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Efficacy and Safety of Mammalian Target of Rapamycin Inhibitors Following Intestinal and Multivisceral Transplantation

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ORIGINAL ARTICLE

Efficacy and safety of mammalian target of rapamycin inhibitors following intestinal and multivisceral transplantation

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Abstract

This is a descriptive study reviewing the outcomes of mammalian target of rapamycin inhibitors (mTORs) in intestinal (IT) and multivisceral transplantation (MVT). This study included 22 patients, 20 adults, and two children, and an overall mean age of 46 years old at the time of transplantation. Twelve patients (54.5%) received IT, and the remainder (45.5%) MVT. The mean time between transplantation and mTORs initiation was 24 months. The indication was worsening renal function in 13 patients (59%), with 9/13 (69.2%) noted to have an increase in glomerular filtration rate of at least 10 ml/min/1.73m^2. The indication for four patients (18.2%) was a history of neuroendocrine tumor. After mTOR initiation, 50% of patients were reduced or weaned off tacrolimus and 13.7% off prednisone. mTORs were discontinued in 11/22 patients. Six patients (54.5%) stopped due to side effects, two (18.1%) for surgery, and one (9%) for acute cellular rejection. Side effects were edema (33.3%), headaches (33.3%), diarrhea (16.7%), and oral ulcers (16.7%). The average duration of mTORs prior to discontinuation due to side effects was 7 months. mTORs may function in their own niche of patients due to the potential renal safety profile, but use is most limited by tolerance to side effects.

KEYWORDS
immunosuppressive regimens, intestinal failure/injury, intestine transplantation, mechanistic target of rapamycin (mTOR), multivisceral transplantation

1 | INTRODUCTION

Intestine transplantation (IT) is an established treatment for intestinal failure, which may be a result of short bowel syndrome, resection from trauma, vascular catastrophes, Crohn's disease, or specifically in the pediatric population; necrotizing enterocolitis and gastroschisis. Parenteral nutrition is the mainstay therapy, but it has its own set of complications including catheter-related infections and thrombosis, electrolyte abnormalities, and cholestatic liver disease.[1] Patients with such complications are potential candidates for IT, and in the case of advanced cholestatic liver disease, multivisceral transplantation (MVT).

Intestine transplantation rates are significantly lower than that of other solid organ transplants with only 104 patients receiving IT in the United States in 2018, and 61 of them being MVT. Children previously constituted more than half the transplant recipients, but in 2018 accounted for only 35.6% of transplants.[2] Advances in immunosuppression therapy have allowed for improved rates of success.[3] Immunosuppression consists of induction with either a T-cell-depleting agent or an interleukin-2 receptor antagonist. This

is commonly followed by maintenance with a calcineurin inhibitor, such as tacrolimus, used in conjunction with corticosteroids. Another common regimen adds mycophenolate to the calcineurin inhibitor and corticosteroids. The side effects of immunosuppression include metabolic disorders, increased propensity for infections, renal dysfunction, and development of malignancies. There are alternative agents available including mammalian (mechanistic) target of rapamycin inhibitors (mTORs), which prevent immune cells from proliferating in the presence of cytokines. There is currently a dearth of literature assessing the efficacy and safety of mTORs for IT and MVT recipients. This study reviews the frequency, indication, and outcomes of mTORs use in this transplant population at two centers in the United States.

2 | PATIENTS AND METHODS

This is an observational study evaluating patients at two transplant centers in the United States. The transplant centers were the Henry Ford Adult Intestinal Transplant Program and Duke University Adult and Pediatric Intestinal Transplant Program. Patients included in this study underwent IT or MVT between January 2009 and October 2018, and were initiated on the mTORs, everolimus or sirolimus, at any time post-transplantation. There were no exclusion criteria for an evaluation in this study.

