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Late, Severe, Noninfectious Diarrhea After Renal Transplantation: High-Risk Factors, Therapy, and Prognosis

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ABSTRACT

Objective. Late severe noninfectious diarrhea in renal transplant recipients can lead to malnutrition and even graft loss. The purpose of this study was to evaluate risk factors associated with this condition and summarize therapy for these patients.

Methods. For more than 36 months we observed a cohort of 541 recipients who underwent kidney transplantation from January 2001 to June 2007. They were provided a calcineurin inhibitor (CNI) combined with mycophenolate mofetil (MMF). The four group includes a continuous cyclosporine (CsA); a preconversion to tacrolimus and a postconversion group as well as a continuous tacrolimus group. The rate of severe late noninfectious diarrhea was compared among the four groups. Risk factors were analyzed between the diarrhea and nondiarrhea cohorts. Clinical characteristics, efficacy, and safety were observed after modifying the immunosuppressive protocol for late severe noninfectious diarrhea recipients.

Results. Twenty-eight recipients presented with late sever noninfectious diarrhea. No patients displayed chronic diarrhea in the CsA (n = 145) or preconversion group (n = 95). The rate of diarrhea was 7.31% in the postconversion and 7.35% in the tacrolimus group. Using multivariate Cox proportional hazards analysis, factors associated with an increased risk of noninfectious diarrhea were cytochrome P450(CYP) 3A5 *3/*3 type, chronic renal allograft dysfunction, and patient ingestion of *Tripterygium wilfordii* Hook F. All diarrheal recipients experienced weight loss, hypoalbuminia, and an increased serum creatinine. All affected patients underwent adjustment of the immunosuppressive regimen to achieve remission. Renal allograft survival in recipients with diarrhea was worse than that in nondiarrheal recipients receiving tacrolimus combined with MMF.

Conclusion. Tacrolimus with MMF increased the risk of late severe noninfectious diarrhea among renal transplant recipients compared with hosts treats with CsA plus MMF. The CYP3A5 *3/*3 type, chronic renal allograft dysfunction, and *T wilfordii* supplementation were high-risk factors for late diarrhea. Prompt adjustment of immunosuppression was an effective, feasible therapy for these patients.

BOTH NEW AND conventional immunosuppressive drugs provide excellent patient and organ survival rates following kidney transplantation. However, the adverse events of immunosupressive drugs can reduce the efficacy of these drugs, thereby adversely influencing renal allograft and even recipient survival.

Gastrointestinal (GI) adverse events are common in transplant recipients.[1] Severe diarrhea can lead to weight

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0041-1345/13/$–see front matter
http://dx.doi.org/10.1016/j.transproceed.2013.02.131

loss and dehydration,[2] decreased quality of life,[3] increased serum creatinine,[4] fluctuating immunosuppressive drug levels,[5–7] as well as loss of renal allograft and life.[8] Causes of severe diarrhea can be noninfectious, or infectious–bacterial, viral, fungal.[9] Infectious diarrhea diagnosed by clinical symptoms is treated with antimicrobials; noninfectious diarrhea requires conversion of the regimen.

Studies evaluating the risk of severe diarrhea have shown that tacrolimus and mycophenolate mofetil (MMF) are associated with an increased risk of noninfectious diarrhea.[8,10,11] Patients receiving mycophenolic acid (MPA) are at higher risk for noninfectious diarrhea, especially among those displaying MPA 12-hour trough levels of at least 2.40 mg/L.[10] However, other studies have reported contrary results.[11] Tacrolimus levels increase during severe diarrhea and decrease with its relief,[5–7] but cyclosporine (CsA) trough concentrations do not show this tendency.

