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Journal of Orthopaedic Science 25 (2020) 466–471

Contents lists available at ScienceDirect

Journal of Orthopaedic Science

journal homepage: http://www.elsevier.com/locate/jos

Original Article

Transitional changes in the incidence of hip osteonecrosis among renal transplant recipients☆

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ARTICLE INFO

Article history:
Received 24 January 2019
Received in revised form
24 April 2019
Accepted 11 June 2019
Available online 4 July 2019

ABSTRACT

Background: Immunosuppressive therapy for renal allograft recipients has changed substantially since the introduction of the anti-CD25 monoclonal antibody, basiliximab. We hypothesized that recent improvements in immunosuppressive treatment may reduce the incidence of osteonecrosis of the femoral head (ONFH). This study aimed to investigate transitional changes in the incidence of OFNH among renal transplant recipients by MRI.

Methods: Participants comprised 110 patients who had undergone renal transplantation from 2003 to 2012, during which time basiliximab was in regular use at our institute (Recent group), and 232 patients who had undergone RT between 1986 and 2003 (Past group). We compared ONFH incidence between the two groups and evaluated risk factors for ONFH, including immunosuppressants (calcineurin inhibitors, basiliximab, and/or steroids) and postoperative renal function.

Results: Incidence of ONFH was lower in the Recent group (0%) than in the Past group (3.4%; $p = 0.043$). In the Recent group, age was greater, ABO/human leukocyte antigen incompatibility was worse, while steroid dose was decreased and post-transplant renal function was improved. Cumulative methylprednisolone dose at postoperative week 2 and delayed graft function were identified as risk factors for ONFH.

Conclusion: Risk of ONFH after renal transplantation has fallen with the advent of regular use of basiliximab, although this agent does not appear to be a factor directly associated with the incidence of ONFH.

Study design: Clinical prognostic study (Level III case control study).

1. Introduction

Osteonecrosis of the femoral head (ONFH) is well recognized as a musculoskeletal complication after renal transplantation (RT). With advances in immunosuppressive therapy, improved post-transplant renal function and reduced corticosteroid dose are reported to have led to a decrease in the incidence of ONFH [1–4]. However, according to recent screening studies using magnetic resonance imaging (MRI), this incidence ranged from 3.8% to 25.5% [3,5–11], inferring that ONFH remains a significant complication among renal allograft recipients.

Immunosuppressive therapy for renal allograft recipients has changed substantially since the introduction of the anti-CD25 monoclonal antibody, basiliximab (Simulect; Novartis, East Hanover, NJ). When administered as induction therapy during the early postoperative period, improvements in postoperative renal function have been reported [12–15]. Decreases in the doses of steroids and calcineurin inhibitors have also been reported [15] and indications for RT have therefore been expanded to include higher-risk patients with older age and increased human leukocyte antigen (HLA) mismatch. However, the impact of basiliximab

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https://doi.org/10.1016/j.jos.2019.06.009
0949-2658/

administration on the incidence of post-transplant ONFH has not yet been determined, and few MRI screening studies have been conducted since its introduction [3].

We hypothesized that recent improvements in immunosuppressive treatment may reduce the incidence of ONFH even with wider indications for RT. The purpose of the present study was two-fold: 1) to investigate transitional changes in the incidence of OFNH among renal transplant recipients by MRI; and 2) to investigate factors related to ONFH for the entire cohort.

2. Materials and methods

The ethical review board of our institution approved the design of this study (registration number: 13271). The Recent group included 110 patients (61 men, 49 women; mean (±standard deviation) age, 43 ± 13 years, range, 16–70 years); mean body mass index (BMI), (21.9 ± 3.3 kg/m^2) who underwent MRI of both hips after RT between April 2003 and June 2012 (i.e., during the period in which basiliximab was regularly used). During the period, 155 patients underwent RT. The Past group included 232 patients (143 men, 89 women; mean age, 34 ± 13 years; mean BMI, 21.9 ± 3.4 kg/m^2) who had undergone RT between January 1986 and March 2003 (i.e., prior to the regular use of basiliximab). During the period, 332 patients underwent RT. There was no significant difference in the rates of MRI screening between the groups. (69.8% (232/332) vs 70.9% (110/155), p = 0.80, chi-square test). All patients were notified about the reported incidences of ONFH after RT, benefits and risks of MRI, and possible treatment options, and given the opportunity to object.

