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African American and Caucasian Renal Transplant Recipients Have Equal Acute Rejection Rates under Sirolimus and Tacrolimus Combination Therapy

Rafik El-Sabrou, Veronica Delaney, Fauzia Butt, Mohamad Qadir, Pat Hanson, Sony Tuteja, David A. McCollum, and Khalid Butt

African American renal transplant recipients (AARTRs) have higher rates of acute rejection episodes and lower rates of survival compared to Caucasian renal transplant recipients (CRTRs). A single-center, retrospective chart review of 114 consecutive adult renal transplant recipients was conducted at Westchester Medical Center, Valhalla, New York. Data were analyzed for the 27 AARTRs and 87 CRTRs receiving sirolimus (SRL), tacrolimus (TRL), and corticosteroid. The AARTR group received more cadaver organs (63%) compared to the CRTR group (40%) ($P < 0.05$). The mean doses of SRL and TRL were higher in the AARTR group, whereas the SRL and TRL trough levels were similar. The 6-month rejection-free graft survival rate was similar between AARTRs and CRTRs (67% and 74%, respectively). However, the 6-month patient survival rates were lower in AARTRs compared to CRTRs (82% and 95%, respectively; $P < 0.05$). SRL and TRL offer a safe combination for controlling acute rejection episodes without increased adverse events in the African American patient population. However, long-term patient survival continues to be lower in AARTRs than in CRTRs.

ABBREVIATIONS:

AARTR	African American renal transplant recipient
CRTR	Caucasian renal transplant recipient
SRL	Sirolimus
TRL	Tacrolimus
Tx	Transplant
HLA	Human leukocyte antigen
DGF	Delayed graft function

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Introduction

It is well documented that African American renal transplant recipients (AARTRs) have higher rates of acute rejection episodes and lower rates of survival compared to Caucasian renal transplant recipients (CRTRs).¹⁻⁵ Several studies since the early 1980s have documented that AARTRs experienced more episodes of acute rejection and poorer long-term outcomes than other ethnic groups.⁶⁻⁸ The introduction of newer immunosuppressive agents has improved outcomes slightly for African Americans, but not as dramatically as seen with Caucasians.^{3,9,10}

Several factors have been associated with poorer survival rates among African Americans. They include greater human leukocyte antigen (HLA) mismatches, pharmacokinetic and pharmacodynamic factors, socioeconomic factors, noncompliance,

and a greater incidence of comorbid conditions. In addition to the greater immune response, manifested by greater immunologic reactivity in the African American population,¹⁴ African American race influences drug disposition of many immunosuppressive agents.¹¹⁻¹³ AARTRs metabolize medications at an increased rate compared to other ethnic groups.² AARTRs have also been found to have low drug absorption and rapid clearance rates as well as greater pharmacodynamic resistance.² Thus, effective immunosuppression in AARTRs requires higher doses of antirejection medications to prevent an increased rate of rejection.

Little data exist on the efficacy of the combination of tacrolimus (TRL) and sirolimus (SRL) in AARTRs. In this retrospective review, we report our experience in 114 consecutive renal transplant re-

TACROLIMUS:

An immunosuppressive agent belonging to the class of agents referred to as calcineurin inhibitors.

SIROLIMUS:

A new immunosuppressive agent belonging to the class of agents referred to as target-of-rapamycin inhibitors.

recipients, comparing outcomes between African Americans and Caucasians.

Patients and Methods

A single-center, retrospective chart review of 117 consecutive AARTRs and CRTRs was conducted at Westchester Medical Center in Valhalla, New York, with the aim of investigating the safety and efficacy of SRL in combination with TRL. The chart review involved patients transplanted between December 1999 and July 2001 who were receiving SRL, TRL, and corticosteroids postoperatively. Three patients receiving either an HLA identical donor organ or an organ from a donor < 3 years in age were excluded, leaving 114 patients to be analyzed. Institutional review board approval was obtained prior to the initiation of data collection.

Patients were started on a maintenance, SRL dose of 2 or 5 mg/day on postoperative day 1 for Caucasian and African American recipients, respectively. In both groups, subsequent doses were adjusted to maintain a trough level between 10 and 15 ng/mL in the first month and between 5 and 10 ng/mL thereafter. Oral TRL was started on postoperative day 1 at a dose of 2 mg every 12 hours. The dose was adjusted to maintain a trough level around 10 ng/dL in the first month and between 5 and 10 ng/dL thereafter. SRL loading, defined as ≥ 10 mg of SRL on day 1, was given to 65% of CRTRs and 79% of AARTRs.