Transient diarrhea in the early period after renal transplantation, whether related to infection or to patient intolerance of the immunosuppressants, can be treated effectively without sever consequences to the renal allograft or recipient. In contrast, chronic severe diarrhea without infectious symptoms can lead to weight loss and dehydration,[3] with an increased loss the renal allograft and of life.[8]

Although the tacrolimus plus MMF combination was effective in the ELITE-Symphony study,[12] noninfectious diarrhea has been associated with this regimen. The aim of the current study was to summarize the risk factors for severe, noninfectious diarrhea among recipients receiving tacrolimus and MMF. Several of our patients experienced severe diarrhea late (more than 6 months) after transplantation. Additionally, we sought to elucidate successful therapy for these patients, seeking to improve the survival of renal allografts and recipients.

The Chinese herb *Tripterygium wilfordii* Hook F has potent anti-inflammatory properties. It has been suggested that it is effective in treating a variety of autoimmune diseases such as rheumatoid arthritis, nephritis, and systemic lupus erythematosus.[13,14] *T wilfordii* has been demonstrated to act as a potent immunosuppressive drug capable of inhibiting T cell activation and proliferation through a variety of mechanisms, including inhibition of T lymphocyte-induced interleukin-2 expression.[15] The researchers have observed that *T wilfordii*, combined with tacrolimus, greatly increases plasma tacrolimus concentrations in kidney transplant recipients. Pilot studies have shown that this effect was not related to CYP3A5 genotype; however, the mechanism is still unclear.[16] Cytochrome P450 3A4 and P-glycoprotein activities increase in transplant patients with persistent diarrhea.[17]

MATERIALS AND METHODS

Patients and Immunosuppressive Protocols

From January 2001 to December 2007, we performed 722 renal transplantations using initial regimens including tacrolimus or cyclosporine (CsA) combined with MMF. We excluded recipients who received other immunosuppressive protocols from the analysis, allowing 541 recipients to be enrolled into the study. They all underwent received cadaveric donor renal transplantations, and were followed for at least three years (median, 60 months). One hundred forty-five recipients received an initial immunosuppressive protocol of CsA combined with MMF, with 95 undergoing conversion to tacrolimus combined with MMF because of CsA side effects or because of chronic renal allograft dysfunction. Patients receiving CsA were analyzed as a preconversion group and again as a postconversion group. The remaining 301 recipients were prescribed an initial immunosuppressive protocol of tacrolimus combined with MMF (Fig 1).

Some patients received anti-CD25 antibody induction therapy and methylprednisolone, (500 mg/day), for the first three days postoperatively. Prednisolone was tapered to 5 mg at 6 months. The initial CsA dosage of 6 mg/kg/d, was tapered to a goal trough level of 100 to 120 ng/mL after six months. The initial 0.15 mg/kg/d dosage of tacrolimus was tapered to a goal through level of 4 to 6 ng/mL after the 6th month. The initial 1.5 g/d dosage of MMF was adjusted to 1.0 to 1.5 g/d according to side effects and abbreviated MPA 0 to 12-hour (C_{0h}, C_{0-5h}, C_{1h}, C_{2h}, C_{8h}) are under the curve (AUC_{0-12h}) estimates.

Definition of Late, Severe, Noninfectious Diarrhea

Late, severe, noninfectious diarrhea was defined as[8]: (1) occurring six months after transplantation; (2) persisting for over one month; (3) without infectious symptoms of the gastrointestinal tract such as fever, vomiting, or abdominal pain; (4) normal routine stool test results without an increases number of white blood cells (WBC) or bacteria, or fungi; (5) loss of body weight over 10% of baseline; and (6) remission without any antibiotics.

Study Design

The 541 enrolled patients followed for at least 36 months were categorized into four groups (Fig 1): constant CsA (CsA + MMF); preconversion group (CsA + MMF before conversion to tacrolimus + MMF); postconversion group (conversion to tacrolimus + MMF from CsA + MMF); and constant tacrolimus group (tacrolimus + MMF).

