

Anti-virus efficacy of cyclosporine in renal transplant recipients with hepatitis C virus-RNA positive

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Abstract

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BACKGROUND: The selection of immunosuppressants and anti-hepatitis C virus drug is currently the focus for the hepatitis C virus-positive patients after receiving renal transplantation.

OBJECTIVE: To investigate the anti-virus replication effect of cyclosporine in hepatitis C virus-RNA positive renal transplant recipients in addition to its anti-rejection effect.

METHODS: Eleven hepatitis C virus-RNA positive renal transplant recipients were enrolled and treated with cyclosporine, prednisone and mizoribine. Hepatitis C virus-RNA level, hemoglobin, liver functions and renal functions were evaluated before treatment and at 6 and 12 months after treatment.

RESULTS AND CONCLUSION: The median of hepatitis C virus-RNA in 11 patients before treatment, and at 6 and 12 months after treatment were 1.22×10^7 copies/mL, 1.11×10^4 copies/mL and 4.19×10^6 copies/mL respectively. At 6 months after treatment, 8 cases of hepatitis C virus-RNA were negative (hepatitis C virus-RNA < 500 copies/mL), and the total response of hepatitis C virus-RNA was 73%, and the sustained virological response was 55% (6/11) at the final follow-up. There was no significant difference of alanine transaminase, serum creatinine and serum uric acid levels before and after treatment ($P > 0.05$), and the hemoglobin level was increased after treatment. During the follow-up, acute rejection only occurred in one patient and was controlled within 3 days after methylprednisolone pulse therapy. Cyclosporine-based treatment would be a better choice for renal transplant recipients combined with hepatitis C virus infection for both the anti-virus replication and anti-rejection effect.

INTRODUCTION

Due to the long-term dialysis and low immune function and other reasons, the renal transplant patients have a high incidence of chronic hepatitis C. Pegylated interferon combined with ribavirin can make hepatitis C virus (HCV) replication of about 50% patients long-term suppressed, but for the patients received renal transplantation, the high rejection rate caused by the program is an unavoidable risk, and the postoperative application of immunosuppressants will further reduce the patient's immune system and accelerate viral replication. How to make a balance point between the selection of anti-rejection and anti-viral replication drug is an important issue facing to the clinicians. Recent studies have shown that there is an important relationship between HCV-RNA replication and protein expression and cyclophilin in the cells^[1], cyclophilin inhibitors as a kind of HCV specifically targeted antiviral drugs have attracted more and more attention.

The cyclosporine of anti-rejection basic medication as a kind of cyclophilin inhibitor has been observed a good anti-virus replication effect in the partial liver transplant patients. Cyclosporine-based therapy program has been used in this study to observe the anti-virus replication effect of cyclosporine in HCV-RNA positive renal transplant patients in addition to the anti-rejection.

SUBJECTS AND METHODS

Design

A comparative clinical study.

Time and setting

The study was performed at Nanjing Drum Tower Hospital, the Affiliated Hospital of Nanjing Medical University between January 2006 and January 2011.

Patients

Eleven patients with HCV antibody positive were treated with renal transplantation in Nanjing Drum Tower Hospital, the Affiliated

Hospital of Nanjing Medical University between January 2006 and January 2011, nine patients in male and two patients in female, the age was rang 27–54, average in (42.5±9.0). All the patients received the renal transplantation firstly, and seven patients received the living donor renal transplantation, four patients received the cadaveric renal transplantation. Before renal transplantation, one patient underwent peritoneal dialysis for 8 months, 10 patients underwent hemodialysis for 2 months to 15 months. Before renal transplantation, nine patients suffered chronic glomerulonephritis uremia, one patient suffered IgA nephropathy uremia patients and one patient had hypertensive nephropathy uremia.

Diagnostic criteria

HCV-RNA positive (> 500 copies/mL) renal transplant recipients: 3 patients with HCV-RNA positive before transplantation; during the follow-up after renal transplantation, 8 patients with HCV-RNA positive (< 500 copies / mL) were changed into negative (> 500 copies/mL).

Inclusion criteria

- ①Patients that received long-term regular follow-up after renal transplantation were included in Nanjing Drum Tower Hospital, the Affiliated Hospital of Nanjing Medical University.
- ②Patients with normal liver function before transplantation and without cirrhosis under liver color Doppler ultrasound were included.
- ③Patients with HCV antibody positive before transplantation were selected.
- ④Patients treated with cyclosporine, mizoribine and prednisone triple immunosuppressive regimen were included.