The type and use of antibody therapy was based on physician preference. In this analysis, basiliximab (20 mg intravenously) was administered on postoperative days 0 and 4 or daclizumab was administered at a dose of 1.5 mg/kg on weeks 0, 2, 4, 6, 8, and 10.

Baseline, demographic, and outcome data were collected postoperatively for 6 months. Demographic data included donor and recipient age, race and gender, underlying renal disease, and use of pretransplant dialysis. Baseline transplant information included transplant number and type, cold ischemia time, number of HLA antigen mismatches, and use of induction therapy. Lab values and immunosuppressant doses and troughs were collected at 1 ± 1 , 7 ± 4 , 30 ± 10 , 90 ± 30 , and 180 ± 30 days posttransplantation. Lab values included serum creatinine levels, glucose concentration, and hemo-

globin and platelet counts. Complications and infections requiring or occurring during hospitalization were documented, including need for post-transplant dialysis within the first week. Data with regard to all rejection episodes and biopsies, graft and patient survival, and date of last known follow-up were collected.

All variables were then summarized by treatment group (AARTR and CRTR). Categorical variables (e.g., gender or race) were summarized using percentages, and continuous variables (e.g., age) were summarized using means and standard deviations. An evaluation of balance between treatment groups was performed using a Fisher exact test, or chi-square test where appropriate, for categorical data and analysis of variance, or an appropriate non-parametric test, for continuous data. Treatment effects were adjusted, when necessary, for differences observed at baseline.

Patient, graft, and rejection-free graft survival at 6 months posttransplantation were analyzed using Kaplan-Meier product-limit survival analysis techniques. For the patient survival analysis, living patients were censored at the time of last known follow-up. For the graft survival analysis, a graft was considered lost when a patient underwent graft nephrectomy, underwent retransplantation, died with a functioning graft, or returned permanently to dialysis. Living patients with functioning grafts were censored at the time of last known follow-up. To calculate rejection-free graft survival, failure was defined as death, graft loss (defined as above), or rejection (defined as treatment for rejection). Living patients with functioning, nonrejected grafts were censored at the time of last known follow-up. For each survival analysis, the log rank test statistic was used to compare survival rates between treatment groups.

Results

Of the 114 patients analyzed, 27 were AARTRs and 87 were CRTRs. Table 1 displays the demographic and baseline transplant characteristics for the 2 groups. All but 2 of the characteristics of the 2 groups were similar. The AARTRs had significantly more African American donors ($P < 0.01$). Also of note, the percentage of cadaver donor organs in the AARTR group (63%) was significantly higher compared to the CRTR group (40%) ($P < 0.05$).

Table 1 | RECIPIENT AND DONOR DEMOGRAPHICS AND BASELINE TRANSPLANT INFORMATION SUMMARIZED BY AFRICAN AMERICANS AND CAUCASIANS

	AFRICAN AMERICAN (n = 27)	CAUCASIAN (n = 87)	P Value
Recipient age	43 ± 15	46 ± 14	ns
Recipient gender			
Female	37%	33%	ns
Male	63%	67%	ns
Donor age	39.3 ± 16.9	43.3 ± 16.4	ns
Donor gender			
Female	37%	53%	ns
Male	63%	44%	ns
Unknown	0%	4%	ns
Donor race			
Caucasian	33%	83%	< 0.01
African American	59%	10%	< 0.01
Other	7%	7%	< 0.01
Underlying disease			
Diabetes mellitus	22%	15%	ns
Pretransplant dialysis			
Yes	93%	80%	ns
Retransplantation			
Yes	15%	23%	ns
Transplant type			
Cadaver donor	63%	40%	< 0.05
Living donor	37%	60%	< 0.05
Ischemia time (hours)			
Cadaver donor	26.7 ± 6.4	27.6 ± 6.5	ns
Living donor	1.6 ± 0.4	2.5 ± 5.0	ns
HLA mismatches	4.1 ± 1.5	3.7 ± 1.4	ns
Induction therapy			
Yes	70%	53%	ns
Follow-up time (days)	159 ± 121	209 ± 116	ns

HLA = human leukocyte antigen.