MRI was performed 3 months after RT using either a 1.0-T superconducting magnet system (SIGNA Horizon LX 1.0T; General Electric Medical Systems, Milwaukee, WI), or one of two 1.5-T superconducting magnet systems (SMT150X; Shimadzu, Kyoto, Japan or Achieva 1.5T A-series; Philips Healthcare, Amsterdam, the Netherlands). Osteonecrosis was defined as an area of normal intensity demarcated by a low-intensity band on T1-weighted imaging [16]. T1-weighted spin-echo images were obtained using a 1.5-T system in the coronal and sagittal planes, with the following settings: repetition time (TR), 500–800 ms; echo time (TE), 12–43 ms; and slice thickness, 2–10 mm. Spoiled gradient-recalled echo pulse sequences were obtained using the 1.0-T system in the coronal plane with the following settings: TR, 4.5–14 ms; TE, 1.84–3.08 ms; flip angle, 30°; and slice thickness, 1.0–1.5 mm with no interslice gap.

The following items were evaluated: ONFH incidence; patient demographic and background factors, including gender, age, BMI, and ABO and HLA incompatibility; duration of preoperative dialysis; type of renal graft (living/cadaveric donor); preoperative immunosuppressant use, including calcium inhibitors (cyclosporine A/tacrolimus) administered initially or at the time of hospital discharge; concomitant basiliximab administration; steroid administration at 2, 4, 6, and 8 weeks after RT, as prednisolone (PSL), methylprednisolone (MPSL), and total steroid doses (converted to PSL-equivalent doses); postoperative renal function, including delayed graft function (DGF), blood urea nitrogen (BUN) and creatinine (Cr) levels at 8 weeks after RT, and acute transplant rejection; and duration of hospitalization. PSL-equivalent doses were calculated by adjusting the MPSL dose on the basis of anti-inflammatory potency, using a conversion factor of 1.25. Acute transplant rejection was diagnosed as follows: a 40% increase in BUN or a 20% increase in Cr level compared with those at a previous sampling, daily urinary output ≤750 ml, and diagnosis by biopsy. DGF was defined as a patient requiring hemodialysis in the first week after RT.

We compared these items between the Recent and Past groups using the Mann–Whitney U-test, chi-square test, and Fisher's exact probability test for statistical analyses. In addition, we investigated factors influencing the incidence of ONFH for the entire cohort. Uni- and multivariate logistic regression models were used to identify significant risk factors for ONFH for the entire cohort. The adjusted odds ratio (OR) for predicting ONFH was determined for each factor identified by univariate logistic regression analysis. SPSS for Windows version 20.0J statistical software (SPSS, Chicago, IL) was used for all statistical analyses. A 5% significance level was applied to all tests.

3. Results

No cases of ONFH were recorded in the Recent group (0%; 95% confidence interval (CI), 0%–3.3%), although eight cases of ONFH were recorded in the Past group (3.4%; 95% CI, 1.5–6.7%; one-sided Fisher's exact probability test, $p = 0.043$). Intergroup comparisons of background and demographic factors revealed significant increases in age, BMI, number of patients with ABO and HLA incompatibilities, and living kidney donors in the Recent group (Table 1). Comparison of postoperative immunosuppressant use showed increased frequency of tacrolimus use, increased number of patients with concomitant use of basiliximab, and decreases in MPSL, PSL, and total steroid dose at postoperative weeks 2, 4, 6, and 8 in the Recent group (Table 1). Regardless of the increase in risk factors for RT such as older age and increased number of ABO/HLA-incompatible transplants among patients, decreases in steroid administration and improvements in postoperative renal function have been observed in the Recent group. In addition, significant decreases were seen in the number of cases with DGF, concentrations of BUN and Cr at 8 weeks after transplantation, incidence of acute transplant rejection, and duration of hospitalization over time (Table 1).