Clinical data included patient information of age, gender, diabetes mellitus (previous or new onset), previous gastrointestinal tract disease, MMF dosage, and average trough concentration of tacrolimus. Late, severe, noninfectious diarrhea was compared among the four groups, particularly the CsA + MMF versus tacrolimus + MMF group, seeking to test the hypothesis that the tacrolimus + MMF cohort was at higher risk of severe, noninfectious diarrhea. Further, we analyzed data on recipients with vs without late, severe, noninfectious diarrhea to identity risk factors for the disorder: age, gender, diabetes mellitus (previous or new onset), previous gastrointestinal tract disease, chronic renal allograft dysfunction, CYP3A4 genotype,[17] as well as allograft and recipient survival.

Statistics

Differences among data expressed as mean values ± standard deviations were analyzed by the Student *t* test or one-way analysis of variance (ANOVA). Multiple comparisons were evaluated by the Student-Newman-Keuls (SNK) or least significant difference (LSD) posthoc tests. Qualitative data described as percentages were analyzed using the (χ^2) or Fisher exact test, an indicated. According to the data distribution, survival analyses were performed employing

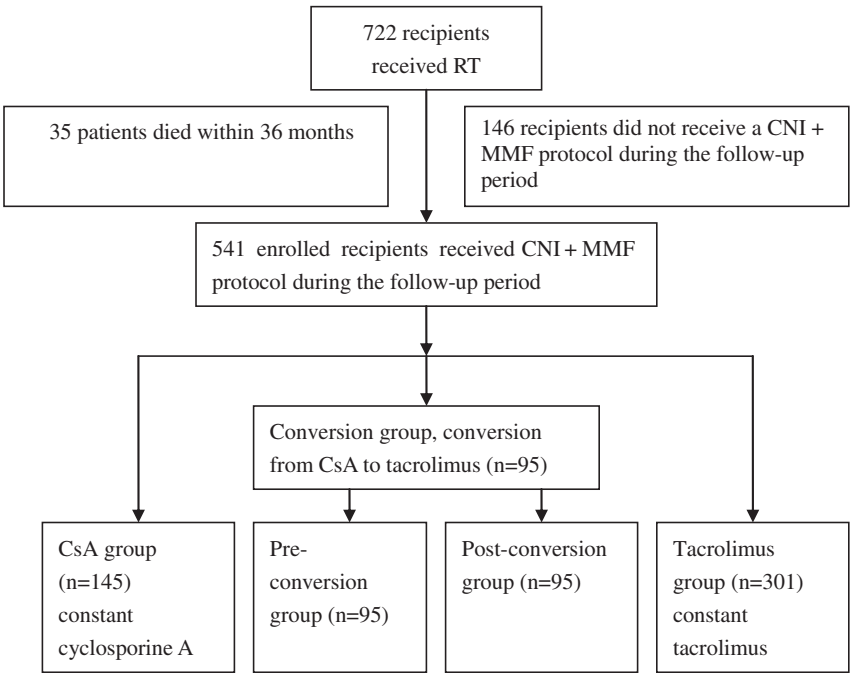

Fig 1. Procedure for enrolled patients and group definition subgroups. RT, renal transplantation; CNI, calcineurin inhibitors.

the product-limit method (Kaplan-Meier), with differences assessed by the log-rank test. All *P*-values were two-sided; a *P*-value of less than .05 was considered to be statistically significant. All analyses were performed using SPSS software (Version 13.0, SPSS Inc, USA).

RESULTS

Clinical Data and Rate of Late, Severe, Noninfectious Diarrhea in the Four Groups

The 541 enrolled patients were categorized into four groups (Table 1). There were neither significant differences among the demographic characteristics of the four groups nor between-group differences in the clinical characteristics of diabetes mellitus and previous gastrointestinal tract disease. The average MMF dosage changed from the preconversion to the postconversion group, albiet not significantly.

