Avascular necrosis less frequently found in systemic lupus erythematosus patients with the use of alternate day corticosteroid

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Background/aim: Avascular necrosis (AVN) is the death of bone due to compromise of blood flow. The etiology of AVN is multifactorial; corticosteroid usage is the second most significant factor after trauma, and systemic lupus erythematosus (SLE) is the most common underlying disease. The objective of this study was to assess the factors of AVN in SLE patients.

Materials and methods: The study included 127 patients with SLE who fulfilled 1997 American College of Rheumatology (ACR) revised criteria. Demographic data, age at SLE diagnosis, disease duration, disease activity, body mass index, clinical findings, antiphospholipid syndrome, steroid usage, dose and duration, comorbid diseases, and smoking history were recorded.

Results: AVN was found in 11 of 127 (8.7%) SLE patients. Hyperlipidemia (P < 0.001), cushingoid body habitus (P < 0.001), and proteinuria (P = 0.013) were found at higher rates in the AVN group. All of the 11 AVN cases had osteoporosis (P < 0.02). In multivariate regression analysis, daily steroid usage was the only factor for development of AVN in SLE.

Conclusion: The hypothesis of our study was that an alternate day steroid regimen may decrease AVN frequency in SLE patients.

Key words: Avascular necrosis, alternate day steroid usage, systemic lupus erythematosus

1. Introduction

Avascular necrosis (AVN) is bone death due to compromise of blood flow that leads to arthralgia, bone destruction, and loss of function in the joint. AVN etiology is multifactorial, and steroid usage is the second most important factor after trauma. Systemic lupus erythematosus (SLE) is the most common underlying disease in AVN [1]. In 1960, Dubois and Cozen reported AVN in SLE patients [2]. The prevalence of AVN in SLE patients is around 3%–52%, according to diagnostic methods and evaluation of symptomatic or asymptomatic patients [3]. The risk factors for AVN in SLE patients were shown to be young age, sex, cushingoid body habitus, Raynaud’s phenomenon, thrombophlebitis, vasculitis, nephritis, cerebritis, interstitial pneumonitis, pleural effusion, antiphospholipid syndrome, preeclampsia, hypertension, anemia, thrombocytopenic thrombotic purpura, smoking, and migraine [4]. The objective of this study was to evaluate associated factors for the development of AVN in our SLE cohort.

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2. Materials and methods

A total of 127 consecutive SLE patients (86.6% female) were enrolled in this cross-sectional study during 10 months in our outpatient clinic. Ethical approval was received from the local ethical committee. Inclusion criteria of this study were being ≥18 years old and fulfillment of the 1997 American College of Rheumatology (ACR) revised criteria for the classification of SLE [5].

Demographic data, clinical, and laboratory features were recorded from a standard questionnaire and from the patients’ files. Potential associated factors of AVN such as sex, age, body mass index, age at disease diagnosis, disease duration, smoking history, hypertension, diabetes mellitus, coronary artery disease, hyperlipidemia, anemia, osteoporosis, menopause, SLE disease activity score, antiphospholipid antibodies positivity, and corticosteroid usage were noted.

SLE disease activity index score (SLEDAI-2K) [6] was recorded for assessment of disease activity. SLEDAI scores were also calculated according to the situation 6 months prior to AVN diagnosis.
Cases with antiphospholipid syndrome were defined according to the 1999 classification criteria [7]. Lupus anticoagulant positivity and/or anticardiolipin antibody positivity were recorded one by one separately. Anti-beta 2 glycoprotein I antibodies could not be evaluated.

The corticosteroid usage of the patients was analyzed very carefully, from SLE diagnosis to introduction to the study of all the patients individually. The duration and dosage of the corticosteroid therapy, daily or alternate day regimen, and intravenous pulse steroid usage were recorded separately. In addition to total steroid dose, total daily or alternate day, total pulse steroid doses, and mean daily steroid doses were calculated. High-dose steroid was defined as >30 mg/day steroid usage at any time [8]. In our clinic, we prefer daily and pulse steroid use with induction treatment; and we prefer alternate day steroid use in the maintenance treatment.

AVN was diagnosed according to routine clinical practice, in symptomatic patients by plain X-ray and/or magnetic resonance imaging (MRI).