The overall results were surveyed for risk factors for ONFH. According to the analysis of individual factors, total MPSL dose at postoperative weeks 2, 4, 6, and 8, total steroid dose at postoperative weeks 2, 4, 6, and 8 and DGF were identified as significant risk factors (Table 2). PSL administration at postoperative weeks 2, 4, 6, and 8 was not a risk factor. We performed multivariate analysis (logistic regression analysis) for age, gender, and total MPSL dose at postoperative week 2, and DGF. Significant risk factors for ONFH were total MPSL dose at postoperative week 2 (OR, 2.90; 95% CI, 1.04–8.07; $p = 0.04$) and DGF (OR, 5.97; 95% CI, 1.36–26.26; $p = 0.02$) (Table 3). When the MPSL doses at postoperative weeks 4, 6, and 8 were selected as a risk factor rather than that at week 2, the following were the adjusted values: for week 4, OR was 2.29 (95% CI, 1.03–5.13; $p = 0.04$); for week 6, OR was 1.83 (95% CI, 1.02–3.28; $p = 0.04$); and for week 8, OR was 1.71 (95% CI, 1.03–2.83; $p = 0.04$). MPSL administration at week 2 showed the highest adjusted OR.

The types of ONFH according to Japanese investigation committee classification, their natural course and surgical treatment were summarized in Table 4.

4. Discussion

Improvements in post-transplant renal function and reductions in corticosteroid dose may have led to a decrease in the incidence of ONFH [1–4]. Renal graft function after RT has been improving with advances in immunosuppressive agents such as cyclosporine A [2,17] and tacrolimus [12–14]. Several other immunosuppressive agents including sirolimus, everolimus, mycophenolate mofetil, and basiliximab have been introduced in combination with cyclosporine A or tacrolimus and have also improved postoperative renal function [18]. In contrast, few reports have been published about

Table 1
Comparisons of patient background, immunosuppressive therapy, ONFH incidence and posttransplant renal function between the Recent group and Past group.

	Recent group (n = 110)	Past group (n = 232)	p value
Patient background			
Sex (women/men)	49/61	89/143	0.33[a]
Age (years)	43 (13)	34 (10)	<0.001[b]
Body mass index (kg/m^2)	21.8 (3.3)	20.4 (2.8)	0.001[b]
ABO type incompatibility	34 (30.9%)	16 (6.9%)	<0.001[a]
HLA incompatibility (0–6)	2.8 (1.4)	2.1 (1.0)	<0.001[b]
Duration of preoperative dialysis (months)	45 (54)	41 (47)	0.72[b]
Living donor/Cadaveric donor	106/4	190/42	0.001[a]
Immunosuppressive therapy			
Tacrolimus/Cyclosporine (post-transplant)	59/51	61/171	<0.001[a]
Tacrolimus/Cyclosporine (at discharge)	62/48	74/157	<0.001[a]
Concomitant basiliximab use	98 (83%)	10 (3%)	<0.001[a]
Total PSL dose at week 2 (g)	0.49 (0.04)	0.57 (0.07)	<0.001[b]
Total PSL dose at at week 4 (g)	0.67 (0.06)	0.83 (0.08)	<0.001[b]
Total PSL dose at at week 6 (g)	0.80 (0.10)	1.00 (0.12)	<0.001[b]
Total PSL dose at at week 8 (g)	0.91 (0.14)	1.17 (0.11)	<0.001[b]
Total MPSL dose at week 2 (g)	0.58 (0.50)	0.80 (0.65)	0.004[b]
Total MPSL dose at week at week 4 (g)	0.70 (0.71)	1.18 (0.91)	<0.001[b]
Total MPSL dose at week at week 6 (g)	0.75 (0.78)	1.51 (1.20)	<0.001[b]
Total MPSL dose at week at week 8 (g)	0.84 (0.92)	1.64 (1.32)	<0.001[b]
Total steroid dose at week 2 (g)	1.21 (0.63)	1.58 (0.82)	0.003[b]
Total steroid dose at week at week 4 (g)	1.53 (0.90)	2.30 (1.15)	<0.001[b]
Total steroid dose at week at week 6 (g)	1.72 (1.00)	2.92 (1.51)	<0.001[b]
Total steroid dose at week at week 8 (g)	1.93 (1.20)	3.22 (1.67)	0.003[b]
ONFH incidence and post-transplant renal function			
ONFH	0 (0%)	8 (3.4%)	0.043[c]
Delayed graft function	8 (7.2%)	55 (23.7%)	0.004[a]
Blood BUN (mg/dl) (post-transplant week 8)	18.9 (8.8)	24.8 (11.0)	<0.001[b]
Blood Cr (mg/dl) (post-transplant 8)	1.3 (0.4)	1.6 (0.8)	<0.001[b]
Acute transplant rejection (yes/no)	15 (13.6%)	116 (50%)	<0.001[a]
Duration of hospitalization (days)	31 (15)	56 (21)	<0.001[b]