Exclusion criteria

- ①Patients with hepatitis B or cytomegalovirus hepatitis.
 - ②Patients with HCV antibody positive and HCV-RNA continued negative.
 - ③Patients with severe liver dysfunction caused by cyclosporine.
 - ④Death caused by lung infection or other causes.
- The patients were informed that there were risks of uremia and hepatitis C, the long term and short term risks, as well as the commonly used interferon-based anti-hepatitis C treatment program and other related risk, and the patients were strongly asked to undergo renal transplantation and refused to accept the interferon treatment. The patients voluntarily choose the cyclosporine+mizoribine+hormone combination regimen and the research obtained the allowance of the patients and their families which met the relevant

requirements of the “Medical Institution Regulations”.

Drugs

Drugs	Source
Cyclosporine, basiliximab	Beijing Novartis Pharmaceutical Co., Ltd.
Mizoribine	Asahi Kasei Pharma Corporation
Tacrolimus	Astellas Pharma (China) Co., Ltd.
Mycophenolate mofetil, daclizumab	Shanghai Roche Pharmaceutical Co., Ltd.
Methyl prednisolone	The Pfizer International Trade (Shanghai) Co., Ltd.

Methods

Immunosuppressive regimen

All the patients received the cyclosporine+mizoribine+prednisone triple immunosuppressive regimen. Eight pre-transplant HCV-RNA positive patients were observed directly and received the cyclosporine+mizoribine+prednisone triple immunosuppressive regimen, while the other three pre-transplant HBV-RNA negative patients were not observed, and the three patients received the tacrolimus+Mycophenolate mofetil+prednisone triple immunosuppressive regimen after transplantation. After review, the HCV-RNA was changed into positive (> 500 copies/mL) and then included into observation, and treated with cyclosporine+mizoribine+prednisone triple immunosuppressive regimen. All the patients received the induction therapy before transplantation with the basiliximab and daclizumab; when the serum creatinine concentration fell to 300 μmol/L or less, the calcineurin inhibitors medications were used, the starting dose of cyclosporine was 5–6 mg/(kg • d) and the starting dose of tacrolimus was 0.1 mg/(kg • d), then we adjusted the dose according to blood concentration; the mycophenolate mofetil was used from the beginning with the concentration of 0.5–1.0 g/time and twice per day; mizoribine was used with the concentration of 100 mg/time and twice per day; the pre-transplantation methyl prednisolone dose was 120, the intraoperative dose was 500–1 000 mg and the post-transplantation dose was 300–750 mg/d; after 3 days, prednisone was offered instead of methyl prednisolone with the concentration of 120 mg per day, and reduced for 10 mg per day until 20 mg per day and maintained for 1 month, then 15 mg per day was offered after 1 month, 10 mg per day was offered after 3 months, and after 1 year, the concentration was changed into 5 mg per day.

Adjuvant therapy

- ①After the concentration of alanine aminotransferase was more than 40 U/L, the compound glycyrrhizin tablets, five ester capsules or silymarin capsule were taken, and after the concentration of alanine

aminotransferase was more than 80 U/L, intravenous injection of compound glycyrrhizin was performed, and the amount of immunosuppressant was reduced appropriately. ②When the concentration of serum uric acid was more than 420 μmol/L, the high-purine diet should be controlled, and when necessary, the allopurinol tablets or benzbromarone tablets could be used to reduce uric acid. When the concentration of hemoglobin was more than 172 g/L, the valsartan should be used to control polycythemia disease and the enteric-coated tablets of aspirin should be used to prevent thrombosis.

Index detection

TAQMAN fluorescence quantitative method^[1] was used to detect the HCV. The levels of HCV-RNA, alanine transaminase, serum creatinine, hemoglobin and serum uric acid were detected every 3 months, and the levels of the indexes were recorded before treatment and at 6 and 12 months after treatment.

Main outcome measures

Changes of the HCV-RNA of the patients and the blood and liver and kidney indicators were recorded.

Statistical analysis

Statistical analysis was performed using SPSS 19.0 software, and the data were expressed as mean±SD, the one-way variance analysis was used to compare the data between groups, and the pairwise comparisons were performed using the least significant difference test. *P* < 0.05 was considered statistically significant.

RESULTS

Quantitative analysis of the subjects

All the initial 11 subjects were included in the final analysis after followed-up for 15–70 months.

