Effect of sirolimus on renal injury induced by bile duct ligation in rats[1]

Efeito do sirolimo na lesão renal induzida pela ligadura do ducto biliar em ratos

Hulya Ozturk[I], Akan Terzi[II], Hayrettin Ozturk[III], Aysel Kukner[IV]

[I] Associate Professor, Duzce University, Medical School, Department of Pediatric Surgery, Duzce, Turkey.
[II] Specialist in Histology and Embryology, Abant Izzet Baysal University, Medical School, Department of Histology and Embryology, Bolu, Turkey.
[III] Full Professor, Pediatric Surgery, Abant Izzet Baysal University, Medical School, Bolu, Turkey.
[IV] Full Professor, Abant Izzet Baysal University, Medical School, Department of Histology and Embryology, Bolu, Turkey.

ABSTRACT

Purpose: To evaluate the effects of sirolimus (SRL) on renal injury in rats with bile duct ligation. **Methods**: A total of 21 male Sprague-Dawley rats weighing 220-260g were used. Group 1 (Sham-control, n=7) rats were undergone laparotomy alone and bile duct was just dissected from the surrounding tissue. Group 2 rats (BDL/Untreated, n=7) were subjected to bile duct ligation and no drug was applied. Group 3 rats (BDL/SRL, n =7) received a daily dose of sirolimus (0.5 mg·day^{-1}×kg^{-1} dissolved 1 ml in saline) by orogastric tube for 14 days after BDL. At the end of the two-week period, biochemical and histological evaluation were processed. **Results**: AST, ALT, AP and TB levels values were decreased in group 3 when compared to group 2. There was no significant difference in serum levels of BUN and creatinine among all the experimental groups. Histological evaluation of the liver of BDL/Untreated group rats demonstrated marked portal fibrosis and signs of major bile duct obstruction with prominent portal and lobular inflammation. In BDL/SRL group, moderate damage was seen. Tubular injury scores were higher in the BDL subgroups; however, group 3 rats showed considerably fewer lesions in the tubules and interstitium compared to the group 2 rats. In group 2 animals, in the epithelial cells of proximal tubules presented vacuoles and hydropic changes, atrophy and inflammatory cell infiltrate in the medullar interstitium. **Conclusions**: Sirolimus decreased tubulointerstitial lesions in kidney induced by bile duct ligation in rats. The improve effects of sirolimus on renal morphology can be due to improved liver function or due to direct action on the kidney.

Key words: Sirolimus. Common Bile Duct. Ligation. Liver. Kidney. Rats.

RESUMO

Objetivo: Investigar os efeitos do sirolimo (SRL) na lesão renal induzida pela ligadura do ducto biliar em ratos. **Métodos**: Foram utilizados 21 ratos Sprague-Dawley pesando entre 220-260 g. Grupo 1 (Sham-controle, n=7) submetidos a laparotomia e o ducto biliar dissecado do tecido circundante. Grupo 2 (BDL/Não tratado, n=7) foram submetidos a ligadura do ducto biliar e nenhuma droga foi aplicada. Grupo 3 (BDL/SRL, n=7) receberam dose diária de sirolimo (0,5 mg dia^{-1}×kg^{-1} dissolvido em 1 ml em solução salina) por tubo orogástrico por 14 dias após BDL. Após duas semanas era realizada avaliação bioquímica e histológica. **Resultados**: Níveis de AST, ALT, AP e TB estavam diminuídos no grupo 3 comparado ao grupo 2. Não houve diferença significante nos níveis séricos de BUN e creatinina em todos os grupos. Observou-se na avaliação histológica evidente fibrose portal e sinais de obstrução do ducto biliar com evidente inflamação portal e lobular. No grupo BDL/SRL verificou-se dano moderado. Lesão tubular foi maior nos subgrupos BDL; entretanto, o grupo 3 mostrou considerável menos lesões nos túbulos e interstício comparados ao grupo 2. No grupo 2 as células epiteliais dos túbulos proximais apresentaram vacúolos e alterações hidrópicas, atrofia e infiltrado celular inflamatório no interstício medular. **Conclusões**: Sirolimo diminuiu lesões tubulointersticial no rim induzida pela ligadura do ducto biliar em ratos. Os efeitos benéficos do sirolimo na morfologia renal pode ser devida à melhora da função hepática ou devido à ação direta no rim.

Descritores: Sirolimo. Ducto Colédoco. Ligadura. Fígado. Rim. Ratos.

