STATE OF THE ART REVIEWS

mTOR inhibitors for management of encapsulating peritoneal sclerosis: a review of literatures

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ABSTRACT

Background: Encapsulating peritoneal sclerosis (EPS) is an infrequent, serious complication of peritoneal dialysis (PD). EPS may develop after kidney transplantation of PD-treated patients possibly due to the fibrotic effect of calcineurin inhibitors (CNIs). Some experimental and clinical studies proposed inhibitors of mammalian target of rapamycin (mTOR) for EPS management due to their anti-fibrotic and anti-angiogenesis effects. This review evaluated the therapeutic role of mTOR inhibitors in the management of EPS.

Method: Thirteen case reports/series consisted of 20 patients (16 post-transplant and four post-hemodialysis EPS cases) were evaluated. We tried to extract the effect of mTOR inhibitors according to authors’ conclusion and the time of improvement of patients’ symptoms and each treatment modality such as surgery, parenteral nutrition, tamoxifen and mTOR inhibitors.

Results: Of 20 patients, clinical improvement of five patients (25%) is more attributable to mTOR inhibitor therapy. All these five patients were post-kidney transplant EPS cases. Therefore, EPS improvement rate in post-transplant EPS patients was 31.25% (5 of 16 patients). Death after EPS diagnosis occurred in two of seven patients with continued CNIs therapy (28.57%) and 1 of 11 cases (9.09%) who didn’t receive CNIs after EPS diagnosis.

Conclusion: Although the therapeutic effect of mTOR inhibitors against EPS remains unproven, it seems that for patients with post kidney transplant EPS who do not have any contraindication for mTOR inhibitor administration, converting from CNIs to mTOR inhibitors in addition to other EPS treatments may result in improving EPS in approximately one-third of patients and decreasing patients’ mortality.

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Introduction

Encapsulating peritoneal sclerosis (EPS) is specified by sclerotic thickening of the visceral peritoneum leading to reduced bowel movement and intestinal obstruction, thickening of blood vessel walls and marked inflammation.1

EPS is an infrequent but serious complication of long-term peritoneal dialysis (PD). The incidence of this fatal condition has been estimated to be 0.6–3.5%, which may increase to 8.1% when PD treatment continues beyond 4 years. Mortality rate is ~42% 1 year after EPS diagnosis.2

Specific cause of EPS is PD, although other risk factors such as time on PD, number of peritonitis episodes, lower age at the start of PD, and kidney transplantation are involved in developing this fibrotic process.3 Some studies suppose the role of calcineurin inhibitors (CNIs) in developing or aggravating EPS.4,5 Many of these factors play roles in up-regulation of transforming growth factor-β (TGF-β) and vascular endothelial growth factor (VEGF) and subsequent epithelial to mesenchymal transition (EMT), fibrosis and neoangiogenesis.6,7

Treatment of EPS differs from medical therapy for lower stages to surgery for higher stages.8 The medical therapy of EPS consists of bowel rest using total parenteral nutrition (TPN), corticosteroids, tamoxifen and immunosuppressive agents with recent use of inhibitors of mammalian target of rapamycin (mTOR) and avoiding or minimization of CNI administrations in patients with history of PD treatment.9–11

Two experimental studies on chlorhexidine gluconate 0.1% EPS model showed that oral mTOR inhibitors (sirolimus and everolimus) significantly reduced peritoneal thickness, vascularity and fibrosis score.12,13 This effect of mTOR inhibitors on the peritoneum was mediated by inhibition of fibrosis and neoangiogenesis through various molecular mechanisms including increased
expression of E-cadherin (a protective gene for EMT) and decreased α-smooth muscle actin (α-SMA).  

This review aimed to explore the therapeutic role of mTOR inhibitors in the management of EPS.

