

Immunosuppressive effects of Rifampicin on a tuberculosis patient after renal transplant

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ABSTRACT

Rifampicin is a semisynthetic derivative of rifamycin B and inhibits the growth of a variety of bacteria. Rifampicin causes an increase in corticosteroid clearance, and a decrease in the blood concentrations of calcineurin inhibitors by inducing Cytochrome P₄₅₀ 3A4 in the liver. It is generally acknowledged that a substantial increase in the dosage of calcineurin inhibitors is required to achieve the efficacious target concentrations and avoid graft rejection. We report a case of patient who received a living-related donor renal transplant with stable renal function during the rifampicin based anti-tuberculosis treatment, even the blood concentration of tacrolimus (FK506) decreased. Interestingly, acute rejection was observed at the end of anti-tuberculosis treatment, even the blood concentration of FK506 was reduced to target level.

KEY WORDS: Rifampicin, Tuberculosis, Renal transplant, Immunosuppression.

Pak J Med Sci April - June 2011 (Part-II) Vol. 27 No. 3 720-722

How to cite this article:

Wang WG, Wang YT, Zhou HL, Li P, Wang G, Gao BS, et al. Immunosuppressive effects of Rifampicin on a tuberculosis patient after renal transplant. Pak J Med Sci 2011;27(3):720-722

INTRODUCTION

Rifampicin is a semisynthetic derivative of rifamycin B and inhibits the growth of a variety of

bacteria.^{1,2} Since then, most likely due to the satisfactory immunosuppressive performance of cyclosporine, the immunosuppressive activity of rifampicin has been seldom reported.

Rifampicin causes an increase in corticosteroid clearance, and a decrease in the blood concentrations of calcineurin inhibitors by inducing Cytochrome P₄₅₀ 3A4 in the liver.³ When rifampicin is coadministered with calcineurin inhibitors, it is generally acknowledged that a substantial increase in the dosage of calcineurin inhibitors is required to achieve the efficacious target concentrations and avoid graft rejection.⁴⁻⁶ In opposition to this acknowledgement, we report herein a renal transplant recipient with the blood concentration of FK506 only achieved 70% of the target concentration, however, the patient maintained good renal graft function during the 18-month duration of anti-tuberculosis therapy.

We conclude that because of the possible immunosuppressive effects of rifampicin, the allograft rejection did not occur even under a relatively low concentration of calcineurin inhibitor during the anti-tuberculosis therapy.

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- * Received for Publication: November 16, 2010
- * Revision Received: December 18, 2010
- * Revision Accepted: May 17, 2011

CASE REPORT

A 33-year-old female from the northeast of China, received a living-related donor renal transplant at our hospital in June 2007. The patient had no previous history of tuberculosis and had been treated with hemodialysis for 8 months prior to transplant. No induction treatment was conducted prior to transplant. After the transplantation, the immunosuppressive drugs tacrolimus (FK506), mycophenolate mofetil (MMF) and prednisone were used. The initial dose of FK506 was 0.1mg/kg/day, and then modified according to its blood concentration. The initial and maintenance dose of MMF was 1.0g/day. A dose of 500mg/day of methylprednisolone was applied on the day of (D0) and on days D1 and D2 after surgery. On D3, methylprednisolone was replaced by prednisone with the initial dose of 120mg/day, with a gradual reduction of 20mg per day until reaching a dose of 20mg/day. The dose was further decreased to 15, 10, and 5 mg/day at 1, 3 and 12 months after transplantation, respectively.