[1]Research performed at the Laboratory of Experimental Research, Abant Izzet Baysal University, School of Medicine, Bolu, Turkey.

Introduction

Patients with obstructive jaundice may have a higher incidence of renal dysfunction and approximately 6%-8% of patients suffer from acute renal injury, with a mortality of over 68%[1,2]. Causes underlying of the renal morphological and functional changes in obstructive jaundice still not been understood. To explain renal damage has been proposed the three hypotheses: renal ischemia-reperfusion; the devastated barrier; and bilirubin injury[3-5]. Cirrhosis is associated with abnormalities cardiovascular as hyperdynamic circulation. In addition, renal excretory function diminishes, with decreases in glomerular filtration rate and renal sodium excretion[6].

The macrolide fungicide sirolimus (SRL) produced by *Streptomyces hygroscopius*, also known as rapamycin, was initially introduced into clinical practice as an immunosuppressive drug with antiproliferative properties[7,8]. The action of SRL is due to blockade of mammalian target of rapamycin (mTOR)[9]. It has a critical role in promoting cellular growth and differentiation, cell cycle progression, apoptosis and organ size[10,11].

The purpose of the present study is to investigate the effects of sirolimus on renal injury in bile duct-ligated (BDL) rats.

Methods

Twenty one male Sprague-Dawley rats weighing 220-260g were used in the study. All animals were housed at a temperature- and light-controlled room with *ad libitum* access to water and rat chow. All experimental protocols were approved by the Abant Izzet Baysal University School of Medicine Animal Care and Use Committee. The animals were divided into 3 groups. Each rat was anesthetized with ketamine (50mg/kg) and xylazine (4mg/kg). At the end of the procedure each animal was given a subcutaneous analgesia (Bupremorphine, 0.01–0.05 mg/kg).

The rats were subjected to either bile duct ligation (BDL) or sham operation using aseptic techniques, as previously described by Criado *et al.*[12]. Group 1 rats (Sham-control, n=7) underwent laparotomy alone and bile duct was dissected from surrounding tissue. Group 2 rats (BDL/Untreated, n=7) subjected to bile duct ligation alone and rats received 1 ml of saline by orogastric tube. Group 3 rats (BDL/SRL, n =7) subjected to bile duct ligation alone and received a daily dose of sirolimus (0,5mg·day^{-1}×kg^{-1} dissolved 1 ml in saline) by orogastric tube for 14 days after BDL.

The rats were housed in standard cages in a room controlled for daylight (12h), temperature (20^{o} C) and humidity (60%), and maintained on a standard rat pellet diet.

At the end of the two week, all animals were anesthetized with 100 mg/kg Inactin i.p., placed on a thermoregulated table, and a short segment of polyethylene (PE)-240 catheter was inserted into the trachea to assist the spontaneous respiration. After opening the abdomen by a midline incision, the abdominal aorta was punctured and 5ml of blood was taken into heparinized tubes. Plasma was separated by centrifugation for biochemical studies, and the activities of alanine aminotransferase (ALT) (units/l), aspartate aminotransferase (AST) (units/l), alkaline phosphatase (AP) (units/l) and the concentrations of total bilirubin (TB) (mg/dl) in plasma were determined by standard auto-analyser methods on an Abbot Aeroset (USA). Just before the rats were sacrificed, the livers and left kidney were extracted for histopathological evaluation. During this period of surgical preparation, the rats in all groups received 1% of their body weight of Ringer's lactate solution.

Blood urea nitrogen (BUN) (mg/dl) and serum creatinine (mg/dl) were measured by colorimetric method using an autoanalyzer (Technicon RA-1000, Technicon Instruments Corporation, Tarrytown, NY, USA).

Histologic analysis

Liver and kidney tissue were fixed in 10% buffered formaldehyde, and then processed and embedded in parafin and sectioned (5µm). These sections were stained with hematoxylin and eosin, and viewed by light microscopy. A pathologist then performed morphologic evaluation in blinded, randomized sections of the kidney and liver tissue.

Histologic grading of liver-induced damage by BDL was determined by examining each specimen for the following features and allocating increasing points according to the severity of the finding portal inflammation, lobular inflammation, bile duct proliferation and fibrosis; 0 = none, 1 = mild, 2 = moderate 3 = marked, 4 = severe (13).

