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ORIGINAL ARTICLE

Antithymocyte globulin use for treatment of biopsy confirmed acute rejection is associated with prolonged renal allograft survival

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Summary

Antithymocyte globuline (ATG) and OKT3 have been used for treatment of severe biopsy confirmed acute renal allograft rejection (BCAR). We report results on graft and patient survival including 399 subjects diagnosed with BCAR treated with either ATG or OKT3. Multivariable analyses including Banff scores were performed following three different strategies to account for confounding variables. Fifty per cent of subjects in the OKT3 group had a functioning graft 6.3 years after diagnosis of BCAR, but 74% of ATG patients' grafts were still functioning at that time point (log rank $P = 0.006$). Median actual graft survival was only 4.6 years in the OKT3 subjects, but 9.5 years for ATG-treated patients (log rank $P = 0.004$). Multivariable analysis revealed that the risk for functional graft loss was significantly elevated in the OKT3 compared to ATG patients (HR = 1.79, 95% CI 1.06–3.02, $P = 0.029$). The risk for actual graft loss, counting death as event, was also significantly elevated in the OKT3 patients (HR = 1.73, 95% CI 1.09–2.74, $P = 0.019$). The hazard of death was not different between the groups (HR = 1.55, 95% CI 0.87–2.77, $P = 0.137$). These data suggest that rejecting renal allografts treated with ATG exhibit longer graft survival than OKT3 treated transplant kidneys. Causal inference, however, cannot be drawn from this associational study.

Introduction

The rate of biopsy confirmed acute rejection (BCAR) averages between 10% and 30% depending on the patient population analysed and the immunosuppressive regimen used [1]. Most of the BCAR can be treated successfully, but it remains unclear whether patients with treated BCAR exhibit a similar long-term graft survival as comparable grafts without rejection.

An optimal anti-rejection therapy has never been analysed and therefore heterogeneous treatment approaches exist [2–4]. The treatment regimen of BCAR depends on the severity of the Banff score and the transplant centre policy. In many centres, Banff 1 rejections are treated with steroid pulse therapy and Banff 2 and 3 readings with antithymocyte globulin (ATG) or OKT3 [5].

Even if the reversal of BCAR could be achieved with one of these therapies, it remained unclear whether one of these therapies is associated with improved long-term graft function. We therefore identified 399 patients whose clinical records have been stored in the Austrian dialysis and transplant registry with BCAR between 1990 and 2005 and analysed their graft and patient survival.

Patients and methods

Patient population

The Austrian dialysis and transplant registry OEDTR (Österreichisches Dialyse und Transplant Register) was used for analysis as described previously [6–9]. The OEDTR database is updated annually and only 17 patients were lost to follow-up since 1990. From January 1, 1990 to December 31, 2005, 2898 renal transplants of 2567 patients have been recorded from the Medical University of Vienna. We identified 399 patients in the database who experienced either ATG or OKT3 treatment of BCAR. However, the type of ATG is not recorded in our database. Patients treated subsequently with the other drug were excluded from analysis.

Variables used in analysis

To avoid what is known as 'no failure time' in survival analysis, time point zero was defined as the diagnosis of BCAR and not the transplant date. As we were interested in the effect of BCAR treatment, covariables that changed after the rejection therapy were not included as time varying covariables to conduct a pseudo ITT analysis. There was no difference in the maintenance immunosuppression regimen as indicated in Table 1.

Baseline variables and demographics are displayed in Table 1. We included a new variable 'Cr_below2' that indicated whether the serum creatinine decreased below 2mg/dl within 1 month after BCAR therapy start. BCAR was specifically defined according to the Banff 93, 97, 07 criteria in the respective eras [10–12]. Fifty four biopsies taken before January 1994 were initially not scored according to Banff criteria. These biopsies were reclassified by R. O. with the biopsy database of the Department of Pathology of the Medical University of Vienna, where all the biopsies were processed and analysed.

Missing values

Of the variable donor age 10 records were missing, 7 in PRA and 17 in HLA mismatch. In these few cases,

Table 1. Demographic data at time of transplantation (if not stated otherwise) of patients comparing ATG and OKT3 group.