Within the first six post-transplant months, the allograft functioned well. The serum creatinine was $68.3 \pm 3.9 \mu\text{mol/L}$, and the blood concentration of FK506 was maintained at 8-12 ng/mL ($10.1 \pm 0.7 \text{ ng/mL}$). In the sixth month the patient presented with fever (peaking at 39°C), productive cough, chest tightness, fatigue, and night sweats. Treatment with ordinary antibiotics had no effect. Microbiological examination showed a white blood cell count of $4400/\text{mm}^3$, the Mantoux screening test (PPD test) was negative, and the acid fast stain test of the sputum smear and tubercle bacillus culture were positive. Chest X-ray revealed infiltrative pulmonary tuberculosis. The clinical diagnostic result was tuberculosis. The patient was treated with rifampicin (0.45g/day), isoniazid (0.3g/day) and ethambutol (0.75g/day) during the first two months, and rifampicin and isoniazid of the same dosage during the following 16 months. Two weeks after the treatment, the symptoms of fever, productive cough, chest tightness, fatigue, and night sweats disappeared. One month after the treatment, a repeat chest X-Ray showed that the focus had disappeared. Two months after the treatment, the results of the acid fast stain test of the sputum smear and tubercle bacillus culture were negative.

During the anti-tuberculosis treatment, because of the decrease in the blood concentration of FK506, its dose was increased to 2-4 times that of the pre-treatment amount, maintaining the blood concentration at 2.5-5.2ng/mL ($3.4 \pm 0.3 \text{ ng/mL}$), with serum creatinine being $7.1 \pm 2.7 \mu\text{mol/L}$ (Fig. 1). Twenty-three

months after the renal transplant, the patient was fully recovered from tuberculosis and the treatment was stopped. The blood concentration of FK506 subsequently rose to 16ng/mL. The dose of FK506 was reduced to the level before the anti-tuberculosis therapy and the blood concentration of FK506 dropped to 8ng/mL, but the serum creatinine rose

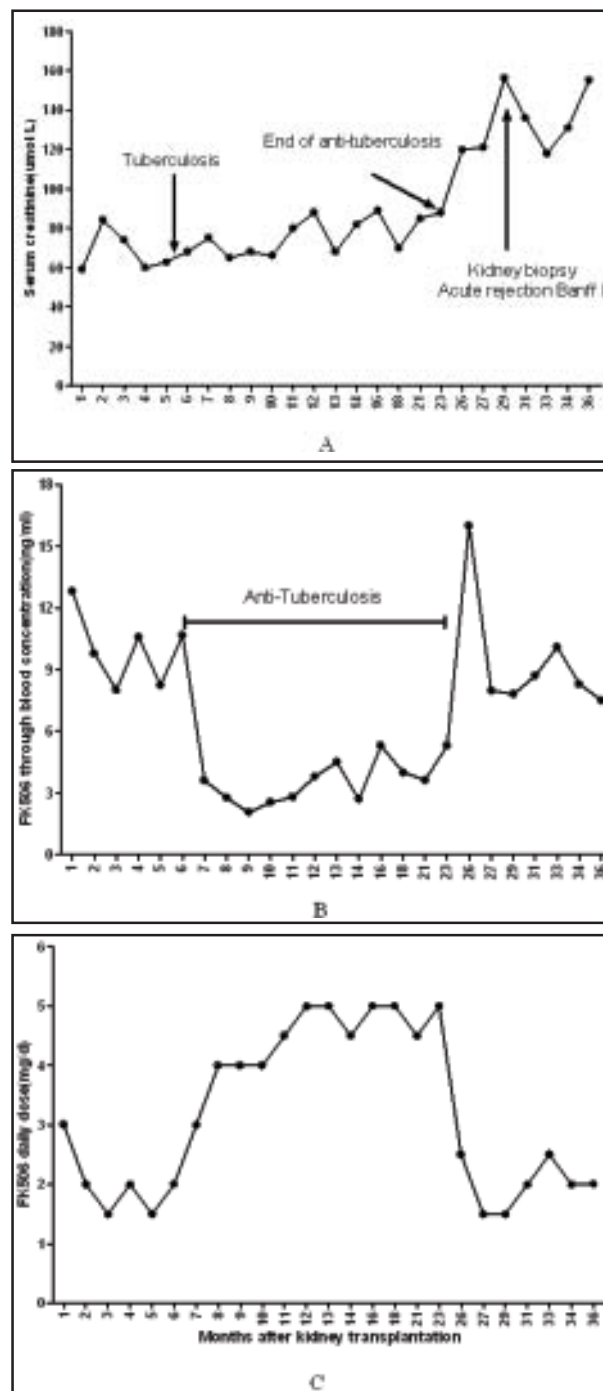


Fig-1: Time course of serum creatinine (A), FK506 trough blood concentrations (B) and daily dose (C).

