 3186 mg, P = 0.21). The use of anticoagulants was not significantly different in the past and recent periods [83% (39 of 47 patients) vs 72% (50 of 69 patients), P = 0.18]. The use of antilipidaemics was not significantly different in the past and recent periods, either [53% (37 of 70 patients) vs 39% (27 of 69 patients), P = 0.10].

Logistic regression analysis showed that only highest daily glucocorticoid dose was significantly related to occurrence of osteonecrosis (odds ratio: 1.05/1 mg/day in- crease, 95% CI: 1.01, 1.07, P = 0.007).

Discussion

To our knowledge, this is first study to investigate transitional changes in the incidence of glucocorticoid-induced osteonecrosis in SLE patients focusing on immunosuppressant drugs and glucocorticoids. Glucocorticoid ad- ministration and the incidence of osteonecrosis were significantly decreased following the introduction of calcineurin inhibitors (tacrolimus and CSA) in 2000. We suggest that these improved immunosuppressive regimens have reduced the demand for corticosteroids, and we hypothesize that reduction of corticosteroid doses will further decrease the incidence of osteonecrosis. At the same time, rheumatologists should still

pay attention to the fact that the incidence of osteonecrosis remains high, at about 26%, after initial corticosteroid therapy.

Many studies have examined the relationship between glucocorticoid administration and osteonecrosis in renal allografts [11, 12], but the association between glucocorticoid dosage itself and osteonecrosis remains controversial. Sakai et al. [11] reported that 16% of renal allograft patients treated with ciclosporin developed osteonecrosis, whereas none of the patients who received tacrolimus had osteonecrosis, suggesting that tacrolimus might be associated with a lower incidence of osteonecrosis com- pared with ciclosporin. Takao et al. [12] observed a lower incidence of osteonecrosis of the hip and knee (4.7%) in renal allograft recipients treated with improved immuno- suppressive regimens (ciclosporin or tacrolimus), which reduced cumulative glucocorticoid doses. However, no reports have been published about trends in the association between immunosuppressive agents/glucocorticoids and osteonecrosis in autoimmune disease.

New treatment strategies for SLE are currently being evaluated. Based on evidence, MMF is recommended as a first-line drug for both remission induction and maintenance therapy of active LN by ACR guidelines for screening, case definition, treatment and management of LN [16]. The multi-target therapy with MMF, steroids and tacrolimus has been proposed for active LN [17]. As adjunctive treatments, HCQ is recommended for all SLE patients with nephritis, unless there is a contra-indication [18]. MMF sup- presses lymphocyte proliferation in vivo, and HCQ inhibits IFN-a production [19]. These new therapies might further reduce the dependence of SLE patients on glucocorticoids, thereby decreasing the risk of osteonecrosis.

This study had several limitations. First, due to its retrospective nature, the immunosuppressive regimens used reflected physician preference and were not uniform. Calcineurin inhibitor use increased after 2000; to address this, patients were divided into two

cohorts depending on whether they were treated before 2000 (past) or from 2000 onwards (recent). Second, we documented the extent of necrotic areas, but could not follow up the patients. Improved immunosuppressive regimens would be expected to reduce the collapse of osteonecrosis and long-term outcome. Third, we only registered inpatients, but not outpatients, to limit the analysis to SLE patients who received high-dose glucocorticoid therapy. The treatment strategy of SLE in our hospital has not changed during the research period. Slight SLE patients, with a skin lesion but without a serious organ lesion or a joint lesion, were treated in an outpatient clinic. Such patients were not routinely screened with MRI because the amount of glucocorticoid was small and the risk of osteonecrosis deemed to be low. Thus, the precise occurrence of osteonecrosis could not be ascertained. However, the characteristics of the two cohorts of the past and the recent groups were similar in terms of clinical manifestations and disease activity; therefore, we believe that it does not have a big influence on this research. Fourth, the pathogenesis of osteonecrosis itself has not yet been elucidated. Some patients do not develop osteonecrosis even with same regimen of high-dose glucocorticoid therapy [10], although generally the incidence of osteonecrosis gradually increases with increasing glucocorticoid dose and gradually decreases with decreasing glucocorticoid dose [3]. Therefore, the association between glucocorticoid dose and osteonecrosis may be a stochastic and not a deterministic effect. Gene polymorphism may play a role in steroid sensitivity [20]. The prophylaxis for steroid-associated osteonecrosis has not yet been established, and further study of this condition is needed.

In conclusion, the incidence of glucocorticoid-associated osteonecrosis in SLE patients has decreased in association with decreased glucocorticoid administration following the introduction of immunosuppressant agents.

References

[1] Drescher W, Schneider T, Becker C et al. Selective reduction of bone blood flow by short-term treatment with high-dose methylprednisolone. An experimental study in pigs. J Bone Joint Surg Br. 2001; 83:274-7.

[2] Weinstein RS, Jilka RL, Parfitt AM, Manolagas SC. Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids. Potential mechanisms of their deleterious effects on bone. J Clin Invest. 1998; 102:274-82.