The immunosuppression protocols, which include induction and maintenance therapy are included in the Supplemental Material. In brief, the maintenance immunosuppression protocol at Henry Ford Hospital included prednisone (40 mg daily, weaned by 5 mg weekly until 10 mg dose is achieved) continued indefinitely, and tacrolimus started at 2 mg twice daily with target trough levels 12–15 ng/ml. Duke University's adult transplant protocol includes prednisone (20 mg daily, weaned by 2.5 mg biweekly until dose of 5 mg is achieved) continued indefinitely, mycophenolate 1 g twice daily, and tacrolimus 1 mg twice daily with target levels being 12–16 ng/ml. For pediatric patients, the maintenance therapy was prednisone (10 mg/kg daily, weaned daily until a dose of 0.125 mg/kg/day is achieved) continued indefinitely, and tacrolimus 0.05 mg/kg twice daily with a target of 12–16 ng/ml. At any point in initiation, maintenance, or tapering of immunosuppressants, the treating provider may have diverged from the hospital protocol per their clinical judgment.

All decisions including initiation of mTORs, changes to the immunosuppression regimen or dosages, and frequency of laboratory evaluation were left to the discretion of the treating physician. There was no structured protocol for initiating mTORs, but providers typically started at a dose of 1mg for adults with goal trough levels 4–6 ng/ml, and 0.5 mg for pediatrics with goal trough levels 3–5 ng/ml. Trough levels were checked on a weekly or biweekly basis when titrating the dose, and monthly once goal troughs were achieved. Once the mTOR trough was at goal, tacrolimus was tapered for goal levels of 4–6 ng/ml at Henry Ford Hospital, and 3–5 ng/ml at the Duke University. There was no official institutional protocol for tapering mycophenolate at the Duke University. The tapering regimen was at the discretion of the provider with no formal protocol in place.

Data were gathered from the electronic medical record. Information collected included type of transplantation and indication, date of both transplantation and initiation of mTOR therapy, and indication for mTORs. Data were also collected regarding patients' renal function including the presence of chronic kidney disease prior to transplant, estimated glomerular filtration rate (GFR) before and after mTOR therapy, and evidence of proteinuria. GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation for adults and using the updated Schwartz formula for pediatric patients. The frequency of evaluating renal function was at the discretion of the provider with typically yearly measurements. Proteinuria was noted based on the urine albumin-to-creatinine ratio, or standard urine dipstick evaluation. Changes in proteinuria were defined as mild if noted to be up to 30 mg/dl or 1+ proteinuria. This was also checked on a yearly basis. Other immunosuppressant therapy used in patients' care was also recorded. Outcomes including side effects, infections, rejection were noted. If mTORs therapy was discontinued, the reason for discontinuation was recorded along with the total duration of mTORs therapy.

3 | RESULTS

The total number of patients undergoing IT and MVT at the two centers was 72, with 62.5% adults, and 37.5% pediatrics. mTORs were initiated in 30.6% (22/72) patients. This patient population had a mean age of 46 years at the time of transplantation, with 90.9% (20/22) being adults, and 9.1% (2/22) being pediatrics. The ages ranged from 2 to 62 years of age. Isolated IT was received by 54.5% (12/22) patients, and 45.5% (10/22) patients received MVT. The indications for transplantation in order of frequency were short bowel syndrome (45%), dysmotility (22%). Five patients had a history of neoplasm including four with neuroendocrine tumor (NET), and one with desmoid tumors. mTORs were initiated between months 1 and 78 after transplantation, with median time being 15 months, and mean time 25 months. For patients that were started on mTORs due to history of neoplasm, the mean time for mTORs initiation from the date of transplant was 19 months. The mTOR of choice was sirolimus in 63.6% (14/22) patients, and everolimus in 36.4% (8/22) patients.

The indication for mTORs initiation was worsening renal function in 59.0% (13/22) patients and the history of neoplasm in 18% (4/22) patients, specifically neuroendocrine tumor (NET). Other indications included the addition of immunosuppression, development of ulcerative enteritis, eosinophilic esophagitis, anxiety, and headaches.