DELAYED GRAFT FUNCTION:

Slow recovery of the renal allograft requiring dialysis, often due to multiple risks (prolonged cold ischemia time, marginal donor, etc.) at the time of transplantation.

The observed rates of delayed graft function (DGF), defined as the need for dialysis within the first week posttransplantation, were 33% for the AARTR group and 23% for the CRTR group. This difference was not found to be significantly different.

Figure 1 presents mean SRL dose and trough levels over time for the 2 groups. Although the mean doses of SRL were found to be significantly higher in the AARTR group compared to the CRTR group on days 7, 30, and 90 ($P < 0.05$), there was insufficient data to show a statistically significant difference in the corresponding SRL trough levels. TRL doses were significantly higher in the AARTR group on days 7 and 30 ($P < 0.01$) (Fig. 2). However, TRL trough levels were similar throughout the 6-month follow-up period.

The 6-month incidence of treated and biopsy-confirmed rejection episodes were similar between the 2 groups (Table 2). The Kaplan-Meier rejection-free graft survival curves for the 2 groups are presented in Figure 3. The 6-month rejection-free graft survival rates were 67% ± 10% for the AARTR group and 74% ± 5% for the CRTR group. This difference in rejection-free graft survival was not significant (log rank test statistic = 0.971, P value = 0.324, $df = 1$). Figure 4 is a graph of the Kaplan-Meier patient survival curves for the 2 groups. Four patients in each group died within the 6-month follow-up period. The 6-month patient survival rate of 82% ± 9% for the AARTR group was significantly lower than the rate of 95% ± 3% for the CRTR group (log rank test statistic = 4.191, P val-

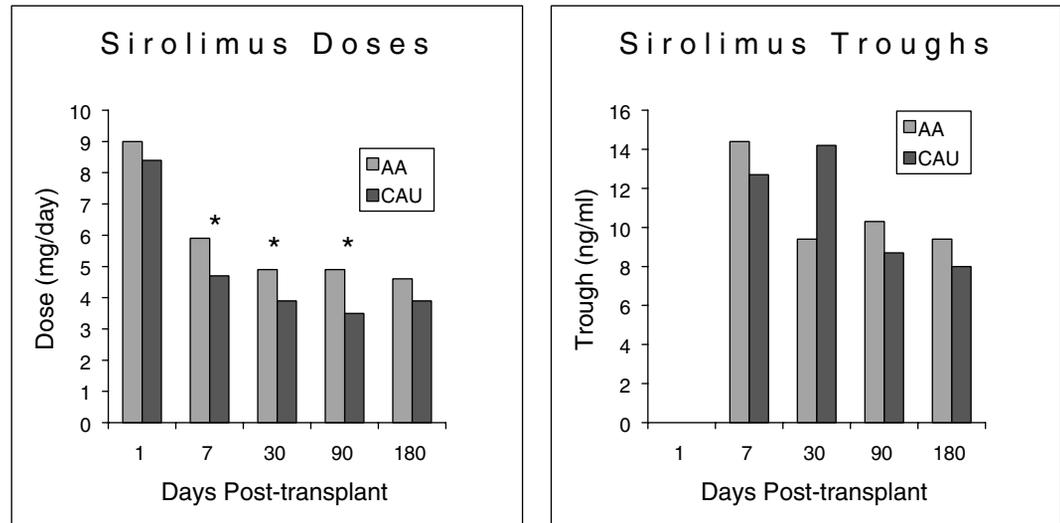


Figure 1. Mean sirolimus dose and trough levels over time for the 2 treatment groups. The African American (AA) renal transplant group received significantly higher doses of sirolimus on days 7, 30, and 90 compared to the Caucasian (CAU) renal transplant group (* $P < 0.05$).