Slides of the kidney were reviewed in a blinded manner and scored with a semiquantitative scale to evaluate the presence and extent of granulovaculoar degeneration of renal tubule as reported by Tajiri *et al.*[14]. They were scored as the follows: 0, no renal tubules were injured; 1, ,25% of renal tubules were injured; 2, 25–50% of the renal tubules were injured; 3, .50–75% of the renal tubules were injured; and 4, .75%–100% of renal tubules were injured.

Statistical analysis

Data were entered and analyzed on an IBM compatible personal computer using SPSS version 9.0. All values were expressed as mean±SD. The significance of the data obtained was evaluated by using analysis of variance (ANOVA). Differences between means were analyzed by using the post-ANOVA (Tukey's b) test. *P* values of less than 0.05 were considered significant.

Results

Biochemical measurements

The bile duct ligation resulted in jaundice in rats. As shown in Table 1, AST, ALT, AP and TB levels were significantly increased in the group 2 and 3 in comparison with the group 1 (for all $p<0.001$). However, AST, ALT, AP and TB levels values were decreased in group 3 when compared to group 2 (for all $p<0.05$). There was no significant difference in serum levels of BUN and creatinine among all the experimental groups (Table 1).

TABLE 1 - Kidney and liver function parameters in the different experimental groups.

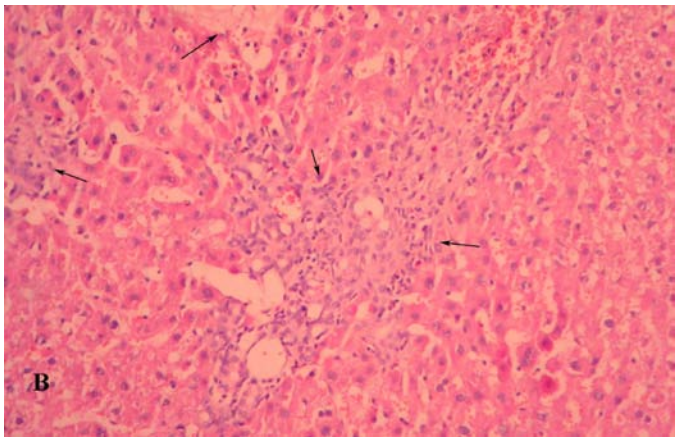
Biochemical Parameters	Groups Sham-control	BDL/Untreated	BDL/SRL
BUN (mg/dl)	40,2 ± 4,1	44.5 ± 3,2	41.4 ±4,7
Creatinine (mg/dl)	0.2 ±0,1	0.3 ± 0,1	0.2 ± 0,2
AST *U/L*	64± 6	2100± 657*	1300± 385*†
ALT *U/L*	41± 8	334± 122*	176± 67*†
AP *U/L*	384± 78	705± 89*	459± 67*†
TB *mg/dL*	0.12± 0.04	8.87± 1.16*	5.64± 0.47*†

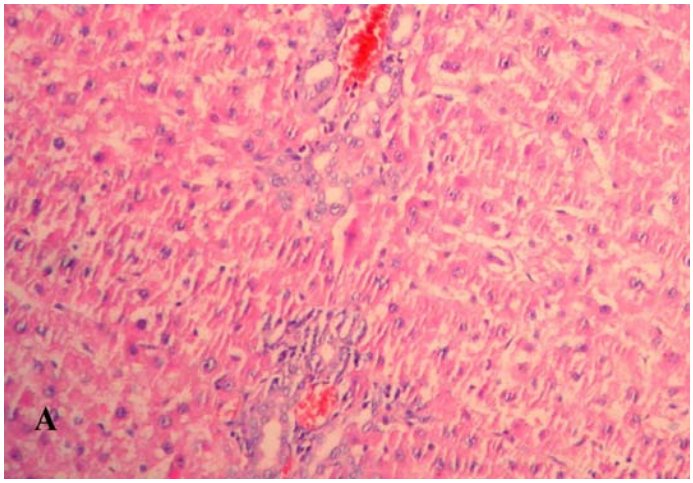
Values are as means±SD.
Abbreviations are: BUN, blood urea nitrogen ; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AP, alkaline phosphatase; TB; Total bilirubin.
* P < 0.05 vs. Sham-control. † P < 0.05 vs. BDL/Untreated

Liver morphology

No morphological damage was observed in any of the rats in the Sham-control group (Figure 1A).