Baseline data

The baseline data of the 11 renal transplant recipients with HCV-RNA positive were showed in Tables 1 and 2.

Changes of the HCV-RNA in renal transplant recipients before treatment

The 11 patients with HCV-RNA > 500 copies/mL were treated with cyclosporine+mizoribine+prednisone triple immunosuppressive regimen, and the medians (copies/mL) of the HCV-RNA in the patients before treatment and at 6 and 12 months after treatment were 1.22×10⁷ copies/mL, 1.11×10⁴ copies/mL and 4.19×10⁶ copies/mL respectively; at 6 months after treatment, there were eight cases of HCV-RNA positive changed into negative (HCV-RNA< 500 copies/mL),

and the overall response rate was 72.73% (8/11); at 12 months after treatment, among the eight HCV-RNA negative patients, two cases of HCV-RNA negative were changed into positive (HCV-RNA > 500 copies/mL), while the other six patients were followed-up to March 2012, and the HCV-RNA was kept in negative, the sustained virologic response rate was 54.55% (6/11).

Table 1 Baseline data of 11 renal transplant recipients with hepatitis C virus-RNA positive

Case	Gender	Age (yr)	Dialysis times (mon)	Primary disease	Donor	Follow-up time (mon)
1	Male	48	4	Chronic glomerulonephritis	Cadaver	70
2	Female	54	15	Chronic glomerulonephritis	Cadaver	62
3	Male	36	2	IgA nephropathy	Mother	55
4	Male	35	8	Chronic glomerulonephritis	Wife	54
5	Female	38	4	Chronic glomerulonephritis	Mother	53
6	Male	45	3	Chronic glomerulonephritis	Wife	45
7	Male	46	16	Hypertensive nephropathy	Cadaver	41
8	Female	54	10	Chronic glomerulonephritis	Cadaver	38
9	Male	27	5	Chronic glomerulonephritis	Mother	27
10	Male	32	8	Chronic glomerulonephritis	Cadaver	21
11	Male	45	5	Chronic glomerulonephritis	Nephew	15

Table 2 Number of hepatitis C virus (HCV) and the levels of alanine transaminase (ALT), serum creatinine, serum uric acid and hemoglobin of the patients before renal transplantation

Case	HCV (copies/mL)	ALT (U/L)	Creatinine (μmol/L)	Uric acid (μmol/L)	Hemoglobin (g/L)
1	5.65×10 ⁷	32	63	435	76
2	6.52×10 ⁴	33	122	411	130
3	1.05×10 ⁵	20	84	449	114
4	3.65×10 ⁴	21	104	334	116
5	3.30×10 ⁵	35	60	287	148
6	3.56×10 ⁵	36	70	385	110
7	6.65×10 ⁶	27	95	434	98
8	3.90×10 ⁵	33	76	275	151
9	1.97×10 ⁶	12	66	244	98
10	5.02×10 ⁶	27	118	211	89
11	3.83×10 ³	31	94	406	147

Changes of the blood, liver and kidney indicators in the renal transplant recipients before and after treatment

After treated with cyclosporine+mizoribine+prednisone triple immunosuppressive regimen, the hemoglobin, liver and kidney function were reviewed at 6 and 12 months after treatment (Table 2). Statistical results showed that there was no significant difference of alanine transaminase, serum creatinine, serum uric acid levels at different time points (*P* > 0.05). Four patients received

the hepatoprotective therapy by taking compound glycyrrhizin tablets, the five ester capsules or silymarin Capsule continuously, and the liver function of the four patients was normal; among the four patients, alanine aminotransferase level in one patient had risen more than 400 U/L, and intravenous injected with compound glycyrrhizin was performed to reduced the level, after the alanine aminotransferase level dropped to 80 U/L, the oral liver drug was taken instead of injection. There was significant difference of the hemoglobin between different time points (before treatment and at 6 and 12 months after treatment) ($P < 0.05$), while there was no significant difference between 6 and 12 months after treatment ($P > 0.05$) (Table 3).

