Abstract

Background: In patients with intestinal transplantation (ITx), renal function is easily impaired due to long-term parenteral nutrition and side effects of tacrolimus. Everolimus was used in patients with renal insufficiency in our study.

Methods: Everolimus was administered as a third immunosuppressive agent in addition to tacrolimus and steroids for renal sparing in patients who received ITx. Everolimus levels, complications, and renal function were assessed.

Results: Two patients received everolimus after ITx. Patient 1 was a 13-year-old boy who underwent ITx for an allied disorder of Hirschsprung's disease. After induction therapy with rATG, maintenance therapy consisted of tacrolimus and steroids. Everolimus was introduced 3 months after ITx for renal sparing. Seven months later, the patient required partial intestinal graft resection due to bowel obstruction. Everolimus was suspended for only 2 weeks. Four years after ITx, the trough level of tacrolimus was maintained at 3 to 5 ng/mL. The trough level of everolimus was maintained at 3 to 5 ng/mL. Patient 2 was a 32-year-old man who underwent deceased ITx for short gut syndrome. Induction and maintenance immunosuppression was the same as for patient 1. Everolimus was introduced 1 month after surgery. Two years after ITx, trough levels of tacrolimus and everolimus were the same as in Patient 1. No rejection was observed in either patient, and renal function was well

maintained. No side effects caused by everolimus have been observed.

Conclusions: Everolimus could be used safely and effectively after ITx. Early use of everolimus after ITx did not affect wound healing.

Introduction

The first intestinal transplantation (ITx) in Japan was performed in 1996. By the end of 2020, the total number of ITx procedures reached 35 [1]. ITx will become established as a standard therapy for intestinal failure and secondary multiorgan failure that can improve long-term survival and quality of life [2]. However, renal function after ITx is sometimes impaired due to long-term parenteral nutrition and post-transplant calcineurin inhibitor (CNI) therapy. Compared with all other solid organ transplantations, ITx is associated with the highest risk of developing chronic renal failure [3].

Everolimus (EVR), a mammalian target of rapamycin (mTOR) inhibitor, is a derivative of sirolimus (SRL) with a similar mechanism of action. Both are renal sparing. SRL is a macrocyclic triene antibiotic that was initially found to have antifungal properties that might also act as a primary immunosuppressant or antitumor agent. It is currently used as an immunosuppressant to prevent rejection of renal and cardiac transplants in Japan. We used EVR in patients after ITx for renal sparing and preventing rejection. Then we evaluate the safety and efficiency of EVR for ITx.

Methods

Everolimus was administered as a third immunosuppressive agent in addition to

tacrolimus and steroids for renal sparing and preventing rejection in patients who received ITx. Everolimus levels, complications, and renal function were assessed. Renal function was evaluated with serum creatine or serum cystatine- C. Estimated glomerular filtration rate (eGFR) was calculated based on serum creatine. Equation to calculate eGFR is as follows. eGFR (mL/min/1.73 m2) = 194 x Serum creatinine(-1.094) x Age(-0.287) x 0.739 (if female)[4]

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki Congress and the Istanbul declaration regarding donor source regarding donor source. Donors must not be from prisoners, or from those individuals who are coerced or paid.

Results

Two patients received everolimus after ITx. Patient 1 was 13-year-old boy with an allied disorder of Hirschsprung's disease with short gut syndrome after surgical resection. The patient's height was 133 cm and weight was 27 kg. Patient details are shown in Table 1. He had impaired renal function; his pre-transplant cystatin C level was 1.24 mg/L. He had 50 cm of native intestine proximal to the jejunostomy. Deceased ITx was performed due to central blood access. Graft length was 150 cm. The proximal anastomosis was

gastrojejunostomy and the distal anastomosis was single ileostomy. Rabbit anti-thymocyte globulin (rATG) was administered at 1.5 mg/kg for 10 days as induction. Maintenance immunosuppression therapy was performed with tacrolimus (TAC) and steroids. Initial TAC target trough level was at 18ng/ml. Cystatin C level was elevated by 1.45 mg/L. Then EVR was introduced about three months after ITx to protect renal function and prevent rejection. EVR was started with 0.25mg twice a day orally. Initial EVR target trough level was at 3 ng/ml. A summary of the patient's post ITx course is shown in Fig. 1(a). Seven months later, the patient was required to undergo partial intestinal graft resection due to bowel obstruction. However, EVR was suspended for only 2 weeks. No wound healing problems or anastomotic leakage occurred. Four years after ITx, the serum trough level of TAC was maintained at 3 to 5 ng/mL and the trough level of EVR was maintained at 3 to 5 ng/mL. The patient's renal function and immunosuppression details are shown in Table 2 (a). The cystatin C level was between 1.5 mg/L and 2.3mg/L after about two years from EVR administration, then kept around 2.0 mg/ L after about five years from the start EVR. Long term patient renal function was shown in Fig. 1(b). No rejection was observed. No side effects caused by EVR have been observed.

