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Necrosis of the femoral head after renal transplantation

Gunnar Schwarz Lausten[1], Jørgen Steen Jensen[1] and Klaus Ølgaard[2]

The cumulated risk of developing necrosis of the femoral head following renal transplantation was 42/374 in patients treated with steroids and azathioprine, and 4/124 in patients treated with cyclosporine-A and a reduced dose of steroids. 29 of the osteonecrosis cases were bilateral, with the time lapse between the two sides rarely exceeding 6 months. The reduction in the rate of osteonecrosis paralleled a reduction in the number of rejection episodes during the first month after transplantation and in the cumulated dose of steroids 1 month and 1 year after transplantation. We concluded that the risk of femoral head necrosis following renal transplantation is reduced by using cyclosporin-A for immunosuppression, which caused less rejection episodes and consequently a reduction in steroid medication.

During the last 10 years, cyclosporin-A has proved to be a potent immunosuppressive agent, which has permitted considerable reduction in the need for posttransplant steroids (Harder 1984, European Multicentre Trial Group 1986, Griffin et al. 1987, Landmann et al. 1987).

We report the effect of cyclosporin-A and low-dose prednisone on the rate of femoral-head necrosis after renal transplantation.

Patients and methods

We reviewed the records of 498 patients who had one or more renal transplantations with a graft survival of more than 3 months during the period 1968–1987. The average age at the time of renal transplantation was 41 (6–66) years (Table 1).

The standard immunosuppression after renal transplantation underwent only minor changes until 1983, when cyclosporin-A was introduced.

In 374 patients (206 men) the program was prednisone (usually 150 mg/day, gradually reduced to 30 mg/day after 4 weeks, with further reduction later) in combination with azathioprine given in accordance with the leucocyte and thrombocyte counts. Rejections were treated by methylprednisolone 1 gram intravenously as a peak dose, followed by high-dosage prednisone (600 mg/day for 2 days, then 300 mg/day for 2 days, reduced to 150 mg/day within 1 week). Azathioprine was continued in unchanged doses.

In 124 patients (69 men) the dosage of steroids was reduced to about half and combined with cyclosporin-A immediately preoperatively, aiming at a blood level of 200–500 µg/L.

The patients were generally radiographed at onset of pain. Only patients with radiographically confirmed osteonecrosis were included in this study; the date of the first radiographic abnormality was recorded. In 29 patients, both hips were affected, making a total of 75 affected hips. A further two patients with unilateral os-

Table 1. Age and sex distribution in 498 renal transplanted patients treated without (–) or with (+) cyclosporin-A/low-dose prednisone. Number of patients with osteonecrosis in brackets

Age (yr)	Boys	Girls	Failures
1–3 [a]	7	3	2
4–6	9	6	
7–9	5	3	1
10–13	5	4	1
	26	16	4

[a] 1 infant included

Departments of Orthopedics[1] and Nephrology[2], Rigshospitalet, University of Copenhagen, Denmark

Correspondence: Dr. Gunnar Schwarz Lausten, Tornehøj 132, DK-3520 Farum, Denmark

teonecrosis were excluded, as the time of onset could not be established.

Each patient with osteonecrosis was matched with a control without necrosis, according to year, number of transplantations, tissue match, sex, age, and time of follow-up in order to analyze the influence of immunosuppression. The parameters assessed included the cumulated dose of steroids during the first month and the first year after transplantation, number of rejections, serum levels of calcium and phosphate, and glomerular filtration rate 1 year after transplantation.

Seventy-five randomly selected patients from each of the two groups that had been treated with or without cyclosporin were compared regarding the cumulated dose of steroids during the first month and the first year after transplantation. Also, the number of patients with one or more episodes of rejection during the first month was recorded, and the serum levels of calcium, phosphorus, creatinine and glomerular filtration rate at one year after the transplantation were calculated.

The time-related incidence of osteonecrosis was calculated according to Kaplan and Meier (1958). The log rank test and the chi-square test for trend were used to detect differences between the two groups. For further analysis, the Mann-Whitney test and Fisher's exact test were used.

Results

The incidence of osteonecrosis before and after introduction of cyclosporin-A was 42/374 patients and 4/124 patients ($P < 0.01$; Table 1).

At one year, the chance of having femoral head necrosis in the first group was 0.03, increasing to 0.08 at two years, and becoming fairly constant at about 0.13 four years after the transplantation (Figure 1). In the second group, treated with cyclosporin-A and low-dose prednisone, the incidence became constant at 0.04 about one year after the transplantation ($P < 0.05$). No difference in age and sex was found between the patients with osteonecrosis and the entire group receiving renal transplants (Table 1). In the vast majority of cases developing bilateral osteonecrosis, the time lapse between the two hips did not exceed 6 months (Table 2).