The mean GFR for patients starting mTORs for renal dysfunction ranged from 18 to 57 ml/min/1.73 m^2 (mean 29 ml/min/1.73 m^2). Only one of these patients was noted to have chronic kidney disease pretransplant. These patients' GFR improved to a mean of 41.5, median 43.5 ml/min/1.73 m^2. The remainder of patients who had mTORs initiated for reasons other than renal dysfunction had GFR

greater than 60 ml/min/1.73 m^2. All but a single patient in our cohort maintained or improved their renal function, with that patient having worsening renal insufficiency that eventually required dialysis. Time to GFR improvement was not recorded in data collection. There was no proteinuria noted in 72.7% (16/22) patients prior to starting mTORs. Proteinuria was noted to be developing or worsening in 40.9% (9/22) patients, and this was noted to be mild in 55.6% (5/9) patients Proteinuria was not the reason for mTOR discontinuation for any of the patients.

There were a total of five patients with a history of neoplasm who underwent transplantation. Indication for mTOR initiation was a history of cancer in four of these patients, with all four having a history of NET. The 5th patient initiated mTORs for renal insufficiency and had a history of desmoid tumors. All patients at our institutions who had a history of NET during this study period and underwent IT or MVT received mTOR therapy and are included in this study. All patients with a history of NET had a recurrence of NET with locations being liver (2), tricuspid valve (1), and thoracic lymph nodes and bony metastasis (1). The time frame of recurrence was between 1 and 7 years post-transplantation. The patient who had a history of desmoid tumor did not have recurrence after mTOR initiation.

The minor indications for starting mTORs were for added immunosuppression, development of ulcerative enteritis believed to be due to mycophenolate, eosinophilic esophagitis, anxiety, and headaches. There was a patient who developed acute rejection within the first month of transplantation, and everolimus therapy was initiated to reduce further episodes of rejection without increasing goal tacrolimus trough levels. Eosinophilic esophagitis, anxiety, and headaches are side effects of tacrolimus or steroid therapy, and these side effects are reduced after initiating mTORs.

Changes in immunosuppression therapy with mTORs are listed in Table 1. All 22 patients were initially on both prednisone and tacrolimus, with 22.7% (5/22) also being on mycophenolate, and 4.5% (1/22) being on azathioprine. The single patient given azathioprine as an adjunct to their immunosuppression had a history of Crohn's disease. After mTOR initiation, there was a reduction in other immunosuppression in 68.2% (15/22) patients. This includes 18.2% (4/22) patients being weaned off tacrolimus, and 18.2% (4/22) patients weaned off steroids. The goal tacrolimus trough level was reduced in 45.5% (10/22) patients. Of the five patients on mycophenolate, 80% (4/5) were able to completely come off it. The decision and methodology to taper immunosuppression were at the discretion of the treating provider. Information regarding an exact tapering schedule for each patient was not available in the retrospective chart review.

Rejection was noted in 27.3% (6/22) of patients on mTORs, with details regarding rejection episodes being listed in Table 2. Patients with rejection were noted to have below goal trough levels for mTORs and tacrolimus. Upon rejection, patients were treated with parental steroids for 3–7 days. The tacrolimus dose was increased, with an often high than the prior goal trough level. There is insufficient information to compare rejection episodes with no specific data collection made regarding the extent of rejection, and treatment course upon therapy. mTORs were discontinued in 11 patients (50%) after being on for a mean of 11.2 months. Sirolimus was stopped in eight patients, and everolimus in three patients. The reasons for discontinuation were side effects in 54.5% (6/11) patients, surgeries in 18.2% (2/11) patients, and 0.09% (1/11) each for need for dialysis, acute cellular rejection, and death. Side effects resulting in discontinuation were edema (33.3%), headaches (33.3%), diarrhea (16.7%), and ulcers (16.7%). These patients were on mTORs for a mean of 7 months prior to discontinuation. The side effects generally improved within a month of stopping mTOR therapy. The patient who discontinued mTORs due to acute cellular rejection was on mTORs for 10 months. This patient initially had low mTOR and tacrolimus trough levels prior to rejection, but despite increases in doses with goal trough levels achieved, the patient again developed acute rejection prompting discontinuation of the mTOR.