Patient 2 was a 32-year-old man with short gut syndrome. The patient's height was 170 cm and weight was 63 kg. Patient details are shown in Table 1. He had impaired renal

function; the pre-ITx eGFR was 65.3 ml/min/m^2. He had 40 cm of native intestine proximal to the jejunostomy. Deceased ITx was performed due to central blood access. Graft length was 260 cm. The proximal anastomosis was jejuno-jejunostomy and the distal anastomosis was loop ileostomy. rATG was administered at 1.5 mg/kg for 10 days as induction. Maintenance therapy was performed with TAC and steroids. Initial TAC target trough level was at 15ng/ml. EVR was introduced one month after ITx for renal sparing and preventing rejection because post ITx eGFR was about 60 ml/min/m^2. EVR was started with 0.5mg twice a day orally. Initial EVR target trough level was at 3 ng/ml. A summary of the patient's early post ITx course is shown in Fig. 2 (a). Two years after ITx, the serum trough level of TAC was maintained at 3 to 5 ng/mL, and the trough level of EVR was maintained at 3 to 5 ng/mL. The patient's renal function and immunosuppression detail was shown in Table 2 (b). Long term renal function was evaluated with eGFR. The eGFR was about 60 ml/min/m^2 after two years from administrated EVR. Long term patient renal function was shown in Fig. 2(b). The eGFR was preserved by more than 90% of the pre-ITx eGFR. Renal function was preserved. No rejection was observed. No side effects caused by EVR have been observed.

Discussion

Use of EVR in ITx has rarely been reported, but other mTOR inhibitors have been

used as immunosuppression for ITx. Experience with SRL, another mTOR, has been published. SRL, an agent purified from *Streptomyces hygroscopicus* in the soil, suppresses T lymphocyte proliferation. The efficacy of SRL for primary immunosuppression with TAC has been demonstrated after kidney, pancreas, and liver transplantation [5]. For ITx, an immunosuppressive regimen that includes SRL improves graft survival. Furthermore, this regimen significantly decreases the incidence of early rejection and has eliminated early graft loss caused by fulminant rejection. Additionally, it increases 3-year patient and graft survival rates [6]. Luuro et al reported that the use of SRL in combination with TAC seemed to be more effective than monotherapy in reducing the number of rejections. Side effects can limit its use as maintenance therapy [7]. SRL significantly improves graft survival. Similar associations were seen when 1-year conditional survival was examined in an international intestinal transplant registry [8].

Few papers have been published on the use of EVR in ITx. However, studies in liver transplantation showed that EVR acts synergistically with CNIs, offering an opportunity to lower CNI exposure and potentially prevent CNI-related toxicity [9, 10]. Protection of renal function is an important issue for improving the results of ITx. Andres et al reported that over one-third of their patients eventually required SRL to improve renal function and avoid rejection [11]. In our patients, renal function in patient 2 was well preserved with EVR

administration. However, in patient 1, renal function deteriorated during the first two years. The reason was that the TAC level in patient 1 was not reduced at the time when the TAC level was high three months after ITx because the EVR administration was delayed to POD 82 compared to patient 2 (POD 32). Therefore, it is recommended that EVR should be initiated 30 days after ITx. However, even in patient 1, renal function after two years was preserved with EVR. EVR administration can be expected to have a certain effect on long-term renal function. Additionally, in our patients, no rejection was observed. EVR had some effect of preventing rejection after ITx.

Patient 1 needed intestinal anastomosis after introduction of EVR. Delayed wound healing is a common concern with the use of EVR [12]. This result would be concerning if the patient needed further surgical intervention. We started EVR at least 1 month after ITx to promote early wound healing. The use of EVR in combination with TAC seemed to be more effective than monotherapy to spare renal function and rejection. EVR did not affect the intestinal anastomosis. Rao et al reported that a patient who underwent multivisceral transplantation developed persistent CMV viremia [13]. In our patients, there were no severe infections although valganciclovir was administered prophylactically and maintained at a immunosuppressive level lower than in their patient. We had not experienced the adverse effect of EVR. EVR was used safely in our patients.

EVR is a hydroxyethyl derivative of SRL that is more hydrophilic than the parent drug and therefore has greater oral absorption. EVR is rapidly absorbed and reaches a peak blood level after about 2 h. Its half-life is shorter than that of SRL, and oral dosing is adjusted to target a blood level between 3 and 12 ng/mL. In our experience, EVR trough levels around 5 ng/mL do not cause adverse effects. We therefore targeted EVR trough levels of 3 to 5 ng/mL with TAC trough levels around 5 ng/mL after ITx. Dosing of EVR and the CNI was based on data from de novo renal trials. Additional studies in ITx are required to determine appropriate dosing regimens.

Further studies are needed to assess the role of EVR in preventing graft failure when the drug is included in immunosuppressive protocols for ITx recipients. Further trials are warranted to clarify the potential improvement of standard TAC maintenance with EVR conversion or addition.

Conclusions

EVR could be used safely and effectively after ITx. Early use of EVR after ITx did not affect wound healing.

Reference

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