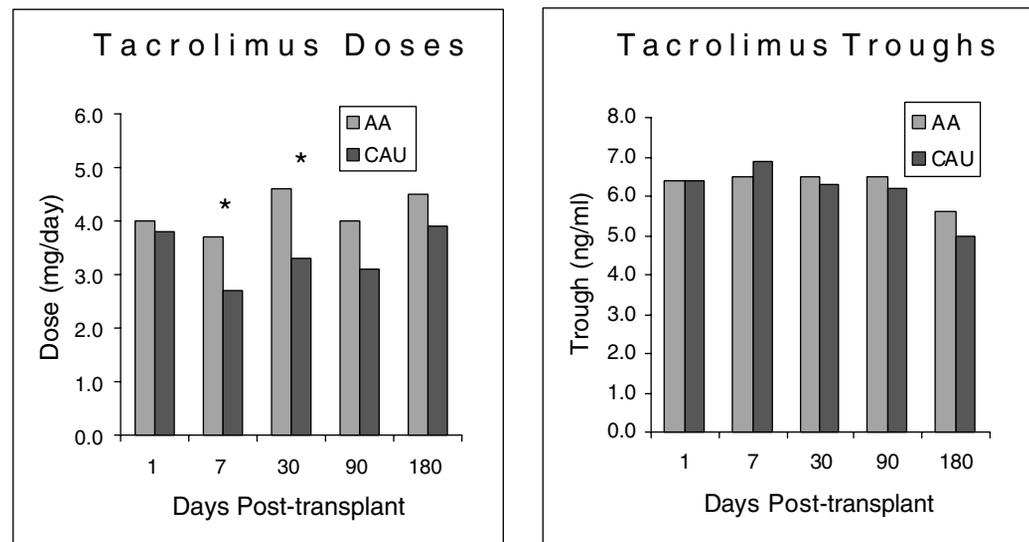


Figure 2. Mean tacrolimus dose and trough levels over time for the 2 treatment groups. The African American (AA) renal transplant group received significantly higher doses of tacrolimus on days 7 and 30 compared to the Caucasian (CAU) renal transplant group (* $P < 0.01$); however, the tacrolimus trough levels were similar throughout.

ue = 0.041, $df = 1$). The causes of death in the AARTR group were 2 cardiac and 2 infectious causes; in the CRTR group, there were 1 cardiac and 2 infectious causes and 1 pulmonary embolism. This may be attributed to the advanced age, longer wait on the transplant list, and associated co-

morbid conditions in the recipients. This is in keeping with other reports of inferior outcome among AARTRs.⁶⁻⁸

Both groups had a similar overall low rate of infections that required or occurred during hospitalization (AARTR, 15%; CRTR, 17%), as well as

