Clinics and Research in Hepatology and Gastroenterology (2019) 43, 403—409

Available online at ScienceDirect www.sciencedirect.com

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ORIGINAL ARTICLE

mTOR inhibitors in pediatric liver transplant recipients

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Available online 6 December 2018

KEYWORDS
liver transplantation;
pediatric;
mTOR inhibitor;
outcome

Summary
Background: During the past decade, mTOR inhibitors (mTORi), everolimus and sirolimus, have been increasingly used after adult liver transplantation (LT). The aim of the present study was to describe the use of mTORi in pediatric LT recipients.
Methods: All pediatric LT recipients who received mTORi before December 2017 from 4 European pediatric LT centers were included and analyzed.
Results: The present retrospective study included 30 patients; 21 were male (70%), median age was 9.3 years (range: 1.2—17.1 years) at mTORi introduction. Main indications for mTORi introduction were pre-existing liver malignancy (43.3%), calcineurin inhibitor (CNI) nephrotoxicity (26.7%), or rejection (23.4%). At last follow-up, mTORi CNIs were withdrawn in 10 patients (10/29, 34.5%). The median dose of mTORi was 1.8 mg/day (range: 0.3—5.0) or 0.058 mg/kg/day (range: 0.01—0.26), and the median trough level was 5.1 μg/L (range: 1.0—15.5). After a

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https://doi.org/10.1016/j.clinre.2018.11.010

median follow-up of 2.8 years (range: 0.2—10.0), 50.0% of the patients presented with at least one adverse event. The main adverse events included hyperlipidemia, proteinuria, dermatitis, and mucitis. Overall mTORi discontinuation rate was 23.3% (10.0% because of adverse event). Introduction of mTORi had no significant impact on renal function.
Conclusion: Our results suggest that mTORi can be used in pediatric LT recipients in different clinical situations, both to reinforce immunosuppressive therapy, and to reduce CNI and related toxicity.

Introduction

Liver transplantation (LT) increases life expectancy for patients with end-stage liver disease for whom there is no medical alternative [1]. During the past 20 years, major therapeutic advances in LT have led to significant improvement in both patient and graft survival, but important concerns remain about long-term side effects of immunosuppressive drugs, which can induce significant morbidity and mortality [2]. This is particularly relevant in the pediatric population owing to the expected very long survival after transplantation. Over recent years, new immunosuppressive strategies based on novel drugs and novel combinations and dosage optimization have been developed with the aim to reduce these adverse events without compromising protection from rejection.

Sirolimus (SRL; Rapamune®, Pfizer, New York, USA) and everolimus (EVR; Certican®, Novartis, Basel, Switzerland) are inhibitors of Mammalian Target of Rapamycin (mTOR) (mTORi) registered for use in solid organ transplantation with the potential of reducing CNI-induced side effects. Nevertheless, despite promising impacts of mTORi, there are some concerns regarding the adverse effects of this class of drugs, including dyslipidemia, wound healing or other dermatological problems [3]. In adult LT recipients, mTORi have been largely evaluated and used during the past decade in order to decrease or resolve CNI adverse effects, especially renal impairment [4—9]. In pediatric LT recipients, the experience is restricted to a small single-center retrospective study [10,11] and a multicenter randomized study, that stopped prematurely [10,11]. The aim of the present retrospective study was to report a multicenter experience on the use of mTORi in an internationally representative sample of pediatric LT recipients.

Methods

Study design

Between January 2005 and March 2017, all pediatric ($\leq$ 18 years) liver transplant recipients in four centers (Hôpital Femme-Mère-Enfant, Lyon, France; Hôpital Bicêtre, Le Kremlin Bicêtre, France; Hôpital Necker, Paris; and Hôpitaux Universitaires de Genève, Geneva, Switzerland), who received mTORi as part of immunosuppressive regimen (off-label use) were included in a retrospective cohort study. These 4 centers perform (and performed) the vast majority (> 90%) of pediatric LT in both France and Switzerland. The aim of the study was to describe the clinical and biological outcome of these patients, with a specific focus on potential adverse events induced by mTORi.

Introduction of mTORi

Initial dose of SRL or EVR was between 0.025 and 0.1 mg/kg mg per day, and trough level was measured after one or two weeks for dosage adjustment to reach trough levels between 3 and 8 μg/L.

If deemed necessary, dosage of CNI (tacrolimus or cyclosporine) was progressively decreased (and eventually discontinued) after mTORi introduction. Other immunosuppressive drugs were used, including mycophenolate mofetil (MMF), steroids, or azathioprine (AZA), according to tolerability.