When comparing patients with and without osteonecrosis, there were no differences in renal function 1 year after the transplantation. However, 35 out of the 46 patients with osteonecrosis experienced one or more episodes of rejection during the first month after the renal transplantation, as opposed to 22 out of 46 matched controls ($P < 0.05$; Table 3).

In the 17 patients with unilateral osteonecrosis, the graft and the affected hip were on the same side in 11 patients and in the contralateral hip in 6 patients (NS).

In the cyclosporine-A/low-dose prednisone-treated patients, the cumulated dose of steroids was lower and there were less rejection episodes during the first

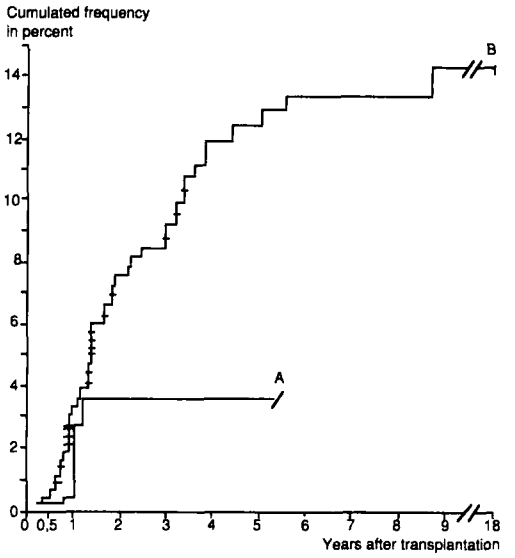

Figure 1. Cumulated frequency of femoral head necrosis.
A. 124 patients treated with cyclosporin-A and low-dose prednisone.
B. 374 patients treated with a normal dose of prednisone.

Table 2. Time dependency of diagnosis in the contralateral hip in 29 patients with bilateral femoral head osteonecrosis

Time of onset (yr)	Number of patients (n 29)
simultaneously	14
<1/2	8
1/2–1	4
1–2	2
>2	1

Table 3. Variables in 46 patients with osteonecrosis and in matched controls (mean values)

Variable	Osteonecrosis		P
	– (n 46)	+ (n 46)	
Prednisone 1 month (g)	4.2	4.1	NS [a]
Prednisone 1 year (g)	13.6	11.2	NS [a]
S-Calcium (mmol/L)	2.52	2.57	NS [a]
S-Phosphorus (mmol/L)	1.02	0.93	NS [a]
S-Creatinine (mmol/L)	0.16	0.14	NS [a]
Glom.filtr.rate (ml/min)	58	58	NS [a]
Patients with rejection	35	22	<0.05 [b]

[a] Mann-Whitney test.
[b] Chi-square test.

Table 4. Variables in 150 patients treated without (–) or with (+) cyclosporin-A/low-dose prednisone (mean ±SEM)

Variable	Cyclosporin-A		P^a
	– (n 75)	+ (n 75)	
Prednisone 1 month (g)	4.2±0.3	1.7±0.09	<0.01
Prednisone 1 year (g)	12.5±0.6	6.5±0.2	<0.01
S-Calcium (mmol/L)	2.54±0.02	2.46±0.02	<0.01
S-Phosphorus (mmol/L)	0.96±0.02	1.02±0.03	>0.01
S-Creatinine (mmol/L)	0.16±0.01	0.18±0.01	<0.01
Glom.filtr.rate (ml/min)	59±2.5	46±2.7	<0.01
Patients with rejection	51	21	<0.01

[a] Fisher exact test.

month after transplantation (Table 4). However, the 4 patients in this group who did develop necrosis of the femoral head, all had one or more rejection episodes during the first postoperative month.

The glomerular filtration rate was lower and, correspondingly, the creatinine level was higher in the cyclosporin-A patients ($P < 0.01$). Further, serum calcium was lower ($P < 0.01$) in these patients, although all the average values were within normal range.

Discussion

Cyclosporin-A is acting by a selective blockade of the interleukin-II release from the activated helper T-lymphocytes (Strom 1984). The use of this immunosuppressive agent has resulted in a considerable reduction in the number of rejection episodes and hence in a reduction in the cumulated dose of steroids given after renal transplantation (Calne et al. 1981, European Multicentre Trial Group 1986).

The slightly reduced glomerular filtration rate in the cyclosporin-A treated patient confirms other studies; it is probably due to the nephrotoxic effect of cyclosporin-A (Harder 1984, European Multicentre Trial Group 1986, Griffin et al. 1987).

The marked difference in the incidence of osteonecrosis following renal transplantation may, to some extent, be explained by differences in methods of evaluation, follow-up time, and the relatively small number of patients in most series (Table 5).