Interestingly, no CsA patients presented with late, severe, noninfectious diarrhea; the same result was observed in the preconversion group (Table 1). However, the rates of late, severe, noninfectious diarrhea in the tacrolimus group and the postconversion group were similar (7.4% vs 7.0%), and higher than the CsA and the preconversion cohorts ($P = .01$). These data indicated that the tacrolimus and MMF combination presented a high risk for late, severe, noninfectious diarrhea compared with the CsA and MMF combination.

Table 1. Clinical Data and Rate of Late Severe Noninfectious Diarrhea in the Four Subject Groups

	Cyclosporine A Group (n = 145)	Preconversion Group (n = 95)	Postconversion Group (n = 95)	Tacrolimus Group (n = 301)	*P* Value
Median age at transplant (y)	36.2 ± 22.4	36.4 ± 19.5	36.4 ± 19.5	36.9 ± 20.4	.221
Male/female	85/60	57/28	57/28	192/109	.105
Primary kidney disease					.286
Glomerulonephritis	85	59	59	158	
Hypertension	12	11	11	28	
Adult polycystic kidney disease	5	4	4	9	
Other	43	21	21	106	
Hemodialysis Continuous Ambulatory Peritoneal Dialysis	128/17	85/10	85/10	268/33	.320
Complement Dependent Cytotoxicity (%)	5–7	5–8	5–8	5–9	.452
Donor (deceased)	145	95	95	301	1
Diabetes mellitus	6	4	8	14	.156
Previous gastrointestinal tract disease (n)	4/145	6/95	6/95	9/301	.453
Dosage of mycophenolate mofetil (g/d)	1.28 ± 1.05	1.31 ± 0.15	1.34 ± 0.18	1.30 ± 0.20	.114
Follow-up period (mo)	46–125	46–72	36–92	36–98	.136
Diarrhea	0	0	7	21	.001