4 | DISCUSSION

This study aimed to review the use of mTORs for IT and MVT immunosuppression over 9 years at two major healthcare centers in the United States. It is based on an observational review of patients' medical records. It demonstrated that mTOR initiation was for renal dysfunction in more than half of all cases, with mean GFR for these patients being 30.7 ml/min/1.73 m^2. All but one of these patients had improvement in GFR, with a mean increase of 14.5 ml/min/1.73 m^2. mTOR was typically initiated between 2 and 72 months post-transplantation with the median time being 16 months. The disease burden of chronic kidney disease is great in transplant patients given the intensity of the transplantation surgery, propensity to infections, and need for immunosuppression that further compromises the renal function as a side effect. Previous studies have shown that GFR drops 50% after the first 3 months of transplantation and down 72% at 1 year.[4] IT recipients have a 25.1% incidence of severe chronic kidney disease with GFR less than 30 ml/min/1.73 m^2 at 5 years post-transplantation.[5] Previous studies have shown that tacrolimus therapy was associated with a 48.3% lower hazard of development of severe CKD in comparison to cyclosporine-based immunosuppression. [5] This was attributed to fewer acute kidney injuries secondary to fewer rejection episodes. [5] Both the time at which mTORs were initiated and the indication in our study exemplify the significant disease burden that renal disease has on transplantation patients.

Development or increase in the level of proteinuria was observed in 40.9% patients. Proteinuria is a substantial side effect of mTORs therapy with a previous study observing it in 64% of patients after initiating sirolimus therapy.[6] Guidelines suggest that initiating mTORs should only be performed in patients with GFR greater than 40 ml/min/1.73 m^2, and with mild proteinuria. If patients have mild proteinuria, they may be treated with angiotensin-converting enzyme inhibitors, but heavier proteinuria may require discontinuation of the drug.[7] The patients in our study only developed mild proteinuria and did not require discontinuation of mTORs due to the level

TABLE 1 Changes in immunosuppressive regimen with mTOR therapy initiation

Additional immunosuppression prior to mTORs	Tacrolimus reduced or discontinued	Prednisone discontinued	Mycophenolate weaned off
Azathioprine, tacrolimus, prednisone	Discontinued	Discontinued	
Tacrolimus, prednisone	Discontinued	Discontinued	
Tacrolimus, prednisone	Discontinued	No	
Tacrolimus, prednisone	Discontinued	No	
Tacrolimus, prednisone	Reduced	Discontinued	
Tacrolimus, prednisone	Reduced	Discontinued	
Mycophenolate, tacrolimus, prednisone	Reduced	No	Discontinued
Mycophenolate, tacrolimus, prednisone	Reduced	No	Discontinued
Mycophenolate, tacrolimus, prednisone	Reduced	No	Discontinued
Tacrolimus, prednisone	Reduced	No	N/Ap
Tacrolimus, prednisone	Reduced	No	N/Ap
Tacrolimus, prednisone	Reduced	No	N/Ap
Tacrolimus, prednisone	Reduced	No	N/Ap
Tacrolimus, prednisone	Reduced	No	N/Ap
Mycophenolate, tacrolimus, prednisone	No	No	Discontinued
Mycophenolate, tacrolimus, prednisone	No	No	No
Tacrolimus, prednisone	No	No	
Tacrolimus, prednisone	No	No	
Tacrolimus, prednisone	No	No	
Tacrolimus, prednisone	No	No	
Tacrolimus, prednisone	No	No	
Tacrolimus, prednisone	No	No	

of proteinuria. No information regarding the use of angiotensin-converting enzyme inhibitors was recorded and we cannot extrapolate on their role in patients' proteinuria and overall care.