from 88 μ mol/L to 155 μ mol/L. The patient presented with kidney pain and reduced urine. A needle biopsy of the transplant proved acute rejection (Banff I). After treatment with methylprednisolone, the serum creatinine decreased to 118 μ mol/L.

It is now the third year after renal transplant. The blood concentration of FK506 is maintained at 8-11ng/mL, the serum creatinine is 118-155 μ mol/L (Fig.1), and there has been no tuberculosis relapse. During the whole course of treatment, the patient's liver functioned normally.

DISCUSSION

Since its discovery, rifampicin has been regarded as the first-line drug and a necessary agent for tuberculosis therapy. Furthermore, most researchers believe that for anti-tuberculosis therapy in renal transplant recipients, it is essential to significantly increase the dosage of calcineurin inhibitors to avoid allograft rejection caused by insufficient immunosuppression.

In our case, the dose of FK506 during the anti-tuberculosis therapy was increased 2-4 times to deal with the drop in its blood concentration caused by rifampicin. Despite the increase in dose, the blood concentration of FK506 was only maintained at a lower level, failing to achieve the target concentration most of the time. In contrast with our concern, this sustained low blood concentration of FK506 during the approximate 18 months of anti-tuberculosis therapy did not lead to allograft rejection. We believe that it is the immunosuppressive effects of rifampicin that made up the deficiency in FK506 concentration. The coadministration of rifampicin and FK506 prevented acute rejection.

The mechanisms governing the immunosuppressive effects of rifampicin are diverse. Rifampin is able to reduce both humoral and cell-mediated immune responses^{7,8}, and influence the secretion of interleukin (IL)-6, IL-10, tumor necrosis factor (TNF) and IgG by regulating a variety of cytokines and antibodies.^{9,10}

In our case, when anti-tuberculosis drugs were discontinued, the FK506 concentration rose gradually to 16ng/mL. Decrease in the FK506 dose made its blood concentration drop to 8ng/mL, equivalent to the level before the anti-tuberculosis therapy, but the serum creatinine increased significantly. Acute rejection was confirmed by renal graft biopsy. Why did the acute rejection occur after discontinuing anti-tuberculosis drugs, while the concentration of calcineurin inhibitor was within the effective therapeutic window? The immunosuppressive effects of rifampicin are possibly the reason. When rifampicin

was discontinued, considerable antibodies were produced in the body.⁹ In addition, rifampicin can hinder macrophages from secreting cytokines.¹⁰ Hence when rifampicin was discontinued, the release of a large number of cytokines activated the effectors cells and induced the rejection. Under these conditions, although the concentration of the calcineurin inhibitor FK506 was within the effective therapeutic window, the immunosuppression was actually insufficient. In conclusion, we suggest that in the early stage of anti-tuberculosis drug withdrawal, the decrease in doses of immunosuppressant and rifampicin needs to be undertaken slowly to avoid allograft rejection.

This is just a single case report, we need more evidence gained from multi-center and large sample studies to confirm common occurrence. We are conducting animal experiments to further investigate the role of rifampicin in transplantation immunity and the underlying mechanism. Apart from its application in anti-tuberculosis therapy, rifampicin may be used in combination with immunosuppressant in the transplantation immunity and renal protection fields.

ACKNOWLEDGMENTS

This research is supported by the Youth Foundation Program of Science and Technology Department of Jilin Province of China (No. 20090176), the Bethune Foundation of Science and Technology Department of Jilin Province of China (No. 200705135) and the Youth Foundation of the First Hospital of Jilin University.

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