Data are presented as mean (standard deviation).
Significance set at $p < 0.05$.
PSL, prednisone; MPSL, methylprednisolone; Total steroid dose, total of PSL dose and MPSL dose, converted to PSL-equivalent dose; BUN, blood urea nitrogen; Cr, blood creatinine; ONFH, osteonecrosis of the femoral head.
[a] Chi-square test.
[b] Mann-Whitney U test.
[c] One-sided Fisher's exact test.

the influence of these new immunosuppressive agents on the incidence of ONFH after RT. Basiliximab, an anti-CD25 monoclonal antibody, is a very strong immunosuppressive agent that exerts its effects through competitive interleukin-2 antagonism [19]. When administered as an induction therapy during the early post-operative period, in conjunction with one or more conventional immunosuppressive drugs, decreases in the incidences of acute transplant rejection and DGF and improvements in survival of the transplanted kidney have been reported [12–15]. Decreases in steroid and calcineurin inhibitor doses have also been reported [15,20,21]. These marked changes in immunosuppressive treatments and postoperative renal function may have reduced the incidence of ONFH. The proportion of ONFH patients receiving steroid treatment for renal transplantation has reportedly decreased recently according to the multicenter hospital-based sentinel monitoring system for ONFH in Japan [22], although the reasons for these decreases in the proportion of ONFH patients receiving renal transplantation remain unclear. In addition, only a small number of reports since 2001 have described MRI screening for ONFH after RT, and the impact of the introduction of basiliximab on the post-transplant incidence of ONFH has yet to be determined. We therefore investigated the incidence of ONFH since the advent of regular basiliximab use and found that postoperative renal graft function had improved, and the MPSL dose and incidence of DGF as risk factors for ONFH had decreased. In addition, the incidence of ONFH had decreased. Basiliximab seems likely to indirectly reduce the incidence of ONFH by reducing the incidence of DGF and allowing reductions in MPSL administration.

Three main limitations need to be considered when interpreting the results from the present study. First, the number of renal transplant recipients with use of basiliximab might be too small to evaluate its effect on the incidence of ONFH. The number of patients included in previous MRI screening studies ranged from 26 to 150 [3,5–10], so the number of patients in the present study is comparable with the numbers in those studies. Second, MRI screening was not performed before RT, so we could not be sure that ONFH had not been present prior to transplantation. Nevertheless, because the incidence of ONFH in our study was lower than that in any previous study evaluated using MRI, the incidence was presumed to have also been low even before transplantation. Third, the timing of MRI screening was earlier compared to other MRI screening studies. This might be one reason the incidence of ONFH at our institute was lower than described in other reports performed during a similar period. We did not encounter any symptomatic cases with ONFH in which MRI had been negative at 3 months after RT, so we considered that the incidence of ONFH occurring after 3 months after RT was unlikely to have been particularly high.

ONFH did not occur in any of the 110 patients who underwent RT between April 2003 and June 2012 at our institution, despite the wider indications for RT in high-risk patients, such as older age and more severe ABO and HLA incompatibilities. In previous MRI

Table 2
Univariate analysis of risk factors for osteonecrosis of the femoral head.