Histologic evaluation of the liver of BDL/Untreated group rats demonstrated marked portal fibrosis and signs of major bile duct obstruction with prominent portal and lobular inflammation (Figure 1B). In BDL/SRL group, moderate damage (dilated central veins and minimal disorganization of the hepatocytes plates, rare PNL and hepatocytes necrosis) was seen (Figure 1C). The histopathological scores were as 0.1±0.1; 3.7±0.7; and 1.8±0.2; in the groups 1, 2 and 3 respectively. The histopathological score was significantly less in the group 3 compared to the group 2 rats ($p<0.05$).





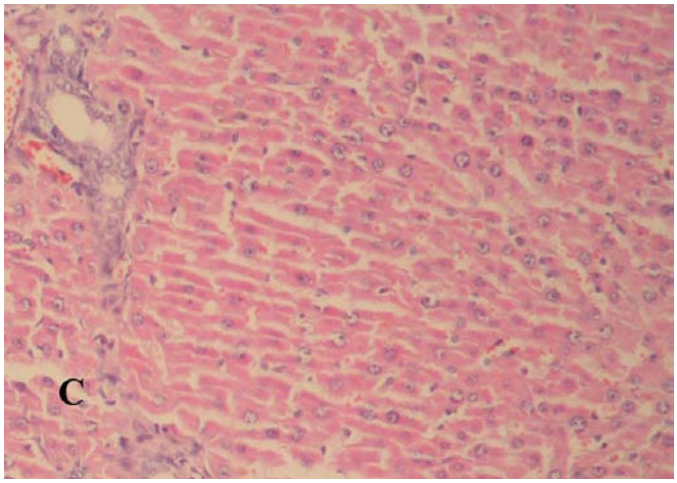


FIGURE 1 - (**A**) No morphological damage was found in the Sham-control group. (**B**) Histologic estimation of the liver of BDL/Untreated group showed portal fibrosis and signs of major bile duct obstruction with portal and lobular inflammation (arrows). (**C**) In BDL/SRL group, moderate damage was observed.

Renal morphology

The values of tubular injury scores measurements for the different groups are shown in Figure 2.

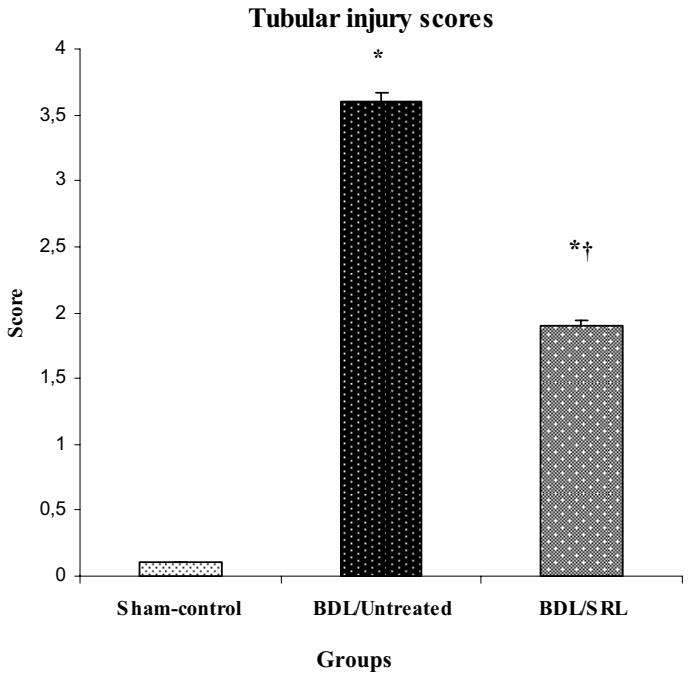
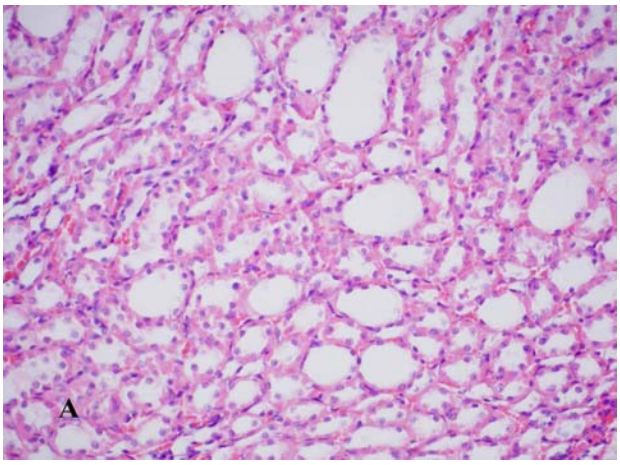
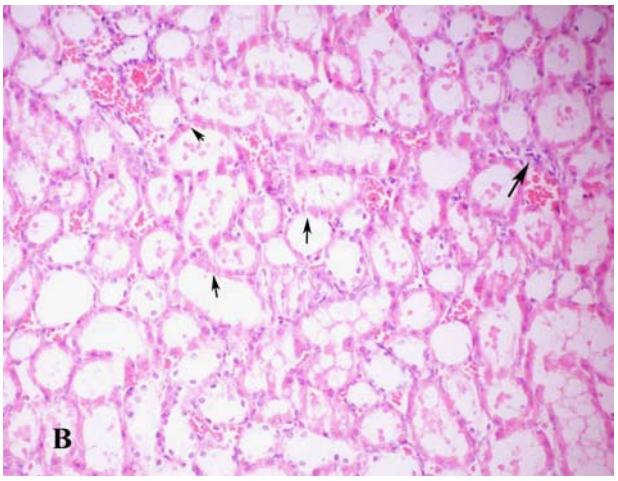