2.1. Statistical analysis
Data analysis was made by SPSS 15.0 (SPSS Inc., Chicago, IL, USA) and LogXact packet program, and P < 0.05 was considered as statistical significance. Descriptive statistics were given as mean ± standard deviation for numerical data and as number and percent for qualitative data. To compare numerical data between the AVN developed group (AVN group) and the AVN nondeveloped group (non-AVN group), an independent t-test was used; to compare percentile data, chi-square test and Fischer's exact test were applied. Independent variables that were significant after evaluation with single variable tests were evaluated by single variable logistic regression and exact logistic regression analysis to determine their odds ratio. To determine significant variables' effects on AVN development, multiple logistic regression analysis was applied.

3. Results
3.1. Demographic and clinical features
AVN was found in 11 of 127 (8.7%) SLE patients. Affected AVN sides were the femoral head (73%), shoulder (27%), knee (27%), and metatarsal head (9%). Multiple site involvement was found in 5 patients, and 24 sites were affected in total. All AVN patients had osteoporosis and were under bisphosphonates, calcium, and vitamin D therapy.

Demographic features, diagnostic criteria, and comorbid factors did not differ between the AVN group and the non-AVN group; hyperlipidemia, however, was significantly higher in the AVN group (P < 0.001). Antiphospholipid syndrome, Raynaud’s phenomenon, vasculitis, and SLEDAI, which were evaluated greatly in previous studies, were the same in both groups. However, cushingoid body habitus, proteinuria, and osteoporosis were significantly higher in the AVN group (P < 0.001, P < 0.013, and P < 0.03, respectively) (Table 1).

3.2. Corticosteroid therapy regimen
Corticosteroid was used by 122 of 127 (96.1%) SLE patients during the treatment protocol (Table 2). All AVN group patients had taken high-dose steroid therapy at some time in their treatment duration. There was no difference in corticosteroid usage ratio, corticosteroid usage duration, total corticosteroid dosage, or total corticosteroid dose/corticosteroid duration between patients with and without AVN. However, daily corticosteroid usage, high-dose steroid usage, and total daily steroid dosage were significantly higher in patients with AVN than in those without AVN. Patients without AVN had used alternate day corticosteroid more frequently.

Based on the results of our study, hyperlipidemia, osteoporosis, daily corticosteroid usage, total daily corticosteroid dose, high dose corticosteroid therapy, presence of proteinuria, and cushingoid body habitus were statistically significant factors for the development of AVN. According to the multivariate logistic regression analysis, daily steroid usage was associated independently with AVN occurrence (Table 3).

4. Discussion
In our study, hyperlipidemia, osteoporosis, daily corticosteroid usage, total daily corticosteroid dosage, persistent proteinuria, high-dose corticosteroid, and cushingoid body habitus variables were found to be individual risk factors for the development of AVN. However, multivariate analysis showed that only daily corticosteroid usage was a unique factor for AVN. From another point of view, alternate day corticosteroid usage was the protective factor for the development of AVN. Interestingly, total corticosteroid dosage and corticosteroid duration did not influence the development of AVN in this study.

The relationship between corticosteroid usage and AVN was first reported in renal transplant patients [9]. Thereafter, physicians noticed the relation between AVN and SLE. In a large cohort of 1729 SLE patients with symptomatic AVN, with more than 40 years of follow-up, multivariate analysis had shown that only corticosteroids were a primary risk for AVN [10]. Its prevalence changed from 3% to 52% between symptomatic patients and asymptomatic SLE patients [3]. AVN prevalence was reported as 6% in a study from Turkey with 868 SLE cases [11], the ratio of which was similar to our study (8.7%). In this study, we only assessed symptomatic patients; thus we can only say “at least” or “symptomatic” prevalence of AVN in SLE patients.
Various conflict risk factors were defined in the development of AVN in SLE patients. Some reports stated that young age is a risk factor for AVN occurrence [12–14]. Indeed, our patients with AVN were younger than those without AVN; however, the difference was not statistically significant. Hypertension, anemia, male sex, and diabetes mellitus were the other potential risk factors in the literature, but we did not find this kind of relationship [11,15]. In those risk factors, hyperlipidemia is an important risk factor for AVN, and some studies suggested that anti hyperlipidemic therapy may decrease AVN risk [16,17]. In a pathogenetic view, corticosteroid treatment may increase adipogenesis and fat hypertrophy in bone marrow, and cause intraosseous pressure increase,