	No. drugs	ATG	OKT3	*P*-value
Samples		368	31	
Days from transplantation to BCAR [median (IQR)]		10 (13)	21 (42)	0.176
Transplant number (1/>1)		301/67	25/6	0.874
Banff score for analysed BCAR (score 1/2/3)		176/174/18	14/15/2	0.910
Creatinine (mg/dl)		7.29 (2.80)	7.32 (3.36)	0.965
Creatinine at time of BCAR (mg/dl)		4.31 (2.47)	3.83 (2.61)	0.508
Donor age (years)		44.9 (15.0)	39.3 (14.5)	0.045
Recipient age (years)		45.3 (13.6)	47.8 (14.6)	0.310
Recipient weight (kg)		71.8 (15.8)	75.0 (10.6)	0.233
Gender (male/female)		215/153	23/8	0.086
Median (IQR) PRA latest		0 (5)	0 (24)	0.476
CIT (h)		17.9 (8.8)	18.8 (8.6)	0.600
DM (negative/positive)		307/61	26/5	0.949
CMV (negative/positive)		110/136	8/12	0.800
Pyelonephritis (negative/positive)		343/25	31/0	0.242*
Hyperlipidaemia (no. drugs 0/1)		309/59	29/2	0.198*
Cholesterol	0	156 (46)	145 (47)	0.420
	1	158 (36)	192 (NA)	NA
Hypertension (no. drugs 0/1/2/3/4/5/6)		76/61/87/84/48/11/1	8/11/3/6/2/1/0	0.122*
Mean arterial pressure	0	99 (15)	110 (NA)	NA
	1	99 (11)	110 (16)	0.019
	2	103 (12)	103 (97)	0.896
	3	103 (12)	99 (7)	0.501
	4	103 (12)	130 (19)	0.004
	5	99 (9)	103 (NA)	NA
	6	83 (NA)	–	NA
Immunosuppression regimen (ID 1/2/3/4)		103/74/20/171	7/6/1/17	0.801

Data represent mean and standard deviation. *t*-test and chi-square test were used for computation of *P*-values.

*Fisher test.

ATG, antithymocyte globuline; BCAR, biopsy confirmed acute rejection; PRA, panel reactive antibody; CIT, cold ischemic time; DM, diabetes mellitus; CMV, cytomegalovirus; NA, not applicable.

Immunosuppression ID – 1: steroid + AZA + CsA, 2: steroid-free, 3: steroid + MMF + CsA, 4: else.

missing values were imputed using records median. A sensitivity analysis showed that when records with missing variables were excluded from the analysis, the HR did not change substantially (Fig. 1).

Outcomes

Functional graft loss time was defined as the time from date of the first biopsy with diagnosed BCAR until transplant failure. Transplant failure was defined as permanent return to dialysis or re-transplantation. For functional graft loss, the record was censored if the patient died. Actual graft loss was defined as either death or functional graft loss.

For patient mortality, time was defined by the first biopsy with diagnosed BCAR until death of the patient.

Statistical analysis

For demographic data, the patients were grouped by their BCAR therapy ATG or OKT3. Variables between the groups were compared using the two-sample *t*-test or Wilcoxon test, and for categorical variables, the chi-square test or Fisher test was used, when appropriate.

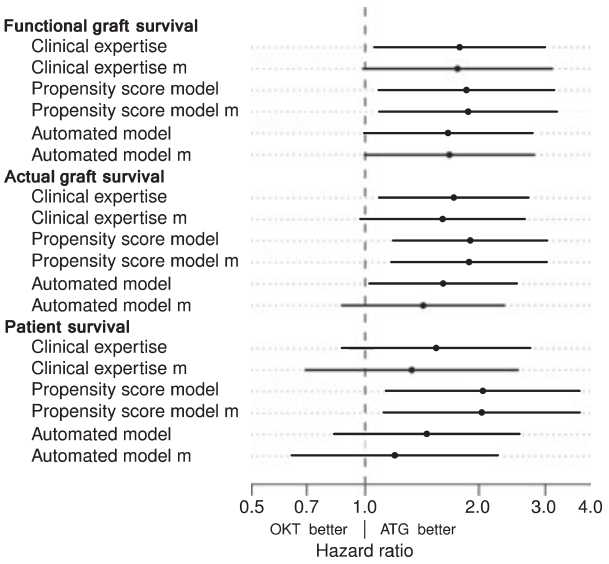

Figure 1 Forest plot of the computed models. Models indicated with 'm' represent models computed with missing data; others have data replaced by the median. The hazard ratio and 95% confidence interval are indicated by a circle and a solid line respectively. A HR = 1 is designated by the dashed line. The models for functional survival do not cross this line suggesting statistically significant lower risk for graft loss in the ATG group ($P < 0.05$).