The reduction in the cumulated incidence of necrosis of the femoral head in the cyclosporin-A/low-dose prednisone-treated patients in our study is in agreement with that of two previous reports (The Canadian Multicentre Transplant Study Group 1983, Landmann et al. 1987). However, the follow-up period in these reports was rather short, and life-table methods were not applied.

Table 5. Incidence of osteonecrosis of the hip after renal transplantation in selected previous reports

Author	Year	Shortest graft survival (months)	No. of transplanted patients	Incidence of osteonecrosis n	%
Bewick et al	1976	18	378	10	3
Elmstedt & Svahn	1981	12	204	24	12
Farge et al	1985	12	206	23	11
Feletti et al	1984	–	227	15	7
Haajanen et al	1985	12	546	29	5
Hawking	1976	–	44	18	41
Heerfordt et al	1976	2	105	14	13
Ibels et al	1978	–	194	40	21
Metselaar et al	1985	–	189	59 [a]	–
Nielsen et al	1985	12	195	22	11
Ruderman et al	1979	14	30 [b]	4	13
Stern & Watts	1979	–	36 [b]	9	25
This report	1988	3	470	46	10

– Not stated.
[a] Including osteonecrosis in other joints.
[b] Only children.

The main advantage of this method is that the risk of osteonecrosis can be estimated at any time following the transplantation. Further, the patients are contributing to the estimated probabilities only during that period for which they have actually been followed.

Our patients were usually not radiographed or scintigraphed unless they had symptoms, which means that some of the patients in this report might have had a "silent" osteonecrosis (Lee et al. 1980, Miki et al. 1987) at an earlier time than reported here.

Both hips became affected in almost two thirds of the probands, but it is noteworthy that the risk of developing necrosis in the second hip seems to be modest later than half a year after the first.

A direct relationship between the dose of steroids and the risk of developing osteonecrosis has not been found in most previous reports (Ibels et al 1978, Felletti et al 1984, Stern & Watts 1979).

Individual variations in the suseptibility to steroid may play a contributing role in the pathogenesis of post-transplant osteonecrosis.

The reduced number of femoral head necrosis in renal transplanted patients after the introduction of cyclosporin-A as an immunosuppressive agent, paralleled a reduction in the number of rejection episodes and in the cumulated dose of steroids. No other suspected risk factors of osteonecrosis were changed during the period of observation. It does not seem likely that cyclosporin-A has a protective or delaying action against necrosis of the femoral head.

The present investigation indicates that pulsed high

Table 6. Data for 46 patients with osteonecrosis of the femoral head after renal transplantation

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	X	Y
1	M/29	42	R	10		(+)	+/+	98		51	5	–	1	(+)	2	4	1	10.0	6.0	3.0	0.5	6/2*	1/6*
2	M/23	12	R	10	A		+/+	94		44	5	–	1	+	3	4		11.0	8.0	1.0	1.0	6/4	4/6
3	M/18	12	L	13		+		88		99	25	+	3	(+)	2	3		10.0	6.0	3.0	2.0	4/4	4/5
4	F/42	36	R	9		+		86		91	25	+	6	–	3	3		10.0	4.0	2.0	1.0	5/3	3/5
5	F/23	96	L	13			+/+	84		90	25	+	4	Intervue by tel									
6	M/30	60	L	10	M	+		80		85	25	+	5	–	5	5		6.5	5.5	2.0	2.0	5/2*	3/6
7	M/20	3	R	12		+		78		90	20	+	8	+	2	3		10.0	6.0	2.0	1.0	8/5	4/7
8	M/26	72	L	10	L M	(+)	+/+	76		80	15	(+)	4	+	2	5		10.5	5.0	3.0	1.0	5/3	4/6
9	M/49	12	R	4		(+)		76		100	25	+	4	+	3	4		11.5	7.5	2.5	1.0	6/6	5/7
10	M/27	24	R	10	M		+/+	76		86	15	+	7	(+)	2	5		8.0	5.0	2.0	2.0	9/4*	6/8
11	F/20	3	L	3		+		73		100	25	+	8	+	2	4		11.0	7.5	3.0	2.5	6/5	5/6
12	M/18	36	R	13		(+)	/+	72		84	20	–	4	+	2	5		11.5	9.0	3.0	3.0	6/6	5/6
13	F/34	108	R	5		+		69		95	25	+	7	(+)	3	4		6.0	4.5	2.0	1.5	6/3	3/5
14	F/18	102	R	2	M	(+)	/+	69		72	5	–	2	+	2	4		15.0	9.0	3.0	2.0	6/2*	3/5
15	F/17	12	L	9		(+)	/+	69		81	10	+	5	+	2	3		12.0	5.0	4.0	1.0	5/4	4/5
16	F/35	5	L	9		(+)	/+	68		81	15	(+)	5	+	2	3		14.0	8.5	3.0	1.0	7/4	4/6
17	F/38	12	L	9	A	(+)	/+	68		67	15	–	3	+	3	3		8.0	6.0	2.0	2.0	5/3	3/5
18	F/32	156	L	5	M		+/+	66		67	15	(+)	2	+	2	3		12.5	7.0	2.5	2.0	7/2*	4/5
19	M/26	15	R	5			+/+	62		70	20	(+)	3	(+)	2	5		8.0	6.0	1.0	1.0	5/4	4/5
20	M/26	12	R	10		(+)	/+	62		76	20	(+)	4	(+)	2	4	2	12.0	5.0	3.5	1.0	6/3	5/5
21	F/20	12	L	5		(+)	/+	62		95	25	+	4	+	2	4		14.0	4.0	3.0	1.0	6/3	3/4
22	F/17	12	R	10		+		62		90	15	+	3	+	2	3		14.5	6.0	3.5	1.0	6/4	4/5
23	M/21	15	R	10	A	(+)	/+	62		90	25	+	7	(+)	2	4		8.5	5.0	1.5	1.0	7/6	5/6
24	M/26	15	L	10		+		61		86	25	(+)	4	+	3	4		8.5	8.0	3.0	3.0	6/3*	3/6*
25	M/28	60	L	10	M	(+)	/+	60		100	25	(+)	6	+	2	4		9.0	7.5	3.0	3.5	7/5	6/7
26	M/41	6	R	1		(+)	/+	58		91	25	+	4	+	2	5		11.0	6.0	2.0	1.0	6/4	4/5
27	M/48	12	R	10		+		58		98	25	+	3	(+)	3	4		4.5	4.0	1.0	1.0	6/3	4/6
28	M/19	14	L	7		+		53		90	15	(+)	7	Intervue by tel									
29	M/22	24	L	10		(+)		–						Not available									