### Table 1. Demographic and laboratory features of patients with and without AVN.

|                        | AVN (+) n = 11 | AVN (-) n = 116 | P-value |
|------------------------|----------------|-----------------|---------|
| Female, n (%)          | 9 (82)         | 101 (87)        | 0.6     |
| Age (mean ± SD)        | 34.5 (10.6)    | 39.1 (14.2)     | 0.3     |
| Age at SLE diagnosis (mean ± SD) | 28.5 (11.4)    | 32.3 (14.2)     | 0.4     |
| Disease duration months (mean ± SD) | 82.6 (74.3)    | 88.7 (67.5)     | 0.8     |
| Malar rash, n (%)      | 6 (54.5)       | 54 (46.6)       | 0.8     |
| Photosensitivity, n (%)| 8 (72.7)       | 71 (61.2)       | 0.5     |
| Oral ulcer, n (%)      | 1 (9.1)        | 31 (26.7)       | 0.3     |
| Discoid rash, n (%)    | 0 (0)          | 12 (10.3)       | 0.6     |
| Arthritis, n (%)       | 9 (81.8)       | 89 (76.7)       | 1.0     |
| Neurologic involvement, n (%) | 2 (18.2)       | 18 (15.5)       | 0.7     |
| Renal involvement, n (%) | 7 (63.6)     | 49 (42.2)       | 0.2     |
| Serositis, n (%)       | 2 (18.2)       | 25 (21.6)       | 1.0     |
| Hematologic involvement, n (%) | 5 (45.5)   | 54 (46.6)       | 1.0     |
| Raynaud’s phenomenon, n (%) | 7 (6.6)    | 40 (36.0)       | 0.1     |
| Vasculitis, n (%)      | 1 (9.1)        | 18 (15.7)       | 1.0     |
| ANA, n (%)             | 11 (100)       | 114 (98.3)      | 1.0     |
| ACA, n (%)             | 4 (36.4)       | 26 (22.4)       | 0.3     |
| LA, n (%)              | 3 (27.3)       | 20 (17.4)       | 0.4     |
| APL carriers, n (%)    | 6 (54.5)       | 31 (26.7)       | 0.1     |
| APLS, n (%)            | 5 (45.5)       | 17 (54.8)       | 0.4     |
| Persistent proteinuria ≥ 500 mg/day, n (%) | 4 (36.4) | 12 (10.3) | 0.013 |
| Anemia, n (%)          | 6 (54.5)       | 75 (64.7)       | 0.5     |
| SLEDAI -2K (mean ± SD) | 5.3 (3.5)      | 4.0 (4.8)       | 0.9     |
| Comorbid diseases, n (%)|              |                 |         |
| Hypertension           | 5 (45.5)       | 27 (23.3)       | 0.06    |
| Diabetes mellitus      | 0 (0)          | 11 (9.5)        | 0.6     |
| Coronary arterial disease | 0 (0)    | 4 (3.4)         | 1.0     |
| Hyperlipidemia         | 4 (36.4)       | 11 (9.5)        | <0.001  |
| BMI ≥ 25               | 7 (63.6)       | 57 (49.1)       | 0.53    |
| Smoking                | 4 (36.4)       | 29 (25.0)       | 0.47    |
| Cushingoid body habitus, n (%) | 8 (72.7) | 28 (24.3)       | <0.001  |
| Osteoporosis, n (%)    | 11 (100)       | 68 (66.7)       | 0.03    |