Kaplan–Meier (KM) plots were used to visualize the association of BCAR therapy with graft loss and patient mortality. Significance between the groups was calculated by log-rank test and the Wilcoxon test.

Multivariable Cox model building strategies

We used three different approaches to construct the time-to-event analyses, namely a clinical experience model, a propensity score model and an automated confounder model. This approach was chosen to show the similarity of the parameter estimates independent of the strategy of analysis, which suggests robust estimates.

Clinical expertise model

All variables that we considered as clinically important for long-term graft function in subjects with BCAR were included in this model. To avoid overfitting, our analyses were restricted to six parameters (see residual statistics in Data S1).

Propensity scores

As this study was not designed as a randomized trial, we used propensity scores to adjust for potential confounding by indication as described previously [6]. The 31 variables which were included into the logistic regression analysis of the propensity score are provided in Data S1. The final analysis was then stratified for quintiles of the propensity score.

Automated model

We identified all variables that changed the HR of OKT3 use by more than 10% in a bivariable analysis as confounders (see Data S1). These objectively derived variables were then included in the final multivariable analysis as has been described before [6].

The proportional hazard assumption was checked for all Cox models by computing the Schoenfeld residuals (Data S1). A *P*-value less than 0.05 was considered significant. The statistical analysis was conducted using SAS for windows 9.1.3 SP4 (The SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

None of the variables of patient demographics was significantly different between the groups ATG and OKT3, except donor age and mean arterial pressure for patients who were given one or four different drugs (Table 1). Of the 399 subjects with BCAR, 270 (73%) in the ATG group and 23 (74%) in the OKT3 group ($P = 0.921$) received steroid puls therapy before ATG or OKT3 was initiated.

Functional graft loss

Death-censored graft loss was delayed in the ATG-treated subjects compared to OKT3 patients (Fig. 2). Half of the subjects in the OKT3 group exhibited a functioning graft at 6.3 years after the diagnosis of BCAR, but 74% of the ATG patients' grafts were still functioning at that time (log rank $P = 0.006$).

Half of the ATG patients had still a functioning graft after 5.8 years, but only 41% of the OKT3 patients exhibited a functioning graft at that time (log rank $P = 0.006$, Wilcoxon $P = 0.002$). The first quartile of functional graft survival for ATG was 5.4 years, whereas for OKT3 group, it was 0.6 years (Fig. 2).

The risk for functional graft loss was numerically higher in the OKT3 subjects compared with ATG-treated patients with BCAR no matter what strategy of analysis was used (Table 2). When adjusted for the variable year of transplantation, which was the only variable changing the hazard ratio (HR) of OKT3/ATG use and graft loss by more than 10% in a bivariable model, the HR was 1.67 (95% CI: 1.00–2.81, $P = 0.051$) suggesting a significant era effect.

The HR of functional graft loss was 2.6 fold higher if the serum creatinine did not drop below 2 mg/dl within 30 days after rejection therapy (95% CI: 1.07–6.33, $P = 0.035$). 61.8% of subjects in the ATG group reached a creatinine below two compared to 55.6% in the OKT3 group ($P = 0.736$).

The Schoenfeld residuals showed a violation for the proportional hazard assumption of the variable 'Banff score', which is a requirement for the Cox proportional hazard model (webFigure 2c, Data S1). Therefore, we calculated a model stratified by this variable resulting in a significant HR for OKT3 use and graft loss (HR = 1.75, 95% CI: 1.03–2.96, $P = 0.037$).

Table 2. Associations between OKT3 use and functional graft loss using different model-building strategies.