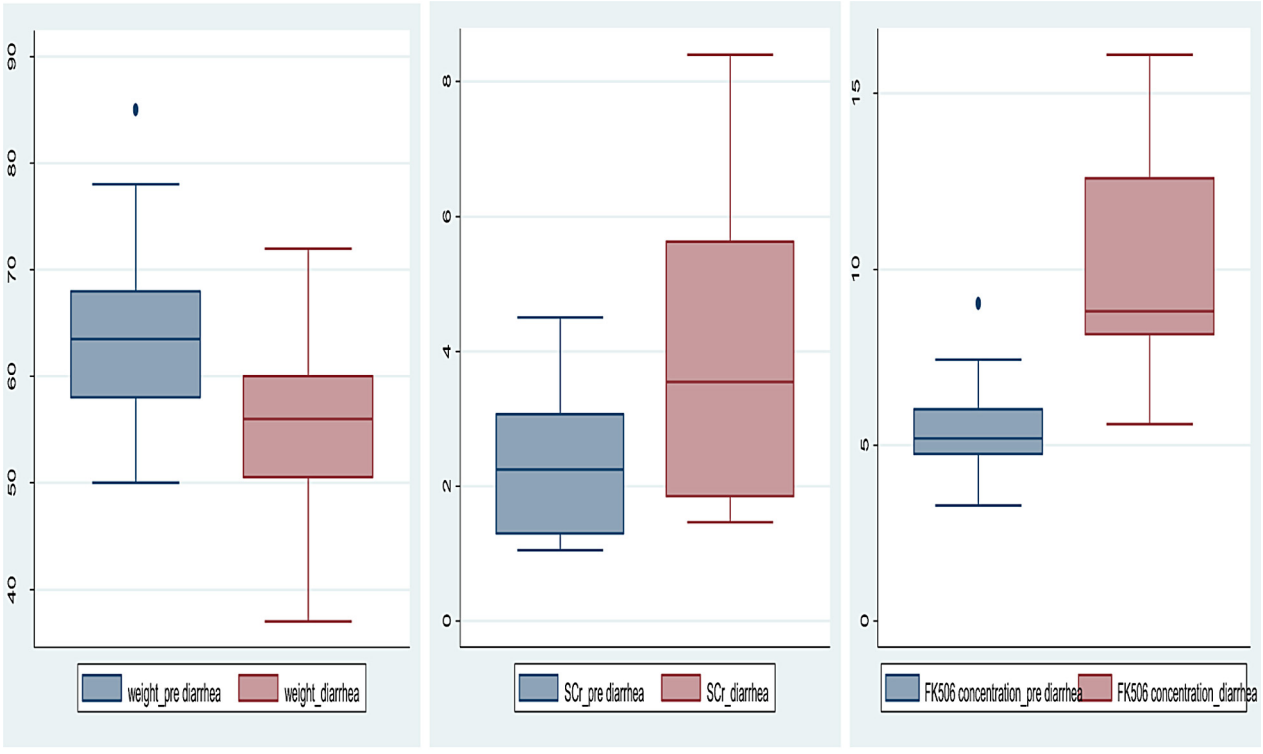

Fig 2. Changes in body weight, serum creatinine, and tacrolimus trough concentration prior to and during diarrhea episodes.

Clinical Information on Patients With Late, Severe, Noninfectious Diarrhea

Twenty-eight recipients experiences late, severe, noninfectious diarrhea at 6 to 96 months posttransplantation (mean, 47.7). The duration of diarrhea ranged form 1 to 10 months, (average 3.39). The average tacrolimus concentration prior to diarrhea onset did not differ significantly from that in the nondiarrhea group. Changes in body weight, serum creatinine, and tacrolimus trough concentrations during the prediarrheal and diarrheal periods are shown in Fig 2.

High Risk of Late, Severe, Noninfectious Diarrhea in the Tacrolimus + MMF Group

All recipients with late, severe, noninfectious diarrhea were prescribed tacrolimus + MMF. The 396 total recipients on the tacrolimus + MMF combination protocol (postconversion group and tacrolimus group) were separated into a diarrhea (n = 28) vs a nondiarrhea group (n = 368). Using logistic regression analysis to determine risk factors for the diarrhea group, we examined the impact of age, gender, CYP3A4 genotype, diabetes mellitus (previous or new onset), pervious gastrointestinal tract disease, chronic renal allograft dysfunction (serum creatinine > 1.24 mg/dL), and concomitant administration of *T wilfordii*. The CYP3A5 genotype 3*/3*, chronic renal allograft dysfunction, and concomitant administration of *T wilfordii* were three significant risk factors for late, severe, noninfectious diarrhea (Table 2).

Effect and Safety of Immunosuppressive Protocol Adjustments and Conversions

Four possible changes in treatment were considered for the 28 recipients with severe diarrhea: (1) adjustment in the

Table 2. Factors Examined for Late, Severe, Noninfectious Diarrhea in the Tacrolimus + MMF Group

	OR	SE	*Z*	*P* > |*Z*|	95%	CI
CYP3A5 genotype 3*/3*	7.992326	5.400257	3.08	0.002	2.13	30.05
Gender	2.105829	1.273719	1.23	0.218	0.64	6.89
Age (>40 y)	1.244669	.6097479	0.45	0.655	0.48	3.25
Previous gastrointestinal tract disease	4.104755	5.859487	0.99	0.323	0.25	67.35
Chronic renal allograft dysfunction	5.32113	2.797312	3.18	0.001	1.90	14.91
Diabetes mellitus	2.253731	2.06945	0.88	0.376	0.37	13.63
Combined with *Tripterygium wilfordii* Hook F	12.45149	9.814674	3.20	0.001	2.66	58.37