Methods

The sources of the present review were obtained by searching Science Direct, Springer, Ovid, Google Scholar, PubMed, Scopus, and Proquest without time limitation. Searches were limited to English language sources. The keywords used as search terms were “encapsulating peritoneal sclerosis”, “sclerosing encapsulating peritonitis”, “post transplant encapsulating peritoneal sclerosis”, “encapsulating peritoneal sclerosis mTOR inhibitors”, and “encapsulating peritoneal sclerosis immunosuppression”. Reference lists of relevant articles were hand searched for further related articles. Included articles have been presented chronologically.

Results

The first case report on the clinical use of sirolimus in the management of EPS was a middle-aged patient who developed EPS after ~17 years of PD treatment and following several episodes of peritonitis. Sirolimus monotherapy was started without any response after 10 weeks despite performing enterolysis during this time. After 10 weeks, sirolimus was replaced by prednisolone 20 mg/day. This change in treatment resulted in significant improvement in patient’s bowel movement and general conditions and marked reduction in C-reactive protein. Therefore, sirolimus was not effective to manage EPS in this patient.

The retrospective Pan-Thames EPS survey in 11 PD centers from London and South-East England reviewed 111 cases of EPS. In this survey, the overall mortality of all 111 patients was 53% with a median survival of 14 months and a median time from EPS diagnosis to death of 7 months. The median survival was 15 months in patients who were treated with tamoxifen (n = 17), 12 months in those who treated with immunosuppressive drugs (n = 24), 21 months in patients who received both tamoxifen and immunosuppressive drugs (n = 13), and 13 months in patients who received no specific treatment (n = 46). Excluding the patients who died around diagnosis, underwent adhesionolysis or were transplanted, reported survival times of patients who had only medical treatment were 7 months (range 1–119 months) in eight patients who were treated with immunosuppressant drugs ± steroids, 15 months (range 1–58 months) in 17 patients who received tamoxifen, 14 months (range 6–38 months) in eight patients who were administered tamoxifen plus steroids ± immunosuppressants compared with 13 months (range 1–84 months) in 46 patients who did not receive any specific treatment. This survey included 21 patients who received kidney transplantation before or after EPS diagnosis. All of these transplanted patients received CNI-containing immunosuppressive regimen. Pharmacological therapies were changed in three of these transplanted patients from their CNI containing immunosuppressant regimens (one patient on cyclosporine and two patients on tacrolimus in addition to mycophenolate mofetil and steroid) to sirolimus monotherapy after EPS diagnosis without addition of tamoxifen. One another patient received sirolimus + mycophenolate mofetil + steroid + tamoxifen. As authors noted in the discussion section of this article, totally patients who were transplanted before or after EPS diagnosis had the best survival (median 20.5 months; range 2–108 months), without comparing those patients who changed to sirolimus monotherapy, those who continued their previous immunosuppressant drugs and those who were administered tamoxifen in addition to their immunosuppressant drugs. Therefore, we could not draw any specific conclusion on the potential effect of sirolimus on EPS management in this survey.

Mohamed et al. reported two cases of EPS in kidney transplants recipients. Both patients received huge immunosuppressive regimen (steroid pulse + plasmapheresis + rituximab) due to antibody mediated rejection before experiencing EPS. Both patients received tamoxifen; gut resting with TPN and undergone adhesiolysis. The immunosuppressive regimen was changed in one of them to reduced dose of tacrolimus and adding sirolimus and withdrawing mycophenolate mofetil. This patient died due to severe sepsis and multi-organ failure. The other patient was taking steroid, tacrolimus and sirolimus before presenting EPS. Sirolimus was changed to mycophenolate in this patient after antibody mediated rejection. This patient showed EPS improvement by TPN, tamoxifen and adhesiolysis. As conclusion, sirolimus therapy in this study did not improve clinical outcomes of EPS patients. It have to be considered that sirolimus was added in first patient lately and in a deeply compromised clinical status.