[3] Shigemura T, Nakamura J, Kishida S et al. Incidence of osteonecrosis associated with glucocorticoid therapy among different underlying diseases: prospective MRI study. Rheumatology (Oxford) 2011; 50:2023-8.

[4] Oinuma K, Harada Y, Nawata Y et al. Osteonecrosis in patients with systemic lupus erythematosus develops very early after starting high dose glucocorticoid treatment. Ann Rheum Dis 2001; 60:1145-8.

[5] Moon KL Jr, Genant HK, Helms CA et al. Musculoskeletal applications of nuclear magnetic resonance. Radiology 1983; 147:161-71.

[6] Sakamoto M, Shimizu K, Iida S et al. Osteonecrosis of the femoral head: a prospective study with MRI. J Bone Joint Surg Br 1997; 79:213-9.

[7] Iida S, Harada Y, Shimizu K et al. Correlation between bone marrow edema and collapse of the femoral head in steroid-induced osteonecrosis. Am J Roentgenol 2000; 174:735-43.

[8] Shigemura T, Nakamura J, Shimizu K et al. Articular col- lapse and surgical frequency in corticosteroid-associated osteonecrosis of the femoral head and the knee: an MRI- based prospective study. Eur Orthop Traumatol 2014; 5:153-60.

[9] Sakamoto MA. prospective study of steroid-induced osteonecrosis by MRI screening. Nippon Seikeigeka Gakkai Zasshi 1994; 68:367-78. In Japanese.

[10] Nakamura J, Ohtori S, Sakamoto M et al. Development of new osteonecrosis in systemic

lupus erythematosus patients in association with long-term glucocorticoid therapy after disease recurrence. Clin Exp Rheumatol 2010; 28:13-8.

[11] Sakai T, Sugano N, Kokado Y et al. Tacrolimus may be associated with lower osteonecrosis rates after renal trans- plantation. Clin Orthop Relat Res 2003; 415:163-70.

[12] Takao M, Sakai T, Nishii T et al. Incidence and predictors of osteonecrosis among cyclosporin- or tacrolimus-treated renal allograft recipients. Rheumatol Int 2011;31:165-70.

[13] Tan EM, Cohen AS, Fries JF et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982; 25:1271-7.

[14] Sugano N, Atsumi T, Ohzono K et al. The 2001 revised criteria for diagnosis, classification, and staging of idiopathic osteonecrosis of the femoral head. J Orthop Sci 2002; 7:601.

[15] Felson DT, Anderson JJ. Across-study evaluation of association between steroid dose and bolus steroids and avascular necrosis of bone. Lancet 1987; 1:902-6.

[16] Hahn BH, McMahon MA, Wilkinson A et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res 2012; 64:797-808.

[17] Bao H, Liu ZH, Xie HL et al. Successful treatment of class V+IV lupus nephritis with multi-target therapy. J Am Soc Nephrol 2008;19: 2001-10.

[18] Bertsias G, Ioannidis JP, Boletis J et al. EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. Ann Rheum Dis 2008; 67:195-205.

[19] Sacre K, Criswell LA, McCune JM. Hydroxychloroquine is associated with impaired interferon-alpha and tumor necrosis factor-alpha production by plasmacytoid dendritic cells in systemic lupus erythematosus. Arthritis Res Ther 2012;14: R155.

[20] Sakamoto Y, Yamamoto T, Sugano N et al. Genome-wide association study of idiopathic

osteonecrosis of the fem- oral head. Sci Rep 2017; 7:15035.

Table 1. Comparison between the past and recent groups.

Period	**Past (1986-1999)**	**Recent (2000-2015)**	***P*-value**
Patients	***n*=116**	***n*=69**	
Age at initial GC, years (range)	31.8 (15-59)	33.0 (15-66)	0.63[a]
Female, *n* (%)	112 (96.6)	58 (84.1)	0.25[b]
Organ lesion at hospitalization, n (%)[c]			
Skin disease	22 (19.0)	12 (17.4)	0.82[b]
Arthritis	40 (34.5)	26 (37.7)	0.61[b]
Serositis	11 (9.5)	12 (17.4)	0.11[b]
Renal failure	25 (21.6)	26 (37.7)	0.02[b]
NPSLE	6 (5.2)	6 (8.7)	0.35[b]
Hematologic disorder	28 (24.1)	24 (34.8)	0.12[b]
Other	10 (8.6)	8 (11.6)	0.73[b]
Complement and antibody			
C3, mg/dl (range)	42.9 (6-128)	49.4 (12-156)	0.09[a]
C4, mg/dl (range)	11.4 (1-60)	10.5 (1-50)	0.06[a]
CH50, U/ml (range)	21.5 (1.6-50)	20.8 (5-67)	0.28[a]
Anti-DNA antibody IU/ml	204.2 (2.5-2710)	210.5 (2-1242)	0.49[a]
Dose of steroids			
Highest daily GC dose, mg/day	59.0 (20-80)	45.7 (10-80)	<0.001[a]
Highest daily GC dose per weight mg/day/kg	1.16 (0.40-2.00)	0.88 (0.25-1.80)	<0.001[a]
Cumulative dose at 3 months, mg	3985 (1420-6690)	3118 (1680-6992)	<0.001[a]
Joints	*n*=464	*n*=276	
No. of hips with osteonecrosis, *n* (%)	82 (35.3)	38 (27.5)	0.12[b]
No. of knees with osteonecrosis, *n* (%)	108 (46.6)	35 (25.4)	<0.001[b]
Overall osteonecrosis, *n* (%)	190 (41.0)	73 (26.4)	<0.001[b]
Type classification of hip ON	*n*=82	*n*=38	