	ONFH (+)	ONFH (−)	Crude OR (95% CI)	p value
	n = 8	n = 334		
Patient background				
Sex (male/female)	6/2	198/136	2.06 (0.41–10.30)	0.38
Age (years)	38 (9)	37 (11)	1.01 (0.95–1.07)	0.80
BMI (kg/m^2)	19.9 (1.7)	21.0 (3.1)	0.89 (0.68–1.16)	0.38
ABO incompatibility	0	50	0.000 (NA)	0.98
HLA incompatibility (0–6)	2.0 (0.9)	2.4 (1.2)	0.77 (0.42–1.39)	0.39
HD duration (days)	33 (33)	42 (49)	1.0 (0.98–1.01)	0.60
Donor kidney (Living/death)	5/3	291/43	0.24 (0.06–1.07)	0.06
Immunosuppressive therapy				
Tacrolimus (post-transplant)	1	119	0.26 (0.03–2.12)	0.21
Tacrolimus (at discharge)	2	134	0.49 (0.10–2.46)	0.39
Basiliximab treatment	1	107	0.30 (0.04–2.49)	0.27
Total PSL dose at week 2 (g)	0.55 (0.08)	0.54 (0.07)	8.52 (0.000–2.31 × 10^5)	0.68
Total PSL dose at week 4 (g)	0.83 (0.09)	0.78 (0.10)	232.97 (0.25–2.21 × 10^5)	0.12
Total PSL dose at week 6 (g)	1.02 (0.11)	0.94 (0.14)	75.74 (0.37–1.54 × 10^4)	0.11
Total PSL dose at week 8 (g)	1.20 (0.12)	1.09 (0.17)	51.45 (0.63–4.15 × 10^3)	0.08
Total MPSL dose at week 2 (g)	1.31 (0.80)	0.72 (0.61)	3.24 (1.31–8.04)	0.01
Total MPSL dose at week 4 (g)	1.72 (1.34)	1.02 (0.86)	2.01 (1.06–3.80)	0.03
Total MPSL dose at week 6 (g)	2.31 (1.63)	1.26 (1.12)	1.87 (1.13–3.12)	0.02
Total MPSL dose at week 8 (g)	2.59 (1.90)	1.37 (1.24)	1.79 (1.14–2.81)	0.01
Total steroid dose at week 2 (g)	2.19 (1.00)	1.44 (0.77)	2.54 (1.24–5.22)	0.01
Total steroid dose at week 4 (g)	2.98 (1.72)	2.04 (1.11)	1.76 (1.07–2.90)	0.03
Total steroid dose at week 6 (g)	3.91 (2.09)	2.51 (1.45)	1.65 (1.11–2.45)	0.01
Total steroid dose at week 8 (g)	4.44 (2.44)	2.79 (1.62)	1.58 (1.12–2.26)	0.01
Post-transplant renal function				
Delayed graft function	5	58	7.93 (1.84–34.12)	0.005
BUN at post-transplant week 8 (mg/dl)	31.6 (13.1)	22.8 (10.6)	1.05 (1.004–1.09)	0.03
Cr at post-transplant week 8 (mg/dl)	2.0 (1.1)	1.5 (0.7)	1.67 (0.98–2.85)	0.06
Acute transplant rejection	5	126	2.70 (0.63–11.49)	0.18
Duration of hospitalization (days)	60 (18)	48 (22)	1.02 (0.99–1.04)	0.12

Data are presented as mean (standard deviation).
ONFH, osteonecrosis of the femoral head; OR, odds ratio; CI, confidence interval; BMI, body mass index; HD, hemodialysis; PSL, prednisolone; MPSL, methylprednisolone; BUN, blood urea nitrogen; Cr, creatinine.

Table 3
Multivariate analysis of risk factors for osteonecrosis of the femoral head among renal allograft recipients.

Factor	Adjusted OR (95% CI)	p value
Age	1.001 (0.95–1.06)	0.96
Sex (male)	2.06 (0.39–10.72)	0.40
MPSL dose at week 2 (g)	2.90 (1.04–8.07)	0.04
Delayed graft function	5.97 (1.36–26.26)	0.02

OR, odds ratio; CI, confidence interval; MPSL, methylprednisolone.

screening studies of ONFH after RT performed between 1986 and 2001 without the use of basiliximab, incidences of ONFH after RT were within the range of 3.4–25.4% [3,5–10]. Although a downward trend was observed in those studies, no MRI screening studies for ONFH have been reported since 2002, and the present study showed the lowest incidence of ONFH after RT among all relevant studies (Table 5).

To elucidate the risk factors for ONFH, all RT recipients who underwent MRI screening at our institute were analyzed. The results showed that DGF and cumulative MPSL administration up to 2 weeks after RT were significant risk factors. Other risk factors for ONFH reported after RT include daily oral steroid dose, BUN

Table 4
JIC classification, natural course and surgical treatment of osteonecrosis of the femoral head.