FIGURE 2 - Comparative of tubular injury score measurements at the groups. *$p<0.05$ compared with group 1. †$p<0.05$ compared with group 2. Vales are mean ±SD. Group 1: sham-operated control ; Group 2: BDL/Untreated; Group 3: BDL/Sirolimus –treated.

No morphological damage was observed in any of the rats in the group 1 (Figure 3A).

In group 2 animals, in the epithelial cells of proximal tubules presented vacuoles and hydropic changes, atrophy and inflammatory cell infiltrate (Figure 3B). Tubular injury scores were higher in the BDL subgroups; however, group 3 rats showed considerably fewer lesions in the tubules and interstitium compared to the group 2 rats (p<0.001) (Figure 3C).





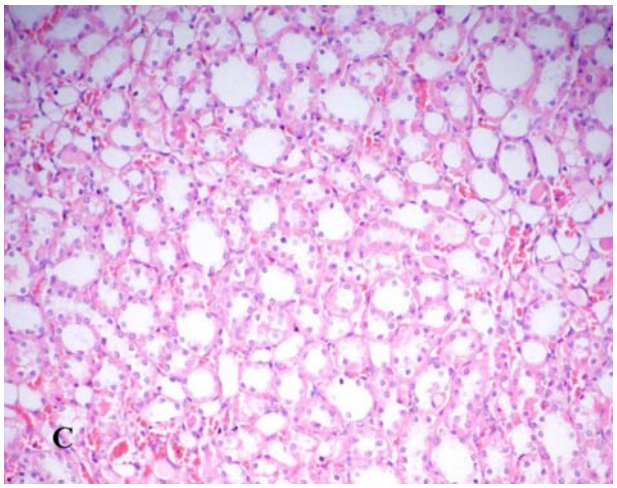


FIGURE 3 - (**A**) No morphological damage was observed in any of the rats in the group 1 (H&E, X100). (**B**) In the group 2 rats were noticed vacuoles, hydropic degeneration and desquamation changes in tubular epithelia and inflammatory infiltrate around hyalinised vessel (H&E, X100). (**C**) These observations were found lower in group 3 rats (H&E, X100).

Discussion

In liver cirrhosis occur frequently important renal complications. These complications include water-balance abnormalities, sodium retention, activation of intrarenal hormones and renal failure known as hepatorenal syndrome (HRS)[15]. Hyperbilirubinemia has been shown to potentially affect renal function. These are associated with a urinary concentration defect, decreased maximal free water clearance and increased fractional sodium excretion[16]. Besides this, a predominant observation is reversible renal vasoconstriction that can lead to hepatorenal syndrome and renal failure. The mechanism of the renal vasoconstriction is unclear, but it may be related to elevated levels of endothelin-1 (ET-1) during cirrhosis[17] that is a consequence of the hyperdynamic systemic circulation. In addition, those effects may be explaining tubular epithelial damage. Bilirubin seems to interfere with epithelial cell transport function, and shown that bile acids directly inhibit sodium/hydrogen exchange in proximal

tubular brush border vesicles[16,18], which also could represent one of the mechanisms for decreased fluid and sodium reabsorption in proximal and also in distal nephrons segment[18]. Rodrigo *et al.*[19] suggested that the renal compromise of obstructive jaundice is characterized by changes in the tubular handling of electrolytes. Tubular epithelial cells seem to be the targets of a systemic response to the liver dysfunction. This response involves a natriuretic effect likely due to hemodynamic, humoral and paracrine mediators yet unaccompanied by changes in the activity of renal (Na 1 K)-ATPase. Recently, however, it has been claimed that others factors, such as lipid peroxides, are involved[20]. The oxidative stress known to occur as a systemic response to cholestasis could give rise to the involvement of organs other than liver, such as the kidney, which could explain the renal morphological and functional alterations here reported[19]. This contention is based on previous studies[21], which found that the antioxidants -lipoic acid and N-acetylcysteine prevented the hyperdynamic circulation induced by either experimental cholestasis or portal hypertension. Another study further supported this notion, as vitamin E prevented the fall in blood pressure and restored PRA to normal (likely because of the improved hemodynamic state)[22].