*Arthrosis

Reoperated on knees

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q
30	F/18	4	R	11		+			60	68	5	–		+	2	5
31	M/20	48	R	10	M	+			48	64	5	–		+	1	3
32	F/20	60	L	10	M A		+/+		48	40	0	–		+	2	5
33	F/18	30	L	3		+			48	48	5	–		+	2	3
34	M/27	24	L	8		(+)	+/+		42	64	5	–		(+)	2	5
35	M/20	60	R	10	L M		+/+		36	68	10	–		+	2	5
36	M/26	36	R	10	M A		/+		24	21	0	–		+	4	3
37	M/21	8	L	10		+			15	68	10	–		(+)	4	3
38	F/19	14	L	10		(+)	/+		13	80	10	–		+	2	5
39	M/28	20	L	10		+			Reop at other hospital					+		

A Case number.
B Sex and age at operation.
C Months between primary trauma and extra-articular stabilization.
D Side.
E Cause of primary knee injury: 1 badminton, 2 ball play, 3 basketball, 4 fall, 5 gymnastics, 6 handball, 7 motocross, 8 sailing, 9 skiing, 10 soccer, 11 volleyball, 12 waterskiing, 13 traffic.
F Surgery before extra-articular repair: A Ant cruciate lig suture. L Removal lat meniscus; M Removal med meniscus.
G Pivot shift sign preop: + pos (+) difficult to provoke
H Anteromedial/anterolateral rotatory instability preop.
I Months follow-up-time.
J Months between extra-articular surgery and intra-articular ACL-reconstruction
K Lysholm score at follow-up or before reoperation.
L Lysholm stability score at follow-up or before reoperation
M Satisfied+/not satisfied – with extra-articular repair.
N Activity score at follow-up.
O Pivot shift at follow-up or before reoperation + pos, (+) difficult to provoke, – negative.
P Lachmann score at follow up or before operation. 5 normal, 4 slight < 1/2 cm; 3 moderate < 1 cm; 2 pronounced > 1 cm; 1 extreme > 2 cm
Q Varus instability at follow-up or before reoperation: 5 normal, 4 slight in flexion; 3 moderate in flexion; 2 moderate in extension; 1 pronounced.
R Other operations between index operation and follow-up. 1 removal medial meniscus, 2 suture medial meniscus.
S Arthrometer measurement: anterior drawer (mm) injured knee at 89 N pull.
T Arthrometer measurement: anterior drawer (mm) uninjured knee at 89 N pull.
U Compliance (mm) injured knee.
V Compliance (mm) uninjured knee.
X Radiographic examination: joint space (mm) injured knee, lateral compartment/medial compartment.
Y Radiographic examination: joint space (mm) uninjured knee, medial compartment/lateral compartment

postoperative steroids are major risk factors in the development of necrosis of the femoral head following renal transplantation (Heerfordt et al. 1978, Stern and Watts 1979, Morris et al. 1982, Haajanen et al. 1985). Consequently, cyclosporine-A and a reduction in the dose of steroids after renal transplantation are recommended.

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