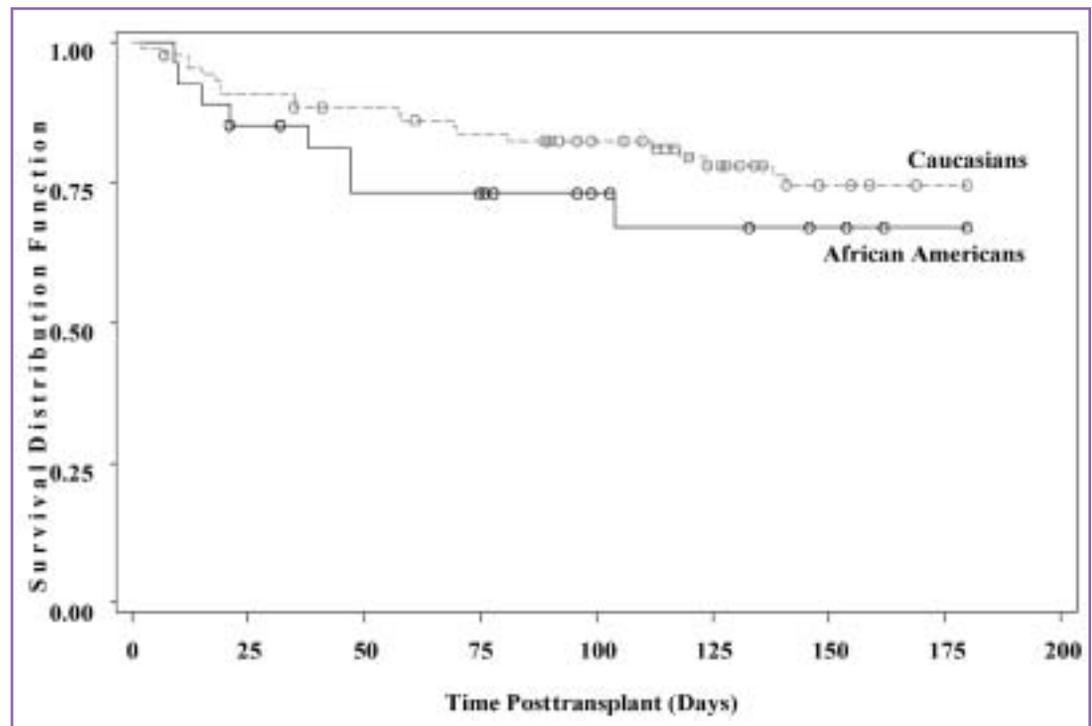


Figure 3. Rejection-free graft survival at 6 months posttransplantation by African American and Caucasian groups. The 6-month rejection-free graft survival rates for the 2 groups were not significantly different.

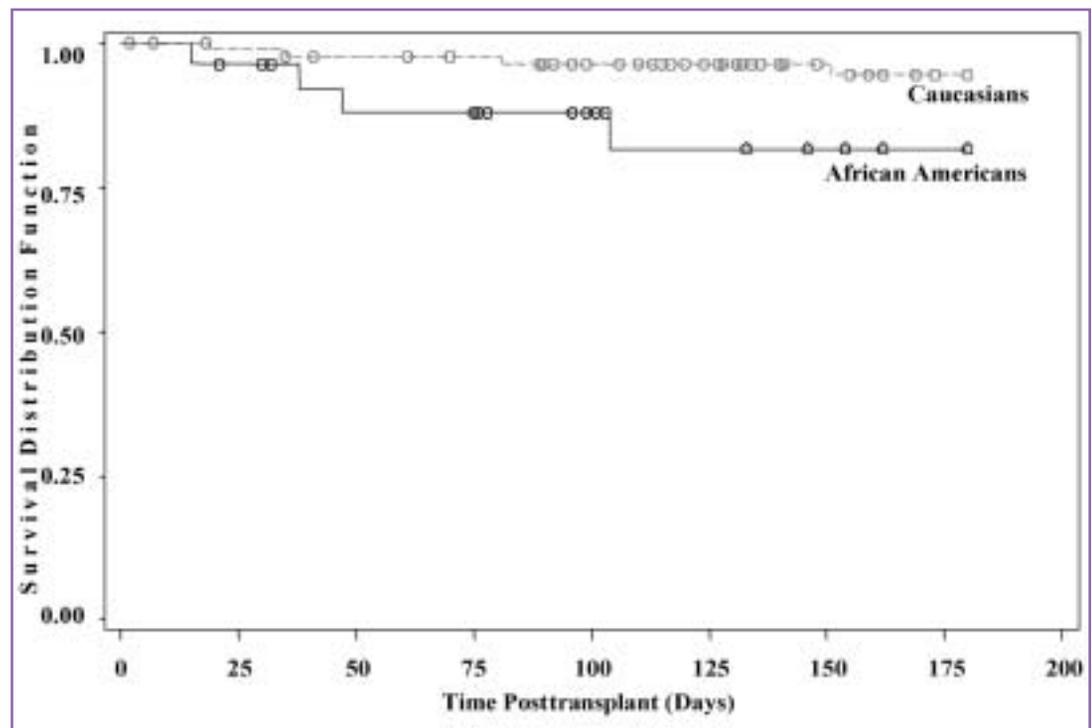


Figure 4. Patient survival at 6 months posttransplantation by African American and Caucasian groups. Patient survival in the Caucasian group was significantly higher than in the African American group ($P < 0.05$).

Table 2 | SUMMARY OF REJECTION EPISODES SUMMARIZED BY AFRICAN AMERICANS AND CAUCASIANS

	AFRICAN AMERICAN (n = 27)	CAUCASIAN (n = 87)	PVALUE
Patients treated for rejection	15%	14%	ns
Biopsy confirmed treated rejection	11%	10%	ns
Patients with multiple rejection episodes	4%	7%	ns

Table 3 | INCIDENCE OF INFECTIONS SUMMARIZED BY AFRICAN AMERICANS AND CAUCASIANS

	AFRICAN AMERICAN (n = 27)	CAUCASIAN (n = 87)	PVALUE
Overall infections	15%	17%	ns
Bacterial infections	7%	14%	ns
Fungal infections	4%	1%	ns
Viral infections	0%	3%	ns
Other infections	4%	1%	ns