Table 3 Comparison of hemoglobin, liver and kidney indicators of the renal transplant recipients before and after treatment ($\bar{x} \pm s$, $n=11$)

Item	Before treatment	6 mon after treatment	12 mon after treatment
ALT (U/L)	27.91±7.48	28.09±8.34	33.66±10.51
Cr ($\mu\text{mol/L}$)	86.58±21.75	89.73±23.26	90.25±22.51
UA ($\mu\text{mol/L}$)	351.91±85.17	378.09±94.31	373.87±82.75
HB (g/L)	116.09±25.34	143.64±15.67 ^a	146.00±18.58 ^a

^a $P < 0.05$, vs. before treatment; ALT: alanine aminotransferase; Cr: creatinine; UA: uric acid; HB: hemoglobin

Adverse reactions and the survival of the recipients and kidney

No delayed graft function was observed in 11 renal transplant patients, one patient had serum creatinine increasing at 2 months after transplantation and reached to 460 $\mu\text{mol/L}$, and after treated with 500 mg/d methylprednisolone for 3 days, the serum creatinine level returned to normal. Cytomegalovirus pneumonia was observed in one patient at 4 months after transplantation, and the serum creatinine level was not increased after anti-virus treatment. All the 11 patients were followed-up to March 2012 and the recipients and the kidneys were survived well.

DISCUSSION

The renal transplant patients are the high-risk groups for hepatitis B and hepatitis C infection as most of the patients need the long-term and frequent hemodialysis before transplantation to sustain the life, and part of patients even need the blood transfusion before and after transplantation to correct the renal anemia. Xiao *et al*^[2] found that the HCV antibody positive rate of the hemodialysis patients was 70.8%, HCV-RNA positive rate was 71.7%, and the HCV infection rate was 82.1%. The HCV infection of the hemodialysis patients is significantly higher than that of the general population, in which the dialysis life and times for blood transfusions

are the major risk factor for the spread of HCV infection in dialysis patients. Guideline of prevention and treatment of hepatitis C^[3] found that the male patients aged over 40 years old who had HCV infection combined with HIV co-infection and leading to the immunocompromised persons may promote the progression of the disease. The commonly used immunosuppressive agents for the renal transplant patients after transplantation may cause the immune dysfunction and weakened the ability of the body to clear the virus and even make the HCV replication more active.

Mathurin *et al*^[4] made a group of case-control studies and observed that the emergence of HCV antibodies is one of the independent risk factors which can affect the 10-year survival rate of the renal transplant patients. But Perez *et al*^[5] found that the alanine aminotransferase level in the HCV-positive renal transplant patients was lower than that in ordinary hepatitis C patients, which can often obscure the assessment of the disease in the hepatitis C patients and delay the treatment of hepatitis C. Therefore, actively controlling of the HCV replication had positive significance to improve the liver function and protect the graft. After timely treatment, a significant proportion of patients (65%) achieve a sustained response effect, some patients are clinical cured^[6]. Therefore, the actively controlling of the HCV replication has a positive significance for alleviating the burden of the liver in renal transplant patients, reducing the occurrence of rejection and prolonging the graft survival rate^[7]. Bi *et al*^[8] found that the comprehensive assessment before transplantation, establishment of a strict follow-up system after transplantation, as well as strengthen the guidance to the patients, pay close attention to the patient's liver function changes, regularly check the genomics change of hepatitis virus and using the corresponding treatment may help to keep short-term safety of the hepatitis C patients.

Till now, pegylated interferon combined with ribavirin is still recognized as the internationally standard regimen of antiviral therapy for non-organ transplant patients with hepatitis C^[3, 9]. The program can make the HCV changed into negative in about half of the patients, but the risk and the significance of the program used in organ transplant patients is still debatable^[7, 10-14]. ①Increasing the risk of rejection of transplanted organs. ②Some patients cannot tolerate. ③Interferon antibody may be induced during the interferon treatment process which may affect the antiviral therapy. ④Patients with hepatitis C type I is the main crowd in domestic, and the patients with this genotype may obtain a 40% to 54% sustained virologic response rate after receiving the standard treatment program of pegylated interferon combined with ribavirin, but the patients with type II/III genotype can obtain a

65% to 82% sustained virologic response rate, and the type I genotype is lower than the type II/III genotype. ⑤The program should be discontinued at 24 to 48 weeks conventionally as it is not the long-term medication. Therefore, it is more necessary to explore a reasonable anti-viral medication for organ transplant patients, and the study of HCV specifically targeted antiviral drugs has obtained more attention. Target for antiviral drugs including the non-structural protein 3/4 serine protease inhibitor, a non-structural protein 3/4 serine protease inhibitor 5B polymerase inhibitor, a non-structural protein 3/4 serine protease inhibitor 5A inhibitors, cyclophilin inhibition agent, hepatitis C virus receptor antagonist and silybin derivatives^[15].