The history of neuroendocrine tumors was a frequent indication for starting mTORs in our study. There is evidence in the literature of mTORs having reduced incidence of neoplastic disease. One study has shown indication to prevent secondary skin cancer prevention post-renal transplantation and another to reduce hepatocellular cancer development post-liver transplantation.[8,9] Chronic immunosuppression in the transplant population results in increased rates of cancer development and ultimately increased mortality. Our study does not provide evidence that mTORs are effective in preventing NET. There may be a role of mTORs in delaying relapse of malignancy, but randomized controlled studies need to be performed for further analysis. In our study, two patients who were started on mTORs for the history of neuroendocrine tumors were able to remain on mTORs and were weaned down or off other immunosuppressants. The last patient with a history of neuroendocrine tumors had to stop mTORs therapy due to the need for cardiac surgery. Having a drug that acts as both an immunosuppressant and reduces the risk of malignancy development may be an advantage of mTORs and may signify the use of this class of medication more frequently in the future.

In our population, six patients (27.3%) developed rejection while on mTORs. Four of the patients were able to continue mTORs, and in fact ultimately reduce their dose of tacrolimus. One patient (4.5%) had to completely stop therapy due to rejection. That patient had been on mTORs for 10 months and experienced multiple rejection episodes while on this agent. Unfortunately, our study did not collect drug levels for the immunosuppression medications, the timing of the rejection, or rates of rejection in patients not on mTORs. It is possible that rejection episodes may have been due to sub-therapeutic levels of tacrolimus and/or the mTORs or be related to the efficacy of their immunosuppression regimen. The incidence of acute rejection in IT adult patients has been previously noted at 44.8% in the first year, and 53.1% in 2 years. This describes an overall rate without taking into account type of immunosuppression. [10] Previous studies have shown that early introduction of sirolimus therapy in the first-year post-transplantation yields fewer and less severe

TABLE 2 Description of rejection episodes including time and treatment of rejection

Patient	Time of mTOR initiation after transplantation	Indication for mTOR	Time of rejection after transplantation	Treatment of rejection
1	2 months	Additional immunosuppression	14 months	Thymoglobulin, and intravenous solumedrol
2	10 months	History of NET	13 months	Intravenous solumedrol
3	2 months	Renal dysfunction	14 months	Thymoglobulin, and intravenous solumedrol
4	17 months	Renal dysfunction	1st episode: 26 months	1st episode: Low levels of mTOR and tacrolimus, both doses were increased
			2nd episode: 27 months	2nd episode: IV solumedrol × 7 days, 1 dose IV immunoglobulin, and 1 dose thymoglobulin, increased tacrolimus dose
5	3 months	Renal dysfunction	1st episode: 9 months	1st episode: Tacrolimus had been stopped due to side effects. Prednisone was increased to 20 mg, and tacrolimus had been restarted
			2nd episode: 13 months	2nd episode: Mycophenolate was re-added to the regimen
6	1 month	Ulcerative enteritis from mycophenolate	2 months	Thymoglobulin and infliximab

rejection episodes. [11] Combination therapy with sirolimus and tacrolimus has also been studied to be more effective at reducing acute cellular rejection than monotherapy alone.[12] Our study did not introduce mTORs until a mean time of 24 months. We also did not have a control group to compare rejection in transplant recipients without mTOR therapy. It is difficult to extrapolate the clinical utility of mTORs in preventing rejection, and we must rely on other literature.

In our study, more than half of the total patients (68.2%) were able to be weaned down or off other immunosuppressants with one patient (4.5%) being able to stop all other anti-rejection drugs. The most frequent indication (27.3%) to stop mTORs was side effects such as edema, headaches, ulcers, and leukopenia. Side effects may be managed conservatively with edema controlled with diuretics (loop or aldosterone receptor antagonists), though this may be limited by renal insufficiency. Headaches can be managed with analgesic therapy and attempts to reduce either prednisone or calcineurin inhibitor dosing. Gastrointestinal symptoms may self-resolve over time, but can be controlled with anti-nausea medications, and anti-motility agents like loperamide; oral ulcers with pharmacy-compounded agents containing topical anesthetics, antacid suspensions, and diphenhydramine. If conservative management fails, and mTOR therapy must be discontinued, side effects of edema, ulcers, and leukopenia generally improved about 1 month after mTOR discontinuation. A previous study has observed peripheral edema in 55% of patients on mTORs, which may not resolve with the discontinuation of these agents.[13] This was noted to be improving in our population, typically over the month after stopping mTORs. Gastrointestinal side effects are also commonly observed with mTORs and include mouth ulcers, oral mucositis, dyspepsia, constipation, diarrhea, nausea, and vomiting.[14,15]