Follow-up

Clinical and laboratory data related to the clinical outcome of the patients were recorded after mTORi introduction. The collected data included mTORi dosage, occurrence of acute rejection, presence of hypercholesterolemia (defined by the ratio of total cholesterol/high-density lipoproteins > 5, or by the presence of therapy), hypertriglyceridemia, diabetes, hypertension, and clinical outcome. Laboratory data were recorded up to the last follow-up available, and included mTORi serum trough level at steady state, blood cell count, liver function tests, estimated GFR (eGFR) according to the Chronic Kidney Disease in Children Schwartz formula, and proteinuria (defined as > 0.3 g/day). Liver biopsies were performed only as clinically needed for assessment of graft dysfunction. Diagnosis of rejection was always proven by biopsy and rejection was graded according to the Banff classification.

Statistical analysis

Quantitative variables were described using mean and standard deviation (SD), or median and range. Categorical values were tabulated and percentages were calculated. Variables were compared using the Student's t-test, and χ^2 test and considered as significant if $P < 0.05$. Statistical analyses were performed using SPSS software, version 13.0 (IBM, Armonk, NY, US).

Table 1 Characteristics of the study population.

	Total population, $n = 30$
Male/Female (*n*)	21/9
Age (years) at mTORi introduction (median, range)	9.3 (1.5—18.2)
Time (years) from LT to mTORi introduction (median, range)	2.9 (0.1—15.1)
Indications for LT (*n*, %)	
Primary liver tumor	13 (43.3%)
Hepatic angiosarcoma	6
Hepatocellular carcinoma (in Alagille syndrome or tyrosinemia)	5
Hepatoblastoma	2
Biliary atresia	9 (30.0%)
Primary sclerosing cholangitis	2 (6.7%)
Auto-immune hepatitis	1 (3.3%)
Alpha 1 antitrypsin deficiency	1 (3.3%)
Alagille syndrome	1 (3.3%)
Progressive familial intrahepatic cholestasis	1 (3.3%)
Fulminant hepatic failure	1 (3.3%)
Cirrhosis of unknown etiology	1 (3.3%)
Immunosuppressive regimen at the time of mTORi introduction (*n*, %)	
CNI monotherapy	19 (63.3%)
CNI in association with MMF	6 (20.0%)
CNI in association with MMF and steroids	1 (3.3%)
CNI in association with steroids	3 (10.0%)
MMF	1 (3.3%)
CNI trough levels	
Tacrolimus (median trough level)	3.8 μg/L (1.3—13.0)
Cyclosporine (median trough level)	74 μg/L (28—120)
Indications for mTORi[a]	
Primary liver malignancy	13 (43.3%)
CNI nephrotoxicity	8 (26.7%)
Rejection	7 (23.4%)
PTLD	4 (13.3%)
Study protocol	1 (3.3%)

LT: liver transplantation; mTORi: mTOR inhibitor; CNI: calcineurin inhibitor; MMF: mycophenolate mofetil; PTLD: post-transplant lymphoproliferative disease.

[a] Total > 100% because patients could have several indications for mTORi use.

Results

Characteristics of the study population

Between January 2005 and September 2017, mTORi was introduced in 30 patients (21 males; median age 9.3 years). Since 1355 patients were followed-up after pediatric LT in the 4 participating centers, this represents 2.2% of the total. Patient characteristics are summarized in Table 1. Median follow-up after mTORi introduction was 2.8 years (range: 0.2—10.0). Twenty-eight patients received EVR and 2 patients received SRL. At the time of mTORi introduction, the immunosuppressive regimen included a CNI in 29 patients (96.7%; tacrolimus $n = 24$, or cyclosporine $n = 5$), MMF in 8 patients (26.7%), and steroids 4 patients (13.3%). Median dose of tacrolimus was 2.1 mg/day (range: 0.5—11.0), or 0.11 mg/kg/day (range: 0.01—0.30), and that of cyclosporine was 105 mg/day (range: 70—140), or 10.0 mg/kg/day (range: 8.0—12.0). Median blood trough level of tacrolimus was 3.8 μg/L (range: 1.0—7.4) and median trough level of cyclosporine was 74 μg/L (range: 28—120); the median dose of MMF was 475 mg/day (range: 600—1500).

Immunosuppressive regimen after mTORi introduction

Median follow-up after mTORi introduction was 2.8 years (range: 0.2—10.0). Three patients who received mTORi died between 4 and 38 months after mTORi introduction, all because of recurrent liver malignancy. No death was directly related to mTORi toxicity.