Basic research shows that the mechanism of anti-hepatitis C virus in cyclophilin inhibitor is different from that in the interferon^[16-18]. Cyclophilin inhibitors combined and targeting with the intracellular receptor cyclophilin can specifically block the key enzyme of non-structural protein 5B synthesized by HCV-RNA to fusion into the replication complex, in order to inhibit the HCV-RNA replication. Combination of cyclosporine and interferon can improve sustained virologic response. Alisporivir(Synthetic cyclosporine analogues) is a non-organ transplant oral cyclophilin inhibitor, it has a strong pan-genotype anti-HCV activity targeting with the host protein^[19-20]. The study suggests that Alisporivir is safety for using and has nothing to do with hepatitis C genotype. Flisiak *et al*^[21] used the Alisporivir for the treatment of 23 patients with dual infection of HIV/HCV, and found that Alisporivir has good anti-HIV/HCV replication activity, and has a more precisely curative effect if combined with pegylated interferon and ribavirin, which provides a better option for patients with dual infection of HIV/HCV.

Although Alisporivir has good prospects, it is not suitable for the long-term application. As one of the oral cyclophilin inhibitors, cyclosporine is commonly used in clinical for organ transplantation, it has the similar molecular structure with Alisporivir^[17] (Figure 1). The *in vitro* and *in vivo* studies have shown that is similar with Alisporivir, cyclosporine has good inhibition effect on HCV.

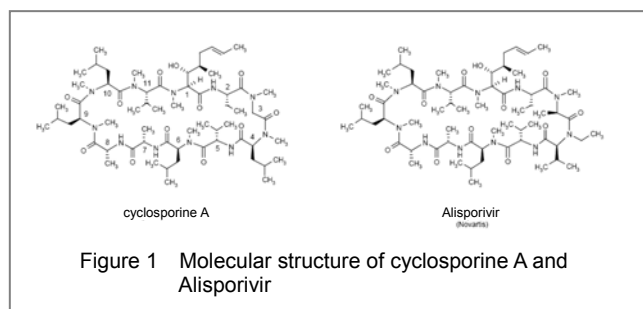


Figure 1 Molecular structure of cyclosporine A and Alisporivir

Inoue^[22] made a analysis on the treatment of chronic hepatitis C and found that the host immune response is

one of the important factors that lead to severe hepatitis C, if the host immune response can be suppressed, even if the virus does not disappear, it may make the patients transferred to the asymptomatic carrier state. They selected the eligible patients with interferon invalid three elements, namely ①genotype 1b, ②patients with a large amount of replication, ③progressive patients in histology. All the eligible patients were treated with cyclosporine, and the HCV was gradually disappeared, and after followed-up for 12 years, the HCV remained the sustained virologic response. They performed 120 cases of clinical observation following, and found that at 4, 12, 24 and 48 weeks after treated with the cyclosporine+interferon combination therapy, the HCV-RNA negative rate were 57.9%, 76.3%, 76.3% and 55.3% respectively, and after treated with interferon alone, the HCV-RNA negative rate were 29.5%, 38.6%, 52.3% and 31.8% respectively.

Firpi *et al*^[23] retrospectively analyzed 56 liver transplant patients treated with cyclosporine immunosuppressant program and 59 patients treated with tacrolimus treatment programs, all recipients were treated with interferon and ribavirin for 48 weeks after the histological changes of activity was confirmed. The sustained virologic response rate in the cyclosporine group was 46%, and significantly higher than 27% of the tacrolimus group. It illustrate that cyclosporine or combined with interferon can inhibit HCV-RNA replication and in a dose-dependent manner, and the mechanism is different from the interferon.

Firpi *et al*^[24] made randomized controlled trials and further observed that cyclosporine has the *in vivo* anti-HCV effect in liver transplant recipients. Twenty patients received tacrolimus and 18 patients received cyclosporine were selected in this study. Among the patients treated with cyclosporine that converted from the tacrolimus, the HCV-RNA level was decreased 0.39×10^6 copies/mL within 1 month.

The study also found that the cyclosporine plays the anti-rejection effect and HCV replication in renal transplant patients, which can make the concentration of HCV-RNA decreased from the 1.22×10^7 copies/mL pre-post treatment to 1.11×10^4 copies/mL 6 months post-transplantation, and obtain a higher sustained virologic response rate of 55%. There is no statistically significance of liver function, kidney function and blood uric acid level before and after treated with cyclosporine +mizoribine+prednisone regimen. Since the enough erythropoietin provided by the transplanted kidney, patients with anemia will be cured and the hemoglobin level will return to normal, or even higher than normal^[25]. The study showed that the hemoglobin level was increased at 6 and 12 months after treatment.