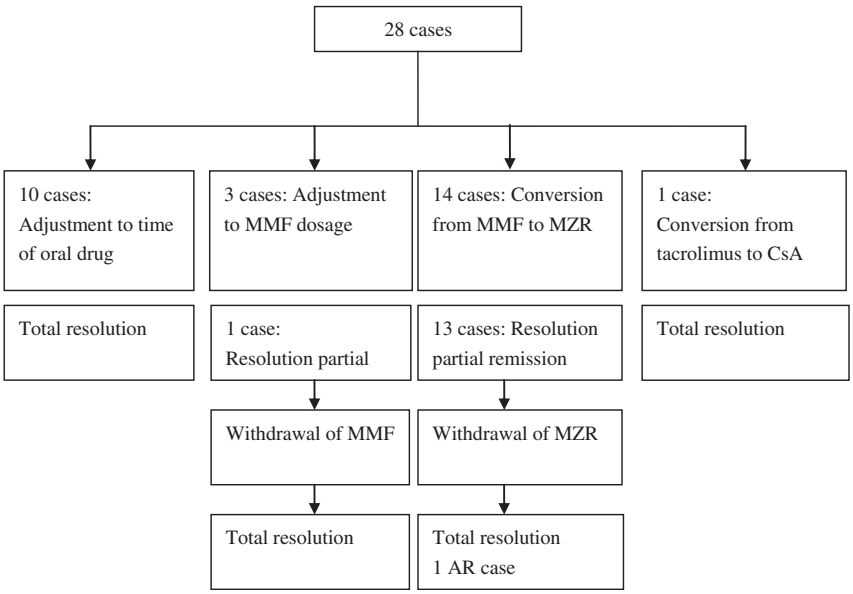

Fig 3. Treatment changes for resolution of severe diarrhea. AR, acute rejection.

duration of oral drug, (2) adjustment of the MMF dosage, (3) immunosuppressant conversion, and (4) withdrawal of an immunosuppressant (Fig 3). Diarrhea in all patients resolved after adjustment of the immunosuppressive protocol. One patient experienced an acute rejection episode in the group that was converted from MMF to mizoribine Body weight, serum creatinine (mg/dL), and tacrolimus tough concentration improved with resolution of the diarrhea (Fig 4), but 2 cases returned to dialysis after resolution of the diarrheal symptoms.

Renal Allograft Loss Rates for the Diarrhea and Nondiarrhea Groups

Renal allograft loss rates in the diarrhea versus nondiarrhea groups were 10 of 28 versus 10 of 368 subjects, respectively ($P = .01$; Fig 5).

DISCUSSION

The side-effect profile determines the selection of an immunosuppressive protocol for renal allograft recipients. Diarrhea has been reported to be a common side effect among more than 50% of recipient after in renal transplantation.[12] Mycophenolate mofetil has been proposed to play an important role in this side effect.[18] However, diarrhea can be induced by both infectious and noninfectious causes. Most episodes of diarrhea following renal transplantation are short term with little influence on allograft or recipients survival.[19]

The current study defined late, severe, noninfectious diarrhea as late in onset (more than 6 months' post-transplantation), severe lasting more than one month, body weight loss, and increased serum creatinine), noninfectious (no fever, no abdominal pain with negative routine stool test and remission without antibiotics.) The incidence of this complication has increased over recent years owing to the greater application of tacrolimus combined with MMF.[20] A previous study demonstrated that this combination increase the risk of noninfectious diarrhea in renal transplantation recipients.[8] Therefore, we designed the present study to evaluate the high risks of noninfectious diarrhea. The difference between the previous study and our study may be that the patients selected in the current study were afflicted with late, severe diarrhea. Our study design included a conversion group, from CsA to tacrolimus, to test the risk of diarrhea among patients receiving tacrolimus combined with MMF compared with CsA combined with MMF. Interestingly, recipients prescribed CsA combined with MMF did not display late, severe, noninfectious diarrhea, which was not consistent with a previous study. The difference may be explained by the definition of diarrhea. Rates of late, severe, noninfectious diarrhea in the postconversion group versus the tacrolimus group was similar (7.33% vs 6.97%), indicating that tacrolimus combined with MMF represent a high risk for diarrhea. This outcome was consistent with that of the previous study,[8] an effect that may be attributable to interactions between the two drugs.