At last follow-up, the median dose of mTORi was 1.8 mg/day (range: 0.3—5.0) or 0.058 mg/kg/day (range: 0.01—0.26), and the median blood trough level was 5.1 μg/L (range: 1.0—15.5). mTORi was associated with CNI in 19 patients (63.3%; tacrolimus $n = 17$, or cyclosporine $n = 2$), associated with MMF in 7 patients (23.3%), and used as monotherapy in 4 patients (13.3%). CNIs were withdrawn in 10 patients (34.5%). The median dose of tacrolimus was 2.0 mg/day (range: 0.5—4.0) or 0.05 mg/kg/day (range: 0.01—0.16), and median dose of cyclosporine was

Table 2 mTORi adverse events.

	Total population $n = 30$
Adverse events	15 (50.0%)
At least one adverse event	15 (50.0%)
Several adverse events	4 (13.3%)
Time (months) from mTORi introduction to first-effect (median and range)	6 (0.2-106.9)
Adverse events	
Hyperlipidemia (hypercholesterolemia)	5 (16.7%)
Proteinuria	4 (13.3%)
Dermatitis	3 (10.0%)
Mucitis/oral ulcer	3 (10.0%)
Pneumonitis	1 (3.3%)
Edema	1 (3.3%)
mTORi withdrawal	7 (23.3%)
Time (months) from mTORi introduction to withdrawal (median and range)	11.5 (0.5—122.0)
Cause of withdrawal (%, *n*)	
Mucitis/oral ulcer	1 (3.3%)
Dermatitis	1 (3.3%)
Pneumonitis	1 (3.3%)
Rejection	1 (3.3%)
Planned discontinuation (after treatment and resolution of PTLD)	2 (6.7%)
Planned discontinuation (before kidney transplantation)	1 (3.3%)

mTORi: mTOR inhibitor; PTLD: post-transplant lymphoproliferative disease.

105 mg/day (range: 70—140) or 10.0 mg/kg/day (range: 8.0—12.0). Median blood trough level of tacrolimus was 3.8 μg/L (range: 1.3-13.0) and median blood trough level of cyclosporine was 63 μg/L (range: 25—102); the median dose of MMF was 750 mg/day (range: 500—1500).

Safety and effectiveness of mTORi

During follow-up, 50% of the patients presented at least one adverse event (Table 2). Main adverse events included dermatitis and mucitis. Four patients presented two or more adverse events. The median interval between mTORi introduction and first side-effect was 6.0 months (range: 0.2—122.0). During follow-up, one biopsy-proven acute rejection (mild, according to Banff) occurred in 1 patient (3.3%), after which immunosuppression was increased using higher doses of CNI while the mTORi was discontinued. Overall mTORi discontinuation rate was 23.3% (10.0% because of adverse events). Median duration of mTORi treatment before discontinuation was 11.5 months (range: 0.5—106.9).

The mean ± SD eGFR was 103 ± 54 mL/min/1.73 m^2 at baseline and 89 ± 47 mL/min/1.73 m^2 at the end of follow-up (paired *t*-test, $P = 0.23$). Similarly, when considering only the 9 patients with initial renal function impairment, mean ± SD eGFR was 75 ± 24 mL/min/1.73 m^2 at baseline and 61 ± 38 mL/min/1.73 m^2 at the end of follow-up ($P = 0.10$). Introduction of mTORi did not significantly modify (paired t-test) the white blood cell count, platelet count, or hemoglobin values: 7.2 ± 3.5 vs. 5.6 ± 2.1 G/L, 254.3 ± 117.4 vs. 238.8 ± 112.5 G/L, and 120.0 ± 27.4 vs.107.7 ± 27.5 g/L, before vs. after mTORi introduction, respectively.

Seventeen patients received mTORi because of liver malignancy as an indication for LT or post-LT post-transplant lymphoproliferative disease (PTLD). Among the 13 patients who received mTORi because of an initial malignant liver tumor, 3 presented recurrence and died (angiosarcoma, $n = 2$ and hepatocellular carcinoma (HCC), $n = 1$). The 4 patients who presented with PTLD experienced a favorable outcome, and mTORi was discontinued, as initially planned, in 2.

In the 7 patients who received mTORi because of rejection, 4 had a complete improvement in liver function tests (normal liver enzymes and no further progression of chronic graft dysfunction). One of 7 patients had a partial improvement in liver function tests but did not reach normal values, and in 2 patients no significant positive influence of mTORi on liver function tests was documented.