Therefore, for the renal transplant patients with hepatitis C, cyclosporine+mizoribine+prednisone program is

preferred and it may be the best choice as it can achieve anti-rejection effect, and play a role in inhibiting the replication of the HCV at the same time. This method can not only ensure the long-term compliance with medication, but also cannot add additional drug costs and increase the risk of rejection. For part of the HCV-RNA positive renal transplant patients, single treatment with cyclosporine+mizoribine+prednisone for 1 year cannot make the HCV-RNA negative, while associated with unmanageable elevation of liver aminotransferases and liver ultrasound changes which are difficult to control, so the pegylated interferon combined with ribavirin should be added.

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环孢素治疗丙型肝炎病毒 RNA 阳性肾移植患者的抗病毒复制效应

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文章亮点: ①实验选择既具有抗排斥作用, 又具有特异性靶向抗病毒作用的环孢素治疗丙型肝炎病毒 RNA 阳性肾移植患者。②环孢素+咪唑立宾+泼尼松治疗方案在达到抗排斥治疗作用的同时, 可发挥抑制丙型肝炎病毒复制的作用, 同时对患者肝脏无明显损伤。

关键词: 肾移植; 并发症; 丙型肝炎; 丙型肝炎病毒; 免疫抑制剂; 环孢素; 抗病毒; 器官移植

摘要

背景: 丙型肝炎病毒阳性患者接受肾脏移植后, 免疫抑制剂的选择及抗丙型肝炎病毒药物的选用是目前关注的重点。

目的: 探讨环孢素在丙型肝炎病毒 RNA 阳性肾移植患者中除抗排斥作用以外的抗病毒复制作用。

方法: 纳入 11 例丙型肝炎病毒 RNA 阳性肾移植患者, 于采用环孢素+咪唑立宾+泼

尼松治疗方案时记为入组, 分别对入组前、入组后 6、12 个月时患者丙型肝炎病毒 RNA、血红蛋白、肾功能等指标的变化进行检测。

结果与结论: 入组前、入组 6 个月、入组 12 个月 11 例患者丙型肝炎病毒 RNA 中位数 (copies/mL) 分别为 1.22×10^7 , 1.11×10^4 , 4.19×10^6 ; 入组 6 个月时, 有 8 例患者丙型肝炎病毒 RNA 转阴 (丙型肝炎病毒 RNA < 500 copies/mL), 总应答率为 73% (8/11); 至随访结束, 持续病毒学应答率为 55% (6/11)。且入组治疗前后患者谷丙转氨酶、血清肌酐、尿酸水平差异均无显著性意义 ($P > 0.05$), 患者血红蛋白水平在入组后升高。随访过程中, 仅 1 例发生排斥反应, 甲基强的松龙冲击治疗 3 d 后好转。提示对于合并丙型肝炎的肾移植患者, 选用环孢素为主的治疗方案, 在达到抗排斥治疗作用的同时, 可发挥抑制丙型肝炎病毒复制的作用。

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来自本文课题的更多信息--

作者贡献: 第一作者进行实验设计, 实验实施为第一、二、三、四作者, 第一作者成文, 第五作者审核, 第一作者对文章负责。

利益冲突: 课题未涉及任何厂家或其他经济组织直接或间接的经济或利益的赞助。

伦理要求: 南京鼓楼医院肾脏移植中心具有肾脏移植资质, 所有患者均对用药方案知情同意, 用药方案组合遵循国内外常用方案组合, 符合相关伦理学要求。

文章概要: 观察环孢素在肾脏移植患者中的抗丙型肝炎病毒复制作用, 也得到相似的抑制病毒复制的结果, 而且肝脏损伤并不明显。但限于单中心观察, 此类患者数量还不多, 只能进行自身对照研究, 还无足够患者进行随机对照研究。今后拟进一步进行基础研究和多中心研究。

作者声明: 文章为原创作品, 数据准确, 内容不涉及泄密, 无一稿两投, 无抄袭, 无内容剽窃, 无作者署名争议, 无与他人课题以及专利技术的争执, 内容真实, 文责自负。

(Edited by Li YK/Chen X/Wang L)