Sirolimus is an immunosuppressive drug, which acts by inhibiting the proliferation and clonal expansion of interleukin-2-stimulated T cells through the inhibition of a 70-kDa S6 protein kinase, a kinase necessary for cell cycle progression[23,24]. Sirolimus may also anti-inflammatory effects that are independent of an effect on immune cells[25]. For example, therapeutic concentrations of sirolimus (10 ng/ml) reduced TNF-α production by 37% in IL-1-stimulated proximal tubular epithelial cells[26]. Neef *et al.*[27] suggested that low-dose oral rapamycin (0.5 mg/kg/day) treatment reduces fibrogenesis, improves liver function, and prolongs survival in rats with established liver cirrhosis, as in our study. Low-dose oral rapamycin (0.5 mg/kg/day) could be the implication for the clinical setting. Accumulation of extracellular matrix in fibrotic liver was decreased together with numbers of activated hepatic stellate cells. The mechanism of rapamycin's antifibrotic action in the nonallogeneic situation is likely to be its effect on the proliferation of key cells involved in fibrosis, in particular macrophages and fibroblasts[28]. TGFb is the key cytokine involved here, and this study has shown that rapamycin leads to a profound decrease in its expression[29]. Inman *et al.*[30] demonstrated that sirolimus preserved renal function in rats 5 to 7 days after I/R injury. In addition, it may be that sirolimus has some beneficial vasodilating effects on the preglomerular and postglomerular arterioles.

Pereira *et al.*[31] showed that rats with 2 wk of BDL increased free water clearance reduced urinary osmolality and serum creatinine in comparison to the sham group. In contrast, rats at 6 wk of BDL showed features of HRS, including significant increase in serum creatinine and reductions in creatinine clearance, water excretion and urinary sodium concentration. Rats with 4 wk of BDL exhibited an intermediate stage of renal dysfunction. They suggested that BDL produced progressive renal dysfunction without structural changes in the kidney, characterizing HRS. In our study, there was no significant difference in serum levels of BUN and creatinine among all the experimental groups. Our rat the model has its limitations as 2 wk of BDL and blood received at the end of the two week. Blood can be drawn from the tail vein in rats daily, also an earlier and a later time point of analyzing the livers and kidneys would be advantageous. In the present study, in BDL/Untreated animals, in the epithelial cells of proximal tubules presented vacuoles and hydropic changes, atrophy and inflammatory cell infiltrate in the medullar interstitium. However, in rats treated with sirolimus were showed considerably fewer lesions in the tubules and interstitium compared to the group BDL/Untreated rats. The improve effects of sirolimus on renal morphology can be due to improved liver function, less bilirubin, etc. or due to direct action on the kidney such as anti-inflammatory, antifibrotic and beneficial vasodilating effects. In a retrospective study consisting of 16 long-term (>3 years) orthotopic liver transplantation recipients with different degrees of renal insufficiency ranging from mild to severe, conversion from cyclosporine or tacrolimus to sirolimus-based immunosuppression resulted in variable improvement in renal function and no rejections at 6-month follow-up[32]. Sirolimus immunosuppression can be advantageous in patients that underwent liver transplantation suffering from concomitant hepatorenal syndrome[33].

Conclusion

Sirolimus decreased tubulointerstitial lesions in kidney induced by bile duct ligation in rats. These effects of sirolimus may be related to improve liver function, less bilirubin, etc. or anti-inflammatory, antifibrotic and beneficial vasodilating effects that are independent of an effect on immune cells.

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Correspondence:
Hayrettin Ozturk
Professor in Pediatric Surgery
Abant Izzet Baysal University, Medical School,
Department of Pediatric Surgery
14280 BOLU, Turkey
Phone: 90 374 2534656 / 3220
Fax: 90 374 2534615
ozturkhayrettin@hotmail.com

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