ACA: Anticardiolipin antibody positivity, ANA: Antinuclear antibody, APL carriers: antiphospholipid antibody carriers, APLS: Cases whom have both anticardiolipin and/or lupus anticoagulant positivity and abortus, thrombosis clinic, AVN: Avascular necrosis, BMI: body mass index, GFR: glomerular filtration rate, LA: Lupus anticoagulant positivity.
interrupt blood flow to the femoral head, and result in ischemic AVN [18]. In the present study, we found that hyperlipidemia was more frequent in the AVN group, but multivariate logistic regression analysis did not show a strong relation between hyperlipidemia and AVN. Cozen and Zhang et al. reported that AVN was frequent in active, severe lupus patients [15,19]. However, it is well known that severe organ involvement is associated with high-dosage corticosteroid usage, and we did not demonstrate this connection. Antiphospholipid syndrome is another risk factor for AVN that was investigated by most studies with conflicting results [20–23]. Our study has not suggested this relation. Osteoporosis, a frequent complication of corticosteroid and SLE, was found in all of our AVN cases. All of them were also receiving therapy for osteoporosis. High-dose corticosteroid may decrease bone formation rapidly and permanently, and increase bone resorption rapidly and temporarily [24]. Indeed, corticosteroid induced osteoblast and osteocyte apoptosis may be the common mechanisms for osteoporosis and AVN [25].

There was a strong association with daily corticosteroid usage and AVN in our study. In 10 of a total of 16 reports, it was suggested that mean daily, maximum daily, or high corticosteroid dosage was related with AVN occurrence. Eight of 13 reports concerned with cumulative corticosteroid dosage showed its relation with AVN [26]. The main result of our study was the superior effect for the protection of AVN by usage of alternate day corticosteroid. In a study that had compared long-term daily and alternate day corticosteroid, although cumulative corticosteroid dosage was higher in the alternate day group, corticosteroid side effects such as moon face, psychiatric complications, and regression in growth were low in the alternate day group; furthermore, similar remission rates were obtained for both groups [27]. In an animal study, AVN prevalence was 45% versus 8% between the daily corticosteroid group and intermittent corticosteroid group [28].

| Corticosteroid usage, n (%) | AVN (+), n = 11 | AVN (-), n = 116 | P-value |
|----------------------------|----------------|----------------|---------|
| Alternate day corticosteroid usage, n (%) | 5 (45.5) | 101 (91.0) | 0.003 |
| Daily corticosteroid usage, n (%) | 11 (100) | 54 (48.6) | 0.001 |
| Pulse corticosteroid usage, n (%) | 4 (36.4) | 42 (37.8) | 1.0 |
| High dose corticosteroid usage, n (%) | 11 (100) | 78 (70.3) | 0.035 |
| Corticosteroid duration (month) (mean ± SD) | 75.1 (71.5) | 81.6 (68.0) | 0.9 |
| Total corticosteroid dosage (gr) (mean ± SD) | 19.6 (14.6) | 21.4 (20.6) | 0.8 |
| Total corticosteroid dosage (mg) / corticosteroid duration (day) = daily dosage (mean ± SD) | 12.0 (7.5) | 15.7 (22.5) | 0.8 |

High-dose steroid: >30 mg/day steroid usage in any period of therapy; total steroid dose: total steroid dose used throughout therapy duration; steroid duration: steroid therapy duration as month.

NA: Standard errors could not be estimated in exact logistic regression analysis. Inf: Infinitive. AVN: avascular necrosis, SLE: systemic lupus erythematosus

| Table 3. Multivariate logistic regression analysis of predictive factors of AVN in SLE. |
|---------------------------------------------------------------|
| Hyperlipidemia | 1.549 | 0.973 | 0.237 | 4.71 (0.489–63.94) |
| Osteoporosis | 0.379 | NA | 0.765 | 1.46 (0.156–inf) |
| Daily steroid usage | 2.664 | NA | 0.014 | 14.35 (1.645–inf) |
| Total daily steroid dosage (gr) | -0.036 | 0.036 | 0.297 | 0.964 (0.889–1.03) |
| Persistent proteinuria ≥ 500 mg/day | 0.520 | 0.865 | 0.836 | 1.682 (0.194–14.19) |
| High dose steroid | 1.324 | NA | 0.251 | 3.758 (0.440–inf) |
| Cushingoid body habitus | 0.452 | 0.855 | 0.916 | 1.571 (0.215–13.57) |
cumulative corticosteroid exposure was similar in both groups, serum cortisol levels of the daily steroid group were fully suppressed, but the intermittent group had partial adrenal recovery. It was interpreted that partial recovery of adrenal suppression in the intermittent steroid group was the factor for low AVN risk. In ALL and renal transplant patients, low AVN prevalence and low infection risk were reported with alternate day corticosteroid [29,30]. Due to the acceptable side effect profile and similar clinical outcome of alternate day corticosteroid with daily corticosteroid, we have routinely preferred alternate day corticosteroid for long-term maintenance corticosteroid therapy in our outpatient clinic for more than 20 years.