Parameter	Hazard ratio	95% confidence interval		*P*-value
Propensity score model				
OKT3 versus ATG usage	1.87	1.09	3.20	0.023
Automated model				
OKT3 versus ATG usage	1.67	1.00	2.81	0.051
Year of transplantation	0.90	0.84	0.96	0.001
Clinical expertise				
OKT3 versus ATG usage	1.79	1.06	3.02	0.029
Donor age	1.01	1.00	1.02	0.190
Banff 2 vs. 1	1.27	0.88	1.83	0.196
Banff 3 vs. 1	3.47	1.86	6.46	<0.001
HLA mismatch	1.03	0.87	1.21	0.769
PRA	1.02	1.01	1.03	<0.001
TXNumber	1.09	0.82	1.46	0.546
Year of transplantation	0.90	0.85	0.96	0.002

ATG, antithymocyte globuline; PRA, panel reactive antibody.

Actual graft loss

Univariable Kaplan–Meier (KM) analysis showed a significant difference between ATG- and OKT3-treated patients (log rank $P = 0.004$, Wilcoxon $P = 0.001$). Median actual graft survival was only 4.6 years in the OKT3 subjects but 9.5 years for ATG-treated patients (Fig. 3).

The use of OKT3 was associated with a higher risk of actual graft loss when compared with ATG therapy (clinical experience model HR = 1.73, 95% CI: 1.09–2.74, $P = 0.019$) (Table 3). The propensity score model revealed a HR of 1.91 (95% CI: 1.19–3.07, $P = 0.007$). Adjusting for the variable year of transplantation, which was found again as the only variable to change the HR by

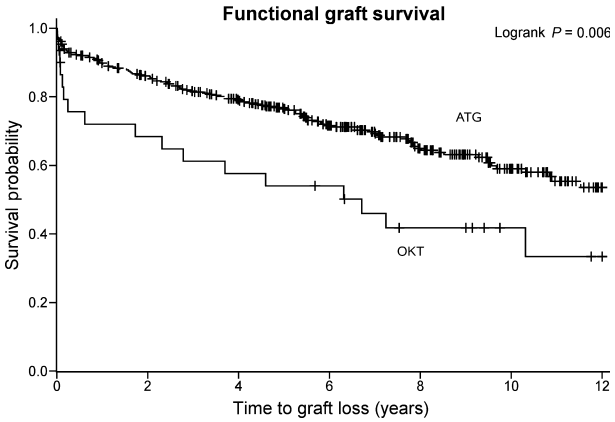

Figure 2 Kaplan–Meier plot of functional graft survival. Dotted line represents group ATG, solid line OKT3, the marks depict censored data. Patients with more than 12 years of survival time have been censored.

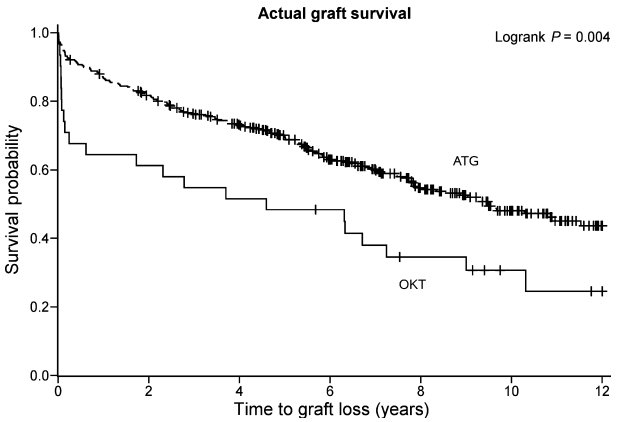

Figure 3 Kaplan–Meier plot of actual graft survival. Dotted line represents group ATG, solid line OKT3, the marks depict censored data. Patients with more than 12 years of survival time have been censored.

Table 3. Associations between OKT3 use and actual graft loss using different model-building strategies.

Parameter	Hazard ratio	95% confidence interval		*P*-value
Propensity score model				
OKT3 versus ATG usage	1.91	1.19	3.07	0.007
Automated model				
OKT3 versus ATG usage	1.62	1.03	2.55	0.037
Year of transplantation	0.91	0.86	0.96	<0.001
Clinical expertise				
OKT3 versus ATG usage	1.73	1.09	2.74	0.019
Donor age	1.01	1.00	1.02	0.213
Banff 2 vs. 1	1.31	0.96	1.78	0.086
Banff 3 vs. 1	2.47	1.35	4.50	0.003
HLA mismatch	1.05	0.91	1.21	0.537
PRA	1.02	1.01	1.03	<0.001
TXNumber	1.07	0.82	1.39	0.622
Year of transplantation	0.91	0.86	0.96	<0.001

ATG, antithymocyte globuline; PRA, panel reactive antibody.