Temple et al. reported a case of EPS after kidney transplantation that was on PD ~88 months before and 7 months after transplantation. Her maintenance immunosuppression initiated with mycophenolate mofetil, tacrolimus, and steroid. Due to impaired graft function, to avoid CNI nephrotoxicity, tacrolimus was changed to sirolimus 7 months after transplantation. She developed EPS ~13 months after transplantation.
After diagnosis, current immunosuppressive regimen was continued along with surgical treatment and initiation of TPN. Because of several surgical interventions and impaired wound healing associated with sirolimus, ~12 months after sirolimus therapy sirolimus was switched to tacrolimus again. Her EPS symptoms finally were controlled with several surgical interventions, TPN, prednisone and cessation of CNI. As seen, this patient developed EPS while was receiving prednisolone and sirolimus. Although it is hard to draw net conclusion on patient’s response to medical therapy including everolimus due to multiple therapeutic approaches that have been done for this patient including several surgeries (one after switching to everolimus); however, since switching CNI to everolimus was done 1 month after starting tamoxifen without considerable symptoms’ improvement during this 1 month and considering patient’s weight gain after CNI interruption and switching to everolimus, the impression goes favorably toward the association of EPS improvement by medical therapy containing tamoxifen plus everolimus.

Another case was a female with a history of 8 years PD treatment who was diagnosed with EPS ~14 months after kidney transplantation. Her maintenance immunosuppressive regimen was started with mycophenolate mofetil, cyclosporine and prednisolone but due to some adverse drug reactions, her regimen changed to sirolimus and prednisolone. She developed EPS 2 years after transplantation, while was receiving prednisolone and sirolimus. After EPS diagnosis, TPN was administered in addition to enterolysis and right hemicolectomy that resulted in improved patient symptoms. As noted, this case developed EPS while was on maintenance immunosuppressive regimen containing sirolimus and prednisolone. Sirolimus neither prevent nor improved EPS symptoms in this patient.

Huddam et al. reported a case of EPS who was ~11 years on PD and then switched to HD. She developed EPS while was on HD. In addition to TPN and surgical intervention, tamoxifen and everolimus were initiated in the patient that resulted in clinical improvement at 3-month follow-up. As seen, everolimus and tamoxifen were started concomitantly in this patient. Therefore, precise conclusion on the effect of everolimus on improvement of EPS symptoms is impossible.

da Silva et al. reported a pediatric patient with a history of 99 months PD treatment who developed EPS ~8 months after second kidney transplantation. Following enterolysis, she received TPN, tamoxifen and high dose prednisolone in addition to her previous immunosuppressive drugs (tacrolimus and mycophenolate mofetil). Tamoxifen was replaced with sirolimus due to hepatocellular toxicity. The clinical status of the patient improved and she remained asymptomatic with a stable graft function at 20-month follow-up.

A case review reported four long-term PD treated patients who experienced EPS post kidney transplantation. All of them received prednisolone, tacrolimus and mycophenolate mofetil as maintenance immunosuppressive regimen. After adhesiolysis surgeries and TPN in these patients, in one patient mycophenolate mofetil was replaced with sirolimus while previous immunosuppressant continued on others. The sirolimus administered patient died due to severe sepsis while the other three patients survived with functioning kidneys for several months to years.

Another article reported a young patient who developed EPS ~9 months after kidney transplantation, following 6 years of PD treatment. After EPS diagnosis and surgery, the patient was prescribed high dose tamoxifen and TPN. One month later his immunosuppressive regimen that contained tacrolimus and azathioprine was changed to everolimus due to lack of response to previous modalities. After another surgery, his symptoms improved with no further peritoneal thickening and encapsulation over 24 months. Although it is hard to draw net conclusion on patient’s response to medical therapy including everolimus due to multiple therapeutic approaches that have been done for this patient including several surgeries (one after switching to everolimus); however, since switching CNI to everolimus was done 1 month after starting tamoxifen without considerable symptoms’ improvement during this 1 month and considering patient’s weight gain after CNI interruption and switching to everolimus, the impression goes favorably toward the association of EPS improvement by medical therapy containing tamoxifen plus everolimus.