The main limitation was the design of the study. We assessed SLE patients cross-sectionally; patient data was recorded from patients and also from medical files. We could not track patients prospectively, therefore, some of the patients who had AVN and joint prosthesis may be withdrawn from our follow-up. Hence, our AVN prevalence should be accepted as an “at least” frequency. We assessed only symptomatic patients through imaging. Thus, it is possible to find a high prevalence when evaluating all patients regularly by X-ray or MRI. Lastly, the number of AVN cases may not be enough for an absolute conclusion about possible AVN risk factors.

In conclusion, to decrease AVN risk in suitable patients, alternate day steroid usage may be encouraged in patients who are candidates for long-term maintenance corticosteroid usage. However, physicians should keep in mind that alternate day corticosteroid usage is also closely related with other appropriate immunosuppressive therapies.

**Conflict of Interest**
The authors declare that they have no conflict of interest. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**References**

1. Fukushima W, Fujioka M, Kubo T, Tamakoshi A, Nagai M et al. Nationwide epidemiologic survey of idiopathic osteonecrosis of the femoral head. Clinical Orthopedics and Related Research 2010; 468: 2715-2724.

2. Dubois E, Cozen L. Avascular necrosis associated with lupus erythematosus. Journal of the American Medical Association 1960; 174: 966-971.

3. Joo YB, Sung YK, Shim JS, Kim JH, Lee EK et al. Prevalence, incidence, and associated factors of avascular necrosis in Korean patients with systemic lupus erythematosus: A nationwide epidemiologic study. Rheumatology International 2015; 35: 879-886.

4. Assouline-Dayan Y, Chang C, Greenspan A, Shoenfeld Y, Gershwin ME. Pathogenesis and natural history of osteonecrosis. Seminars in Arthritis and Rheumatism 2002; 32: 94-124.

5. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis & Rheumatology 1997; 40: 1725.

6. Brunner HI, Feldman BM, Bombardier C, Silverman ED. Sensitivity of the Systemic Lupus Erythematosus Disease Activity Index, British Isles Lupus Assessment Group Index, and Systemic Lupus Activity Measure in the evaluation of clinical change in childhood-onset systemic lupus erythematosus. Arthritis & Rheumatology 1999; 42: 1354-1360.

7. Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branch DW et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis & Rheumatology 1999; 42: 1309-1311.

8. Sekiya F, Yamaji K, Yang K, Tsuda H, Takasaki Y. Investigation of occurrence of osteonecrosis of the femoral head after increasing corticosteroids in patients with recurring systemic lupus erythematosus. Rheumatology International 2010; 30: 1587-1593.

9. Sagakuchi M, Tanaka T, Fukushima W, Kubo T, Hirota Y. Impact of oral corticosteroid use for idiopathic osteonecrosis of the femoral head: a nationwide multicenter case-control study in Japan. Journal of Orthopedic Science 2010; 15: 185-191.

10. Gladman DD, Dhillon N, Su J, Urowitz MB. Osteonecrosis in SLE: prevalence, patterns, outcomes and predictors. Lupus 2018; 27 (1): 76-81. doi: 10.1177/0961203317711012

11. Sayarlioglu M, Yuzbisoglu N, Inanc M, Kamali S, Cefle A et al. Risk factors for avascular bone necrosis in patients with systemic lupus erythematosus. Rheumatology International 2012; 32: 177-182.

12. Heshin-Bekenstein M, Trupin L, Yelin E, von Scheven E, Yazdany J et al. Longitudinal disease- and steroid-related damage among adults with childhood-onset systemic lupus erythematosus. Seminars in Arthritis and Rheumatism 2019; 49 (2): 267-272. doi: 10.1016/j.semarthrit.2019.05.010

13. Faezi ST, Hoseinian AS, Paragomi P, Akbarian M, Esfahanian F et al. Non-corticosteroid risk factors of symptomatic avascular necrosis of bone in systemic lupus erythematosus: A retrospective case-control study. Modern Rheumatology 2015; 25 (4): 590-594. doi: 10.3109/14397595.2014.987366

14. Smith FE, Sweet DE, Brunner CM, Davis JS. Avascular necrosis in SLE. An apparent predilection for young patients. Annals of the Rheumatic Diseases 1976; 35: 227-232.
15. Cozen L, Wallace DJ. Avascular necrosis in systemic lupus erythematosus: clinical associations and a 47-year perspective. American Journal of Orthopedics 1998; 27: 352-354.