Table 4. Associations between OKT3 use and patient mortality using different model-building strategies.

Parameter	Hazard ratio	95% confidence interval		*P*-value
Propensity score model				
OKT3 vs. ATG usage	2.06	1.14	3.74	0.017
Automated model				
OKT3 versus ATG usage	1.46	0.83	2.59	0.190
Year of transplantation	0.87	0.81	0.94	<0.001
Clinical expertise				
OKT3 versus ATG usage	1.55	0.87	2.77	0.137
Donor age	1.01	1.00	1.02	0.198
Banff 2 vs. 1	1.60	1.07	2.39	0.022
Banff 3 vs. 1	1.28	0.54	3.03	0.572
HLA mismatch	1.07	0.89	1.30	0.465
PRA	1.01	1.00	1.02	0.224
TXNumber	0.72	0.46	1.14	0.163
Year of transplantation	0.86	0.80	0.93	<0.001

ATG, antithymocyte globuline; PRA, panel reactive antibody.

more than 10%, the HR dropped to 1.62 (95% CI: 1.03–2.55, $P = 0.037$).

When stratifying for the variable Banff in the clinical experience model, as it violated the proportional hazard assumption (webFigure 3c, Data S1), the HR was 1.74 (95% CI: 1.10–2.75, $P = 0.019$).

Patient mortality

Univariable analysis of patient mortality by KM plots revealed a longer patient survival in the ATG group (log rank $P = 0.042$) (Fig. 4). The KM plots are used only for visualization and are not the statistically correct way of analysing this nonrandomized rejection treatment.

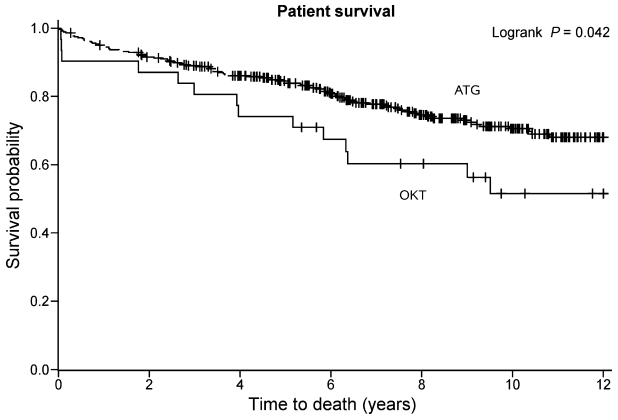

Figure 4 Kaplan–Meier plot of patient survival. Dotted line represents group ATG, solid line OKT3, the marks depict censored data. Patients with more than 12 years of survival time have been censored.

In contrast, the multivariable Cox regression analysis revealed that OKT3 use was not associated with an increased risk for death in the clinical experience and automated model (HR = 1.55, 95% CI: 0.87–2.77, $P = 0.137$; HR = 1.46, 95% CI: 0.83–2.59, $P = 0.190$ respectively) (Table 4). However, a significant HR was computed in the propensity score model (HR = 2.06, 95% CI: 1.14–3.74, $P = 0.017$). As the year of transplantation was the only variable found by the 10% change of HR, these data suggest that OKT3 use was again confounded by the era effect patients.

All results are summarized and visualized in a forest plot (Fig. 1).

In all analyses of functional and actual graft loss as well as patient mortality, we found no interaction of the covariables with OKT3 use suggesting no effect modification.

An analysis for which only the first transplantation of a patient was used revealed comparable results for all types of survival (see Data S1). Also, when patients experienced BCAR in the first 3 months, the results did not change substantially. However, for patient survival, donor age was also classified as a confounder by the 10% rule.

Discussion

In this study, we show that BCAR therapy with ATG was associated with improved functional and actual graft survival. However, patient survival was not significantly better after ATG therapy of allograft rejection.

