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Original Article

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

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A B S T R A C T

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).

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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
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 ONFH 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/m²) 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/m²) 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 20.0 (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
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 postoperative 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 by reducing the incidence of DGF and allowing reductions in MPSL administration.

The 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 previously. 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 previously. 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 previously. The present study.
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]. 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 2 |
| --- |
| **Univariate analysis of risk factors for osteonecrosis of the femoral head.** |
| | ONFH (+) | ONFH (−) | Crude OR (95% CI) | p value |
| **Patient background** | | | | |
| Sex (male/female) | 6/2 | 198/334 | 2.06 (0.41–10.30) | 0.38 |
| Age (years) | 38 (9) | 37 (11) | 1.01 (0.95–1.07) | 0.80 |
| BMI (kg/m²) | 19.9 (1.7) | 21.0 (3.1) | 0.89 (0.68–1.16) | 0.38 |
| ABO incompatibility | 0 | 50 | 0.00 (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 × 10⁴) | 0.68 |
| Total PSL dose at week 4 (g) | 0.83 (0.09) | 0.78 (0.10) | 232.97 (0.25–2.21 × 10⁴) | 0.12 |
| Total PSL dose at week 6 (g) | 1.02 (0.11) | 0.94 (0.14) | 75.74 (0.37–1.54 × 10³) | 0.11 |
| Total MPSL dose at week 2 (g) | 1.31 (0.80) | 0.72 (0.61) | 51.45 (0.63–4.15 × 10³) | 0.08 |
| Total MPSL dose at week 4 (g) | 1.72 (1.34) | 1.02 (0.86) | 3.24 (1.31–8.04) | 0.01 |
| Total MPSL dose at week 6 (g) | 2.31 (1.63) | 1.26 (1.12) | 2.01 (1.06–3.80) | 0.03 |
| Total MPSL dose at week 8 (g) | 2.59 (1.90) | 1.37 (1.24) | 1.79 (1.14–2.81) | 0.01 |
| Total steroids dose at week 2 (g) | 1.44 (0.77) | 2.54 (1.24–5.22) | 0.01 |
| Total steroids dose at week 4 (g) | 2.04 (1.11) | 1.76 (1.07–2.90) | 0.03 |
| Total steroids dose at week 6 (g) | 2.51 (1.45) | 1.65 (1.11–2.45) | 0.01 |
| Total steroids dose at week 8 (g) | 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.

| 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 |
| 3 | M | 39 | 33 | L | C1 | Yes | THA |
| 4 | F | 42 | 30 | R | C2 | Yes | Femoral osteotomy |
| 5 | M | 49 | 14 | R | A | No | No |
| 6 | M | 42 | 15 | R | A | No | No |
| 7 | F | 24 | 4 | R | C1 | Yes | No |
| 8 | M | 48 | 20 | R | C2 | No | No |

JIC, Japanese Investigation Committee; RT, renal transplantation; M, male; F, female; R, right; L, left; THA, total hip arthroplasty.

Radiographic follow-up ended at 4 years after renal transplantation.
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.

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.

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