Mammalian target of rapamycin inhibitors make a case for an alternative immunosuppression drug for IT and MVT patients with a niche in chronic kidney disease and malignancies. The greatest barrier to mTOR use in this study was the drugs' side effects.

5 | CONCLUSION

This multicenter observational study suggests that mTORs may function in its own niche as an immunosuppressant due to its renal safety profile. Tolerance of therapy remains challenging with 50% patients stopping mTOR therapy due to side effects in 55% of these patients. All patients with a history of neoplasm re-developed neoplasm despite use with mTOR therapy. Long-term prospective, multicenter studies with larger populations are needed to establish if these medications can be effectively used in this very challenging patient population.

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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REFERENCES

1. Matsumoto CS, Subramanian S, Fishbein TM. Adult intestinal transplantation. *Gastroenterol Clin North Am*. 2018;47(2):341-354.
2. Lacaille F. Thirty years after the first intestinal transplantation in 1987: which indications are left in 2018? *Curr Opin Organ Transplant*. 2018;23(2):196-198.
3. Bharadwaj S, Tandon P, Gohel TD, et al. Current status of intestinal and multivisceral transplantation. *Gastroenterol Rep*. 2017;5(1):20-28.
4. Herlenius G, Fagerlind M, Krantz M, et al. Chronic kidney disease–a common and serious complication after intestinal transplantation. *Transplantation*. 2008;86(1):108-113.
5. Huard G, Iyer K, Moon J, Doucette JT, Nair V, Schiano TD. The high incidence of severe chronic kidney disease after intestinal transplantation and its impact on patient and graft survival. *Clin Transplant*. 2017;31(5):e12942.
6. Morelon E, Kreis H. Sirolimus therapy without calcineurin inhibitors: Necker Hospital 8-year experience. *Transplant Proc*. 2003;35(3 Suppl):52s-57s.
7. Schena FP, Pascoe MD, Alberu J, et al. Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the convert trial. *Transplantation*. 2009;87(2):233-242.
8. Euvrard S, Morelon E, Rostaing L, et al. Sirolimus and secondary skin-cancer prevention in kidney transplantation. *N Engl J Med*. 2012;367(4):329-339.
9. Jeng LB, Thorat A, Hsieh YW, et al. Experience of using everolimus in the early stage of living donor liver transplantation. *Transplant Proc*. 2014;46(3):744-748.
10. Smith JM, Skeans MA, Horslen SP, et al. OPTN/SRTR 2013 annual data report: intestine. *Am J Transplant*. 2015;15(S2):1-16.
11. Fishbein TM, Florman S, Gondolesi G, et al. Intestinal transplantation before and after the introduction of sirolimus. *Transplantation*. 2002;73(10):1538-1542.
12. Lauro A, Dazzi A, Ercolani G, et al. Rejection episodes and 3-year graft survival under sirolimus and tacrolimus treatment after adult intestinal transplantation. *Transplant Proc*. 2007;39(5):1629-1631.
13. Mahe E, Morelon E, Lechaton S, et al. Cutaneous adverse events in renal transplant recipients receiving sirolimus-based therapy. *Transplantation*. 2005;79(4):476-482.
14. Wyeth Pharmaceuticals Inc. Rapamune (sirolimus) [package insert], 2015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021083s059,021110s076lbl.pdf. Accessed August 27, 2019
15. Novartis Pharmaceuticals Corporation. Afinitor (everolimus) [package insert], 2012. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022334s016lbl.pdf. Accessed August 27, 2019

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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