Type A,	*n* (%)	4 (5)	1 (3)	
Type B,	*n* (%)	7 (9)	3 (8)	0.86[b]
Type C1,	*n* (%)	23 (28)	9 (24)	
Type C2,	*n* (%)	45 (59)	25 (66)	

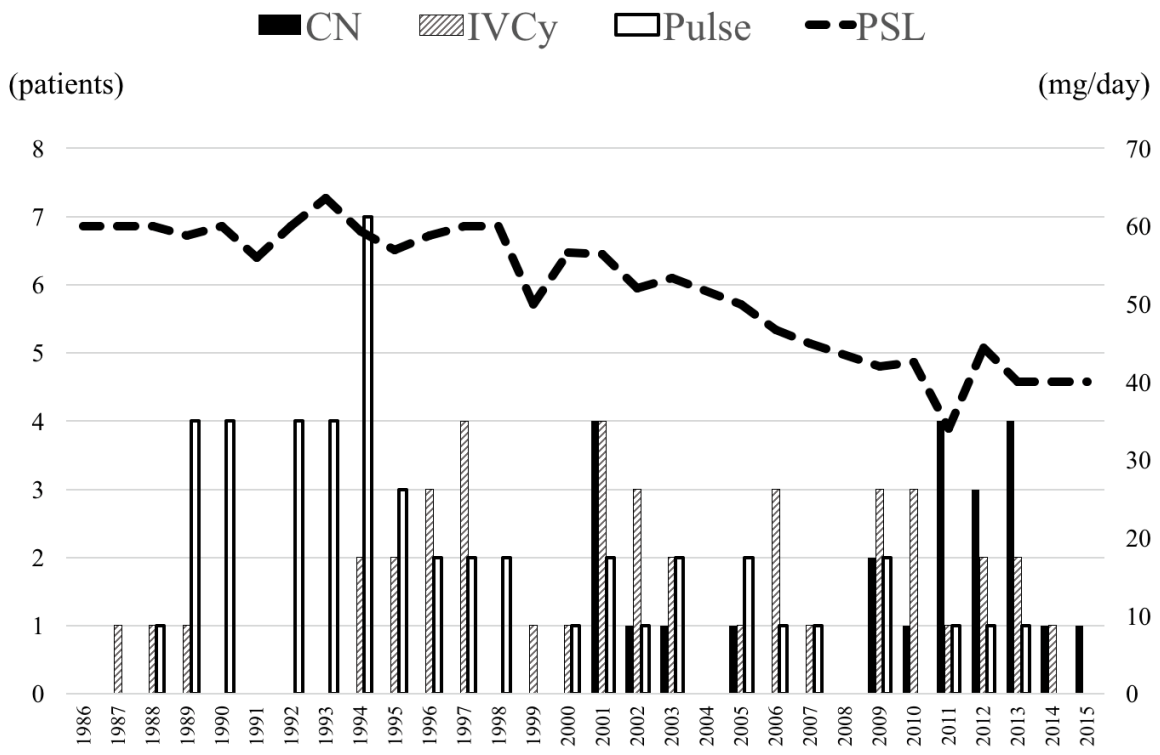
Organ lesion at hospitalization means clinical manifestations in the SLE cohorts.
GC: glucocorticoid, NPSLE: neuropsychiatric SLE, ON: osteonecrosis
[a]Mann-Whitney's U test, [b]Pearson's $\chi 2$ test, [c]Organ lesion at hospitalization was recorded twice for all SLE patients.

Figure legend

Figure 1. Calcineurin inhibitors (CN) were introduced in 2000. Steroid pulse therapy (Pulse) was often administered in the early 1990s, but its use gradually decreased thereafter, with a peak in 1994. In 1986, the highest daily glucocorticoid dose per oral dose (PSL) was 60 mg/day, but it gradually decreased to 40 mg/day by 2015. Intermittent pulse intravenous CYC therapy was used constantly throughout the study period. The left vertical axis indicates the number of patients, while the right vertical axis indicates glucocorticoid dose. The horizontal axis shows years.

Figure

Figure 1. Trends in immunosuppressive agent and glucocorticoid consumption.



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