Previous reports have disclosed that tacrolimus can increase mycophenolic acid concentrations,[21] but that CsA did not show this effect. In our study, the two groups received similar doses of MMF, but we did not evaluate the concentration of MPA in each recipient. The correlation between diarrhea and MPA concentrations is controversial.[10,11] The leak of a difference in the MMF doses between the diarrhea group and the nondiarrhea group is not relevant to the impact of MPA concentration, which may be reduced by the hepatotoxicity of CsA.

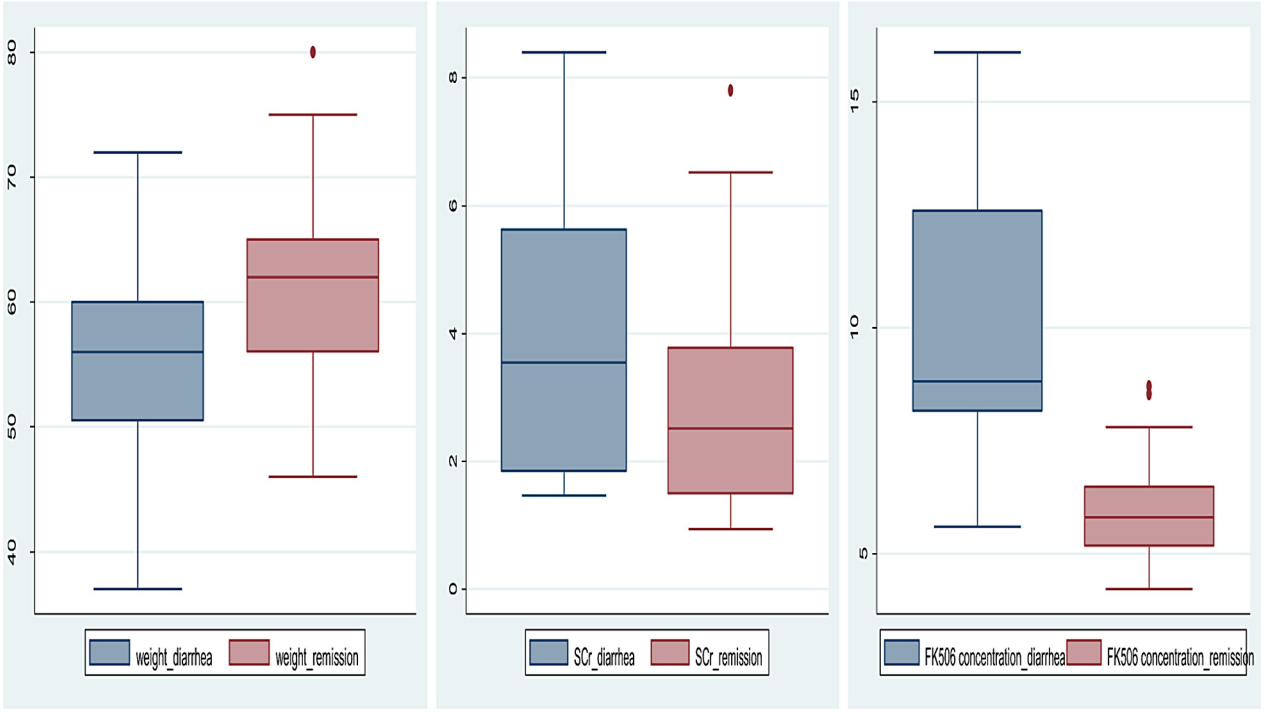

Fig 4. Changes in body weight, serum creatinine, and tacrolimus trough concentration during diarrhea and after resolution.