Case No.	Sex	Age at RT (years)	Follow-up period (years)	Side	JIC type	Occurrence of collapse	Surgical treatment
1	M	32	20	R	C1	Yes	THA
2	M	30	29	R	B	No	No
				L	C1	Yes	THA
3	M	39	33	R	C2	Yes	THA
				L	C1	Yes	Femoral osteotomy
4	F	42	30	R	C1	Yes	THA
				L	B	Yes	No
5	M	49	14	R	A	No	No
				L	A	No	No
6	M	42	15	R	A	No	No
				L	C1	Yes	No
7	F	24	4	R	A	No	No
				L	A	No	No
8	M	48	20	R	C2	No[a]	No

JIC, Japanese Investigation Committee; RT, renal transplantation; M, male; F, female; R, right; L, left; THA, total hip arthroplasty.
[a] Radiographic follow-up ended at 4 years after renal transplantation.

Table 5
Studies of magnetic resonance imaging screening for osteonecrosis of the femoral head (ONFH) after renal transplantation.

Author	Survey period	Transplant patients (cases)	ONFH incidence (%)
Kospecky et al., 1991	1986–1989	104	13.5
Kubo et al., 1997	1988–1992	51	25.5
Shibatani et al., 2008	1988–1999	150	24.6
Fink et al., 1997	1992–1993	43	9.3
Fujioka et al., 2001	1996–1999	57	21
Marston et al., 2002	1997–2000	26	15.4
Lopez-Ben et al., 2004	1999–2001	48	4.2
Present study	1986–2003	232	3.4
	2003–2012	110	0

level 2 months after RT, accumulated steroid dose at 2 months, accumulated steroid dose at 2 weeks, ethnicity (African-American), history of peritoneal dialysis, rejection, delayed graft function, and cyclosporine A administration [1,10,11,23–25]. To date, cumulative steroid dose as of 2 weeks postoperatively has been reported as the shortest-term risk factor for ONFH [24]. The risk factors for ONFH after RT in the present study were in accordance with past findings. This result suggests that ONFH occurs mostly within the first 2 weeks after RT, suggesting the importance of controlling postoperative graft function and reducing cumulative MPSL administration in the first 2 weeks after RT using immunosuppressive agents that are appropriate for the prevention of ONFH.

A recent meta-analysis of ONFH occurrences among patients taking corticosteroids reported positive associations between mean daily corticosteroid doses and ONFH across all diagnoses, including severe acute respiratory syndrome, systemic lupus erythematosus, bone marrow transplantation and renal transplantation, although the correlation between mean daily corticosteroid dose and ONFH incidence was not significant among renal transplant recipients [26]. No evidence of a significant correlation between cumulative corticosteroid dose and incidence of ONFH has yet been provided [26,27]. In renal transplant recipients, daily steroid dose is gradually tapered according to the immunosuppressive regimen, so reflecting an overall picture of steroid treatment using a mean value for daily steroid dose is difficult. In addition, duration of steroid treatment and overall cumulative steroid dose vary widely among renal recipients, and steroid administration after onset of ONFH might be included in the regression analysis. We therefore focused on the correlation between steroid administration including oral steroid administration and pulsed steroid therapy in the 8 weeks after renal transplantation and onset of ONFH at 3 months.

5. Conclusions

The risk of ONFH after RT has fallen since the advent of regular basiliximab use, although this agent does not appear to be a factor directly associated with the incidence of ONFH. Factors related to ONFH incidence were found to be renal graft function and MPSL administration for up to 2 weeks. Since the introduction of basiliximab, immunosuppressive therapy has changed markedly and renal graft control has also been enhanced, which may have led to decreases in the incidence of ONFH.

Funding information

This research is supported by the Practical Research Project for Rare/Intractable Diseases from Japan Agency for Medical Research and development, AMED.

Author contributions

In accordance with ICMJE criteria, NS and ST designed the study and MT wrote the initial draft of the manuscript. HA contributed to the collection and interpretation of data and the assistance of the preparation of the manuscript. The literature data were searched and analyzed by MT and HA. All other authors contributed to the data collection and interpretation. All authors approved the final version to be submitted for publication and agree to be accountable for all aspects of the work.

Conflict of interest

None.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards."

Informed consent

Informed consent was obtained in the form of opt-out on the web-site. Those who rejected were excluded.