16. Wang GJ, Rawles JG, Hubbard SL, Stamp WG. Steroid-induced femoral head pressure changes and their response to lipid-clearing agents. Clinical Orthopedics and Related Research 1983; 174: 298-302.

17. Kuroda T, Tanabe N, Wakamatsu A, Takai C, Sato H et al. High triglyceride is a risk factor for silent osteonecrosis of the femoral head in systemic lupus erythematosus. Clinical Rheumatology 2015; 34 (12): 2071-2077. doi: 10.1007/s10067-015-3075-y

18. Kerachian MA, Seguin C, Harvey EJ. Glucocorticoids in osteonecrosis of the femoral head: A new understanding of the mechanisms of action. Journal of Steroid Biochemistry & Molecular Biology 2009: 114; 121-128.

19. Zhang K, Zheng Y, Jia J, Ding J, Wu Z. Systemic lupus erythematosus patients with high disease activity are associated with accelerated incidence of osteonecrosis: a systematic review and meta-analysis. Clinical Rheumatology 2018; 37 (1): 5-11. doi: 10.1007/s10067-017-3820-5

20. Houssiau FA, N’Zeusseu Toukap A, Depresseux G, Maldague BE, Malghem J et al. Magnetic resonance imaging-detected avascular osteonecrosis in systemic lupus erythematosus: lack of correlation with antiphospholipid antibodies. British Journal of Rheumatology 1998; 37: 448-453.

21. Mok CC, Lau CS, Wong RW. Risk factors for avascular bone necrosis in systemic lupus erythematosus. British Journal of Rheumatology 1998; 37: 895-900.

22. Migliaresi S, Picillo U, Ambrosone L, Di Palma G, Mallozzi M et al. Avascular necrosis in patients SLE: relation to corticosteroid therapy and anticardiolipin antibodies. Lupus 1994; 3: 37-41.

23. Asherson RA, Liote F, Page B, Meyer O, Buchanan N et al. Avascular necrosis of bone and antiphospholipid antibodies in systemic lupus erythematosus. Journal of Rheumatology 1993; 20: 284-288.

24. Hisada R, Kato M, Ohnishi N, Sugawara E, Fujieda Y et al. Antiphospholipid score is a novel risk factor for idiopathic osteonecrosis of the femoral head in patients with systemic lupus erythematosus. Rheumatology (Oxford) 2019; 58 (4): 645-649. doi: 10.1093/rheumatology/key365

25. Zalavras C, Shah S, Birnbaum MJ, Frenkel B. Role of apoptosis in glucocorticoid-induced osteoporosis and osteonecrosis. Critical Reviews in Eukaryotic Gene Expression 2003; 13: 221-235.

26. Powell C, Chang C, Naguwa SM, Cheema G, Gershwin ME. Steroid induced osteonecrosis: An analysis of steroid dosing risk. Autoimmunity Reviews 2010; 9: 721-743.

27. Hiraoka M, Tsukahara H, Matsubara K, Tsursawa M, Takeda N et al. A randomized study of two long-course prednisolone regimens for nephrotic syndrome in children. American Journal of Kidney Diseases 2003; 41: 1155-1162.

28. Yang L, Boyd K, Kaste SC. A Mouse model for glucocorticoid-induced osteonecrosis: effect of a steroid holiday. Journal of Orthopaedic Research 2009; 27: 169-175.

29. Mattano LA Jr, Devidas M, Nachman JB, Sather HN, Hunger SP et al. Effect of alternate-week versus continuous dexamethasone scheduling on the risk of osteonecrosis in paediatric patients with acute lymphoblastic leukaemia: results from the CCG-1961 randomised cohort trial. Lancet Oncology 2012; 13 (9): 906-915.

30. Dumler F, Levin NW, Szego G, Vulpetti AT, Preuss LE. Long-term alternate day steroid therapy in renal transplantation. A controlled study. Transplantation 1982; 34: 78-82.