Hour analysis showed that CYP3A5 genotype, supplementation with *T wilfordii* and chronic renal allograft dysfunction were risk factors among the tacrolimus group. Evaluation of MPA area under the curve (AUC) may be particularly useful in this seeking. CYP3A5 genotype and supplementation with *T wilfordii* also influence tacrolimus metabolism[16,17]; however, concentrations of tacrolimus were not different between the diarrhea and nondiarrhea groups. There was a robust increase in tacrolimus concentration during the period of diarrhea (Fig 2), which was consistent with previous reports.[7] Therefore, the interaction between tacrolimus and MMF on gastrointenstinal dynamics which may be key to this side effect, should be explored in future studies.

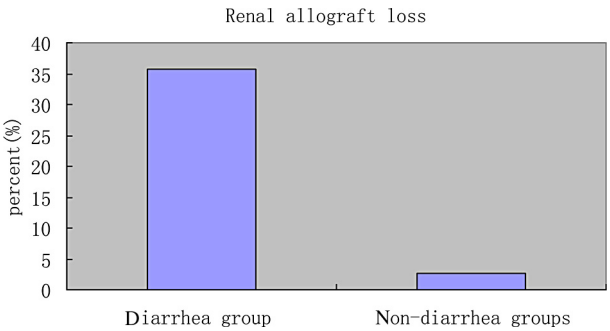

Fig 5. Renal allograft loss rates for the diarrhea and nondiarrhea groups.

T II, an active component purified from the medicinal plant *Tripterygium wilfordii* Hook F, acts as a potent immunosuppressant by inhibiting T cell activation and proliferation. The T II inhibits T-lymphocyte-induced interleukin-2 expression. Previous reports have demonstrated that the combination of Calcineurin inhibitor (CNI) and T II displays a positive effect to decrease acute allograft rejection and promote renal allograft survival. The T II combined with tacrolimus greatly increased tacrolimus concentrations in kidney transplant recipients, which led to a greater incidence of adverse diarrheal events.[16] Therefore, clinicians must monitor tacrolimus concentrations frequently for dose adjustments to avoid herbal-drug interactions with CNI.

Various therapies were presented for our patients (Fig 3). The first step was to adjust the oral duration of tacrolimus and MMF. Simply prescribing tacrolimus and MMF to be injected at different times lead to remissions among about one third of affect patients, a finding that supports the relation of diarrhea to drug-drug interactions.

The second step was to adjust the MMF dose, which led to remission in other recipients. The third step for patients resistant to the previous two alterations was conversion from MMF to mizoribine. The rationale for this conversion is due

to the pharmacokinetics of mizoribine,[22] which is absorbed in the intestine and does not show enterohepatic circulation.[23,24] Interestingly, one patient who underwent conversion from tacrolimus to CsA also experiences a remission. The adverse effect may be explained by influences of tacrolimus and MMF on cytochrome P450 3A4 and P-glycoprotein (P-gp) activities, which are major determinants of oral bioavailability of tacrolimus. Intestinal P-gp activity may be impaired in patients with persistent diarrhea compared to the diarrhea-free controls or healthy volunteers.[17]

The renal allograft survival rate among subjects with late, severe, noninfectious diarrhea was worse than those in the nondiarrhea group, thus corroborating the results of a previous report.[8] These results may reflect the higher rate of chronic renal allograft dysfunction among the non-diarrhea group. The infact of diarrhea may reflect the three cases of severe malnutrition who required parenteral nutrition since this condition threatens recipient survival. Two patients who did not experience remission, were placed on dialysis.

In summary, the incidence of late, severe, noninfectious diarrhea has been increasing in recent years. The tacrolimus + MMF combination has been shown to be a high-risk factor for this side effect. The other risk factors for diarrhea include, CYP3A5 3*/3*, supplementation of *T wilfordii*, and chronic renal allograft dysfunction. Prompt adjustment of immunosuppressive therapy may represent a suitable treatment for affected patients.

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