Table 4 | COMPLICATIONS REQUIRING OR OCCURRING DURING HOSPITALIZATION SUMMARIZED BY AFRICAN AMERICANS AND CAUCASIANS

	AFRICAN AMERICAN (n = 27)	CAUCASIAN (n = 87)	PVALUE
DGF (dialysis within the first week posttransplant)	33%	23%	ns
Deep vein thrombosis	11%	9%	ns
Lymphocele	0%	1%	ns
Wound complications	4%	8%	ns
PTDM	4%	10%	ns

DGF = delayed graft function; PTDM = posttransplant diabetes mellitus.

similar rates of bacterial, fungal, and viral infections (Table 3). Table 4 displays the incidence of several complications requiring or occurring during hospitalization. The observed rates of delayed graft function (DGF), defined as the need for dialysis within the first week posttransplantation, were 33% for the AARTR group and 23% for the CRTTR group. This difference was not found to be significantly different. There was a low incidence rate for the other complications, and these rates were similar for both groups.

No differences were found when comparing serum creatinine, glucose, hemoglobin, or platelet levels between the treatment groups.

Discussion

The present study was conducted to analyze the impact of combining TRL and SRL on outcomes in the African American renal transplant population. Rejection rates with previous immunosuppressive combinations have not been favorable in the African American population. In our study, the 6-month acute rejection rate was equally low in AARTRs (15%) and CRTTRs (14%) under SRL/TRL combination therapy. Podder et al.² also demonstrated that the addition of SRL to the cyclosporine/prednisone regimen reduced the incidence of acute rejection episodes in AARTRs from 43.3% to 19.2%, a value similar to that seen in CRTTRs. In a

IMMUNOSUPPRESSANT TROUGH LEVELS:

The lowest concentration of medication in the body, usually prior to the next dose.

GRAFT LOSS:

Loss of a renal allograft meeting one of the following conditions: graft nephrectomy, retransplantation, death with a functioning graft, or the return to dialysis, permanently.

study by Hricik et al.,¹⁴ 40 AARTRs treated with TRL/SRL under a steroid withdrawal protocol achieved a remarkably low rate of rejection of 4.8%, with a mean follow-up of 8 months. Longer-term follow-up is needed to substantiate the early results.

Graft survival was similar in the 2 groups, although patient survival was lower in AARTRs. There were 4 deaths in each group, and the small number of African American patients may have made the percentage of death statistically significant. AARTRs had more cadaver donors than CRTRs. This could be part of the reason for the decrease in patient survival.

This study also highlighted the need for higher oral dosing of antirejection medications in this high-risk population. The African American recipients in our study required significantly higher doses of SRL and TRL to achieve similar trough levels compared to their Caucasian counterparts. Other studies have reported similar findings.^{1,3,15} Hricik et al.¹ reported a 37% increase in TRL doses in AARTRs compared to non-AARTRs to achieve similar target trough levels. AARTRs also required higher doses of SRL¹⁶ and MMF¹⁷ to achieve efficacy outcomes that were similar to those of non-AARTRs.

It is important to find a balance between adequate immunosuppression while avoiding toxic levels of these medications that could cause increased rates of infection or organ damage. The increased doses of SRL and TRL in our study did not cause an increased development of posttransplant diabetes or infection rates in AARTRs. No significant elevations in serum cholesterol, triglycerides, or creatinine levels were observed. The decreases in hemoglobin, platelet, or white blood cell counts were transient and clinically insignificant.

In this small retrospective review, we conclude that SRL and TRL is a safe combination in preventing acute rejection episodes without an increased risk of infection in the African American patient population. Alternative antirejection combinations need to be considered for AARTRs to reduce acute rejection rates and improve long-term survival. Additional studies are needed to evaluate racial differences in the pharmacokinetics/pharmacodynamics of SRL and TRL. Although the

incidence of acute rejection episodes was decreased in AARTRs with the combination of SRL and TRL, patient survival continued to be lower. Further exploration is needed to examine long-term survival rates among AARTRs treated with the new, more potent immunosuppressant medications in a large, prospective, randomized study.

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