Another case was a female with a history of 8 years PD treatment who was diagnosed with EPS ~14 months after kidney transplantation. Her maintenance immunosuppression from the beginning of transplantation consisted of everolimus, low-dose cyclosporine and prednisone. After surgical intervention, TPN administration and continuing immunosuppression as before with increase in corticosteroid dose the patient condition successfully improved during 7 years follow-up. As obvious, this patient showed EPS several months after immunosuppressive therapy with everolimus and low-dose cyclosporine. Therefore, everolimus did not prevent EPS development in this patient. In addition to surgery, this patient was treated with high dose steroid without need to addition of tamoxifen.

Another patient with a history of 6-year treatment with PD experienced EPS 6 months after moving to HD. Following TPN and surgical intervention, tamoxifen and everolimus were started concurrently. Patient’s symptoms and nutritional status significantly improved at 3-month follow-up. This patient underwent kidney transplantation 5 years later with maintenance immunosuppression containing everolimus and low-dose tacrolimus. During 20-month post-transplant follow-up, he had good kidney function without symptoms of EPS.
Due to simultaneous initiation of tamoxifen and everolimus, the pure effect of each drug on EPS is not clear.

During a retrospective analysis on 226 kidney transplant recipients with history of PD before kidney transplantation, 10 cases were diagnosed as post-transplant EPS. All of these 10 patients were on tacrolimus, mycophenolate mofetil and prednisolone as maintenance immunosuppressants. mTOR inhibitors were started in five EPS diagnosed patients (four patients received sirolimus and one everolimus); in four of them tacrolimus was switched to mTOR inhibitors while in one of them very low-dose tacrolimus was continued in addition to mTOR inhibitor. Other five EPS-experienced patients continued reduced doses of tacrolimus without adding an mTOR inhibitor. All patients received steroid and five patients were treated with tamoxifen (four of them were in mTOR inhibitors group). All patients, except for one case in mTOR inhibitor arm, underwent enterolysis. Only two cases, one in each group, received TPN. Four deaths happened in this study, only one of them was in mTOR inhibitor group (who did not undergo surgical treatment). This study proposed mTOR inhibitors as an effective option for EPS treatment. Although the more use of tamoxifen in mTOR inhibitors arm can disturb such deduction.

A female with a total of 14 years PD treatment received her second kidney transplantation with maintenance immunosuppression consisted of tacrolimus, mycophenolate mofetil and prednisolone. Two years after transplantation tacrolimus was replaced with everolimus due to nephrotoxicity. Three months after this change she complained EPS symptoms while the patient was receiving everolimus. After that, everolimus was switched to tacrolimus in addition to administration of tamoxifen. During 4 years of follow-up, her clinical condition significantly improved beside good graft function.

Clinical data of all patients including different types of EPS management, drugs doses (if available), and clinical outcomes of patients have been shown in Table 1.

**Discussion**

In this review, we evaluated 13 case reports and case series consisted of 20 EPS patients from 1994 to 2015 who received mTOR inhibitors. Between these cases, 16 patients were post kidney transplant EPS and four others showed EPS after changing to hemodialysis. Of 16 patients with EPS diagnosis after kidney transplantation, mTOR inhibitors were initiated in 12 patients after EPS diagnosis while four patients were receiving mTOR inhibitors for several months before EPS diagnosis; two of these patients improved after cessation of mTOR inhibitors and multiple surgeries. Therefore, mTOR inhibitors could not prevent or improve EPS in the last four patients.

Between those 12 cases of post kidney transplant EPS who were administered mTOR inhibitors after EPS diagnosis, the clinical outcomes of three patients were not clarified and three patients died after changing to mTOR inhibitors, although in one of these cases mTOR inhibitor was added lately to the therapy in critical condition. The deaths were due to cachexia, peritonitis, sepsis and multi-organ failure. Six patients showed improvement in clinical course after initiation of mTOR inhibitors, but one of them started tamoxifen and sirolimus at the same time that makes it hard to distinguish between mTOR inhibitor and tamoxifen efficacy. Therefore, it could be concluded that EPS improvement may be attributed to mTOR inhibitor administration in 5 out of 16 (31.25%) post-kidney transplant EPS patients who received mTOR inhibitors or more exactly in 5 out of 12 patients who started mTOR inhibitor therapy after post-transplantation EPS diagnosis.