This finding is in accordance with a previous study from Martins *et al.*, who analysed the induction therapy

of kidney transplanted patients [13]. They compared patients receiving an induction therapy with ATG with subjects without ATG. Martins could demonstrate that graft survival was significantly longer; however, the patient survival was not different. This, however, was a study about induction therapy which was not exactly what we were set out to investigate. Furthermore, ATG use was compared to no induction, which additionally precludes meaningful comparisons of study data.

Only a few articles of small studies directly compared ATG and OKT3 treatment of acute rejection, which was the rational for our analysis [2–4,14]. Mariat and colleagues evaluated in a prospective study, the administering of low-dose OKT3 and low-dose ATG in patients with steroid-resistant rejection diagnosed by biopsy [3]. The authors concluded on the basis of their findings that ATG caused a nonsignificant longer graft survival. The statistical nonsignificance probably represents a type 2 error. In our analysis, we found a significantly improved outcome for graft survival which may be as a result of the considerable larger sample size and longer follow-up.

When measuring the effectiveness of rejection therapy by the reduction of the serum creatinine level after treatment, Mariat and colleagues found no difference between groups. This is in accordance with our analysis; however, when adjusting in the Cox model for a return of the serum creatinine level below 2 mg/dl, the hazard ratio for OKT3 use was even higher than without this adjustment, indicating the importance of this predictor.

Hesse *et al.* have conducted a small study with 10 vs. 11 patients in ALG group and OKT3 group respectively [2]. These patients had an acute rejection in the first 6 weeks after transplantation. The OKT3 treatment group had 100% recovery rate after 3 months. In the ALG group, three transplants were lost, but this was because of other events than rejection. The authors did not find a difference in allograft function determined by serum creatinine.

On the other hand, Alamartine and coworkers, who compared OKT3 and ATG in a study including all kidney transplant recipients with predominant cellular rejection found a longer graft survival for the OKT3 group [14]. The results of this small study, however, need to be viewed with caution as many statistical and trial issues have not been adequately addressed.

Studies which compare ATG or OKT3 with other immunosuppressive agents for the treatment of cellular rejection came to the conclusion that there is a benefit for ATG [15,16], but not for OKT3. The worse assessment for OKT3 is not because of the graft survival but because of the severe side effects related to OKT3 [17]. In our database, immediate clinical side effects of BCAR therapy are not reported, but long-term adverse events such as malignancies and infections were not different between groups. *In vitro* data comparing the efficacy of the two treatments on T-lymphocyte inhibition are numerous, but the transformation of these data into the clinical setting is limited. Examples of such *in vitro* studies are from Bonnefoy-Berard *et al.* [18].

There are some limitations of our study, which are intrinsic to observation study. The donor age was lower in the OKT3 group. We accounted for this fact in the multivariable analyses by including donor age as covariable. Other shortcomings include confounding by indication, nonrandom allocation to therapy, and thus the inability to elucidate causal inference between treatment and outcome. We, however, addressed these restrictions by using established countermeasures such as propensity scores, also known as retrospective pseudo-randomization. We furthermore refrained from all causal statements of treatment and outcomes in this paper. Despite the inherent limitations by design, this is one of the few studies evaluating effectiveness of anti-rejection therapy in renal transplant recipients.

In summary, our retrospective analysis showed that ATG treatment of biopsy confirmed acute cellular rejection was associated with a lower risk of graft loss. Adequately powered randomized clinical trials would be needed to confirm the causal inference of this finding.

Authorship

AK and RO: performed statistical analysis and wrote the paper. RK, AS and BM: collected data and analysed histopathology.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Additional information is available as attachment to the manuscript (DOC-File) and through the website (PDF-File) http://www.meduniwien.ac.at/nephrogene/data/atg

Data S1

Webtable 1: Variables used in propensity score models

Webtable 2: Modification of hazard ratio for OKT3 vs. ATG usage in the automated model, which is calculated as a bivariable model

Webfigure 1: Forest plot of hazard ratios for OKT3 vs. ATG use

Webtable 3–5, Webfigure 2–4: Schoenfeld residuals

Webtable 6–8, **Webfigure 5:** Analyses with first transplantation only

Webtable 9–11, **Webfigure 6:** Analyses with patientes who experienced BCAR in the first three months of the first transplantation

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