Discussion

EVR and SRL exert their immunosuppressive effect by blocking the proliferation of hematopoietic (T and B cells) and non-hematopoietic cells (vascular smooth muscle cells) [12]. Their safety and efficacy/effectiveness has been evaluated in adult solid organ transplantation, including LT [4,5,7—9,13]. Herein we report the third cohort of pediatric LT recipients, following an initial single-center retrospective study that included 18 patients [10,11], and a multicenter randomized study that included 56 patients [10,11]. The population of the present study is heterogeneous owing to the retrospective and multicenter nature of the present study. Nonetheless, this sample is representative of a real-world patient population, and we believe that the results provide additional and comprehensive information on mTORi use in daily practice.

Various strategies have been evaluated to prevent or slow down renal impairment in adult LT recipients, of which mTORi use has emerged as being very effective.

The beneficial impact of both CNI reduction and withdrawal after introduction of EVR on renal function has been demonstrated in two recent large trials. In the H2304, a 24-month prospective, randomized, multicenter, open-label study, de novo LT adult patients were randomized at 30 days to EVR + reduced tacrolimus, tacrolimus monotherapy, or tacrolimus tapering (this arm was stopped prematurely due to a significantly higher rate of rejection). The adjusted change in eGFR from randomization to month 24 was superior with EVR + reduced tacrolimus versus tacrolimus alone (difference 6.7 mL/min/1.73 m^2) [8]. In the SIMCER study, a 6-month, multicenter, open-label study conducted in France, de novo LT recipients were randomized at week 4, to EVR with low-exposure tacrolimus discontinued by month 4 or to tacrolimus-based therapy, both with basiliximab induction and mycophenolic acid [9]. Mean eGFR at week 24 was 95.8 vs. 76.0 mL/min/1.73 m^2 for EVR vs. tacrolimus ($P < 0.001$). These two studies strongly suggest that early introduction of EVR combined with reduction/withdrawal of tacrolimus in de novo LT recipients is associated with a significant renal benefit. In the 24-month, multicenter, single-arm, prospective pediatric study, 56 de novo LT children with or without basiliximab induction were converted at 1–6 months post-transplant from standard CNI therapy (± mycophenolic acid), to EVR with reduced exposure to CNI (mainly tacrolimus). The mean change in eGFR from baseline to month 12 was +6.2 mL/min/1.73 m^2 [11]. In maintenance patients, impact of mTORi introduction is undoubtedly less impressive, especially in the absence of CNI withdrawal. In the RESCUE prospective, randomized, multicenter, 6-month study, the impact on renal function of EVR introduction associated with CNI reduction or discontinuation was evaluated in maintenance adult LT recipients experiencing CNI-related renal impairment. Patients started EVR therapy with CNI reduction or discontinuation, or continued receiving standard-exposure CNI [4]. At month 6, 80% of the patients who had converted to EVR had discontinued the CNI and the mean ± SD change in creatinine clearance from baseline to month 6 was similar between groups (EVR, 1.0 ± 10.2 mL/min; controls, 2.3 ± 7.8 mL/minute). This strongly recalls the results of the present study in maintenance pediatric recipients, who continued to receive CNI for a large part.

In contrast to those patients in whom mTORi was introduced to minimize CNI/immunosuppression, a significant proportion of the patients included herein received mTORi because of persistent rejection, with the aim to reinforce immunosuppressive regimen. This is similar to the first reported experience by Nielsen et al., who used EVR in 12 pediatric LT recipients with chronic graft dysfunction [10]. Four patients completely normalized liver function tests, six had partial improvement, and two did not respond at all. In addition, a favorable impact of EVR in the control of chronic rejection has been reported in adults [14]. The results of the present study confirm that this strategy can be effective in a significant proportion of pediatric patients. In addition, adding mTORi to CNI spares patients from the deleterious effects associated with an increase in other immunosuppressive drugs such as CNI or steroids.

Since mTOR is involved in key pathways controlling cell growth, mTORi have direct effects on tumor cell proliferation. Furthermore, they also have anti-angiogenic properties, due to suppression of vascular endothelial growth factor transduction [15]. The size of the present cohort is of course too small to allow definitive conclusions regarding the impact of mTORi on tumor recurrence in pediatric patients with initial liver tumors. Nevertheless, 10 out of 13 patients experienced no recurrence. In adult patients, the beneficial impact of mTORi on HCC recurrence remains questionable. Clinical data are largely restricted to retrospective and non-randomized prospective analyses [16]. The only prospective randomized controlled trial in this setting evaluated SRL-based immunosuppression [17]. In this open-label international trial, 525 adult LT recipients with HCC initially receiving mTORi-free immunosuppression were randomized 4 to 6 weeks after transplantation into a group on mTORi-free immunosuppression or a group incorporating SRL. Recurrence-free survival was not significantly different between groups. Nevertheless, the subgroup of patients with tumor within Milan criteria (and therefore better prognosis) benefited from SRL regimen [17]. Studies on angiosarcoma, the main indication in our series, are lacking.