Acknowledgments

Authors thank Dr. Hideki Yoshikawa, Dr. Koji Yazawa, and Dr. Naotsugu Ichimaru for helpful advice.

References

[1] Abbott KC, Koff J, Bohen EM, Oglesby RJ, Agodoa LY, Lentine KL, Schnitzler MA. Maintenance immunosuppression use and the associated risk of avascular necrosis after kidney transplantation in the United States. Transplantation 2005 Feb 15;79(3):330–6.
[2] Landmann J, Renner N, Gachter A, Thiel G, Harder F. Cyclosporin A and osteonecrosis of the femoral head. J Bone Joint Surg Am 1987 Oct;69(8):1226–8.
[3] Lopez-Ben R, Mikuls TR, Moore DS, Julian BA, Bernreuter WK, Elkins M, Saag KG. Incidence of hip osteonecrosis among renal transplantation recipients: a prospective study. Clin Radiol 2004 May;59(5):431–8.
[4] Sakai T, Sugano N, Kokado Y, Takahara S, Ohzono K, Yoshikawa H. Tacrolimus may be associated with lower osteonecrosis rates after renal transplantation. Clin Orthop Relat Res 2003 Oct;(415):163–70.
[5] Fink B, Degenhardt S, Paselk C, Schneider T, Modder U, Ruther W. Early detection of avascular necrosis of the femoral head following renal transplantation. Arch Orthop Trauma Surg 1997;116(3):151–6.
[6] Fujioka M, Kubo T, Nakamura F, Shibatani M, Ueshima K, Hamaguchi H, Inoue S, Sugano N, Sakai T, Torii Y, Hasegawa Y, Hirasawa Y. Initial changes of non-traumatic osteonecrosis of femoral head in fat suppression images: bone marrow edema was not found before the appearance of band patterns. Magn Reson Imaging 2001 Sep;19(7):985–91.