Data on the role of mTORi in patients with de novo post-LT malignancies are also scarce. Two retrospective studies suggested that conversion from CNI to mTORi could improve patient overall survival [18,19]. In the present study, mTORi were used in the case of PTLD, in order to discontinue, even transiently, CNI. The outcome was favorable in all 4 patients. This must be compared with the data from the multicenter pediatric study reported by Ganschow et al. [11]. In this latter study, recruitment was stopped prematurely due to high rates of PTLD (and also treatment-related serious infections) leading to hospitalization and premature study drug discontinuation. PTLD occurred in five patients (8.9% of the total population; 3/25 [12.0%] patients aged < 2 years, 2/31 aged 2–18 years [6.5%]). It could therefore be recommended that mTORi should not be used in younger EBV-negative LT recipients, especially in immunosuppressive strategies potentially leading to ''over-immunosuppression''.

The results presented herein on tolerability are of importance as very few data are available on the introduction of mTORi in stable pediatric LT patients. Half of the patients experienced at least one adverse event, which compares well with data in adult maintenance LT recipients. For instance, in the French retrospective cohort Everoliver, adverse events occurred in 84.6% of the patients, and the most frequently reported were gastrointestinal disorders (22.9%), cutaneous rash (18.8%), edema (16.3%), hypertriglyceridemia (14.6%), mouth ulcers (14.2%), and hypercholesterolemia (13.3%) [6]. In the pediatric LT patients reported herein, hypercholesterolemia, proteinuria and cutaneomucous adverse events were the most frequent. Pneumonia was a rare complication, as observed in adults (7.1% in Everoliver). In addition, adverse events leading to drug discontinuation occurred in 10.0% of patients, similar to the 12.9% observed in Everoliver. We previously reported in adults, that occurrence of adverse events was associated with lower physician experience (*i.e.* experience with the drug for more or less than 40 patients) [20], and it can be hypothesized that growing experience in pediatric LT recipients would probably improve the overall management of the drug. In the pediatric study reported by Ganschow et al. in de novo pediatric LT, 71.4% patients presented at least 1 adverse event suspected to be related

to EVR [11]. This was probably related to the early post-operative period, and nearly half of all patients experienced severe infectious complications, which was interpreted as ''over-immunosuppression''. Complications suggestive of over-immunosuppression were not observed in the present cohort. Finally, liver biopsy was not available for all the patients of the present study, but we did observe biopsy-proven acute rejection in only 1/30 patients, suggesting under immunosuppression.

Although our multicenter study contributes to the body of literature by bringing data on safety and tolerability in some of the common indications for mTORi in pediatric LT recipients such as CNI toxicity or need for increased immunosuppression, it does present with some limitations. First, it does not have a control population, which would be difficult to obtain given the rarity of the underlying conditions. Second, it is limited by the lack of histological outcome data in those patients treated with mTORi for rejection. Finally, longer follow-up would be useful.

In conclusion, the results presented herein suggest that mTORi can be used in pediatric LT recipients in different clinical situations, both to reinforce immunosuppression therapy, and conversely to reduce CNI and related toxicity. Although there is some consensus among the centers on the use of mTORi for patients requiring LT for primary liver malignancies, long-term effects on cancer recurrence and renal function need to be further evaluated.

Financial support statement

No financial support to declare.

Authors contributions

Jérôme Dumortier and Christine Rivet had the idea of the project, participated in analysis and interpretation of data and wrote the manuscript.

Eduardo Couchonnal collected the data and performed statistical analysis of data.

Jérôme Dumortier, Florence Lacaille, Christine Rivet, Dominique Debray, Olivier Boillot, Alain Lachaux, Oanez Ackermann, Emmanuel Gonzales, Barbara E. Wildhaber, Emmanuel Jacquemin and Valérie McLin were involved in the medical management of the patients reported here, critically reviewed and approved the manuscript.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgments

The authors are very indebted to Dr Philip Robinson (Direction de la Recherche Clinique et de l'Innovation des Hospices Civils de Lyon) for help in manuscript preparation, as well as Ms Philavanh Guichard (Hospices Civils de Lyon), and Ms Isabelle Friteau (Assistance Publique-Hôpitaux de Paris) for help in data collection.

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