[7] Kopecky KK, Braunstein EM, Brandt KD, Filo RS, Leapman SB, Capello WN, Klatte EC. Apparent avascular necrosis of the hip: appearance and spontaneous resolution of MR findings in renal allograft recipients. Radiology 1991 May;179(2):523–7.
[8] Kubo T, Yamazoe S, Sugano N, Fujioka M, Naruse S, Yoshimura N, Oka T, Hirasawa Y. Initial MRI findings of non-traumatic osteonecrosis of the femoral head in renal allograft recipients. Magn Reson Imag 1997;15(9):1017–23.
[9] Marston SB, Gillingham K, Bailey RF, Cheng EY. Osteonecrosis of the femoral head after solid organ transplantation: a prospective study. J Bone Joint Surg Am 2002 Dec;84-a(12):2145–51.
[10] Shibatani M, Fujioka M, Arai Y, Takahashi K, Ueshima K, Okamoto M, Yoshimura N, Hirota Y, Fukushima W, Kubo T. Degree of corticosteroid treatment within the first 2 months of renal transplantation has a strong influence on the incidence of osteonecrosis of the femoral head. Acta Orthop 2008 Oct;79(5):631–6.
[11] Takao M, Sakai T, Nishii T, Yoshikawa H, Takahara S, Sugano N. Incidence and predictors of osteonecrosis among cyclosporin- or tacrolimus-treated renal allograft recipients. Rheumatol Int 2011 Feb;31(2):165–70.
[12] First MR. Renal function as a predictor of long-term graft survival in renal transplant patients. Nephrol Dial Transplant 2003 May;18(Suppl 1):i3–6.
[13] Jurewicz WA. Tacrolimus versus cyclosporin immunosuppression: long-term outcome in renal transplantation. Nephrol Dial Transplant 2003 May;18(-Suppl 1):i7–11.
[14] Kramer BK, Montagnino G, Del Castillo D, Margreiter R, Sperschneider H, Olbricht CJ, Kruger B, Ortuno J, Kohler H, Kunzendorf U, Stummvoll HK, Tabernero JM, Muhlbacher F, Rivero M, Arias M. Efficacy and safety of tacrolimus compared with cyclosporin A microemulsion in renal transplantation: 2 year follow-up results. Nephrol Dial Transplant 2005 May;20(5):968–73.
[15] Liborio AB, Mendoza TR, Esmeraldo RM, Oliveira ML, Paes FJ, Silva Junior GB, Daher EF. Induction antibody therapy in renal transplantation using early steroid withdrawal: long-term results comparing anti-IL2 receptor and anti-thymocyte globulin. Int Immunopharmacol 2011 Nov;11(11):1832–6.
[16] Sugano N, Atsumi T, Ohzono K, Kubo T, Hotokebuchi T, Takaoka K. The 2001 revised criteria for diagnosis, classification, and staging of idiopathic osteonecrosis of the femoral head. J Orthop Sci 2002;7(5):601–5.
[17] Lausten GS, Jensen JS, Olgaard K. Necrosis of the femoral head after renal transplantation. Acta Orthop Scand 1988 Dec;59(6):650–4.
[18] Thomusch O, Wiesener M, Opgenoorth M, Pascher A, Woitas RP, Witzke O, Jaenigen B, Rentsch M, Wolters H, Rath T, Cingoz T, Benck U, Banas B, Hugo C. Rabbit-ATG or basiliximab induction for rapid steroid withdrawal after renal transplantation (Harmony): an open-label, multicentre, randomised controlled trial. Lancet 2016 Dec 17;388(10063):3006–16.
[19] Amlot PL, Rawlings E, Fernando ON, Griffin PJ, Heinrich G, Schreier MH, Castaigne JP, Moore R, Sweny P. Prolonged action of a chimeric interleukin-2 receptor (CD25) monoclonal antibody used in cadaveric renal transplantation. Transplantation 1995 Oct 15;60(7):748–56.
[20] Boletis JN, Theodoropoulou H, Hiras T, Stamatiadis D, Darema M, Psimenou E, Stathakis C, Kostakis A. Monoclonal antibody basiliximab with low cyclosporine dose as initial immunosuppression. Transplant Proc 2001 Nov–Dec;33(7–8):3184–6.
[21] Ponticelli C, Yussim A, Cambi V, Legendre C, Rizzo G, Salvadori M, Kahn D, Kashi H, Salmela K, Fricke L, Heemann U, Garcia-Martinez J, Lechler R, Prestele H, Girault D. A randomized, double-blind trial of basiliximab immunoprophylaxis plus triple therapy in kidney transplant recipients. Transplantation 2001 Oct 15;72(7):1261–7.
[22] Takahashi S, Fukushima W, Yamamoto T, Iwamoto Y, Kubo T, Sugano N, Hirota Y. Temporal trends in characteristics of newly diagnosed nontraumatic osteonecrosis of the femoral head from 1997 to 2011: a hospital-based sentinel monitoring system in Japan. J Epidemiol 2015;25(6):437–44.
[23] Abbott KC, Oglesby RJ, Agodoa LY. Hospitalized avascular necrosis after renal transplantation in the United States. Kidney Int 2002 Dec;62(6):2250–6.
[24] Saito M, Ueshima K, Fujioka M, Ishida M, Goto T, Arai Y, Ikoma K, Fujiwara H, Fukushima W, Kubo T. Corticosteroid administration within 2 weeks after renal transplantation affects the incidence of femoral head osteonecrosis. Acta Orthop 2014 Jun;85(3):266–70.
[25] Schachtner T, Otto NM, Reinke P. Cyclosporine use and male gender are independent determinants of avascular necrosis after kidney transplantation: a cohort study. Nephrol Dial Transplant 2018 Nov 1;33(11):2060–6.
[26] Mont MA, Pivec R, Banerjee S, Issa K, Elmallah RK, Jones LC. High-dose corticosteroid use and risk of hip osteonecrosis: meta-analysis and systematic literature review. J Arthroplast 2015 Sep;30(9):1506–12. e5.
[27] Yoon BH, Jones LC, Chen CH, Cheng EY, Cui Q, Drescher W, Fukushima W, Gangji V, Goodman SB, Ha YC, Hernigou P, Hungerford M, Iorio R, Jo WL, Khanduja V, Kim H, Kim SY, Kim TY, Lee HY, Lee MS, Lee YK, Lee YJ, Mont MA, Sakai T, Sugano N, Takao M, Yamamoto T, Koo KH. Etiologic classification criteria of ARCO on femoral head osteonecrosis Part 1: glucocorticoid-associated osteonecrosis. J Arthroplast 2019 Jan;34(1):163–168.e1.