Among four patients with post-HD diagnosis of EPS who were treated with mTOR inhibitors, the outcome of one patient was not clear and one patient did not improve. Two patients showed improvement in EPS signs but both of them started tamoxifen and mTOR inhibitor at the same time making the decision on the effect of each drug hard.

Taking into account the roles of other medical intervention such as surgery, parenteral nutrition, tamoxifen and steroid therapy, the exact determination of efficacy of mTOR inhibitors is difficult.

We tried to extract the effect of mTOR inhibitors according to the authors’ conclusion and the time of improvement of patients’ symptoms and each treatment modality. According to this review, from 20 post-HD or post-transplant EPS patients, improvement in clinical picture of five patients (25%) is more attributable to mTOR inhibitor therapy. All patients who more probably improved with mTOR inhibitor therapy were post-kidney transplant EPS and none was post-HD diagnosed EPS; Therefore, EPS improvement rate in post-transplant EPS patients was 31.25% (5 out of 16 patients). Death after EPS diagnosis occurred in two of seven patients with continued CNIs therapy, and one out of 11 EPS patients who didn’t receive CNIs after EPS diagnosis (28.57 vs 9.09%) during reported follow-up periods.

The main limitation of this review is that in some included studies the clinical outcomes of the patients
Table 1. Clinical data of patients with EPS who were treated with mTOR inhibitors.

| Patient | Sex | Time on PD (months) | Time after last Tx to Dx (month) | Time after HD to Dx (month) | Parenteral nutrition | Surgical treatment | Steroid therapy (mg/day) | Tamoxifen | Initial immuno-suppression | mTORi initiation after Dx (level: ng/ml) | CNI continuation after EPS Dx | Outcome after changing to mTORi | Reference |
|---------|-----|---------------------|---------------------------------|----------------------------|------------------------|--------------------|-------------------------|------------|-----------------------------|-----------------------------------|-----------------------------|------------------------------------|-----------|
| 1       | M   | 201                 | —                               | 3                          | Yes                    | Yes                | Yes                     | No         | —                          | SIR (26)                           | No                          | No improve                        | 15        |
| 2       | NI  | 45 ± 11             | 5.4                             | —                          | NI                     | No                 | No                     | No         | CYC + MMF                   | SIR                               | No                          | No                   | 16        |
| 3       | NI  | 45 ± 11             | 5.4                             | —                          | NI                     | No                 | No                     | No         | TAC + MMF                   | SIR                               | No                          | No                   | 16        |
| 4       | NI  | 45 ± 11             | 5.4                             | —                          | NI                     | No                 | No                     | No         | TAC + MMF                   | SIR                               | No                          | No                   | 16        |
| 5       | NI  | 83.7 ± 3.9          | —                               | 5.5                        | NI                     | No                 | Yes                    | Yes        | TAC + MMF                   | SIR (3–5)                         | No                          | No                   | 17        |
| 6       | M   | 72                  | 5                               | —                          | Yes                    | Yes                | Yes                     | 20–40      | TAC + MMF at first 7 months after Tx; TAC was replaced with SIR due to renal impairment | SIR started several months before EPS diagnosis | No                          | No                   | 18        |
| 7       | F   | 95                  | 13                              | —                          | Yes                    | Yes                | Yes                     | No         | TAC + MMF                   | SIR started several months before EPS diagnosis | Yes, but reduced dose was reinitiated 6 months after EPS Dx | Improved after SIR cessation and multiple surgery | 19        |
| 8       | F   | 60                  | 26                              | —                          | Yes                    | Yes                | Yes                     | No         | CYC + MMF + SRL              | SIR started several months before EPS diagnosis | No                          | No, EPS developed when patient was receiving SIR for several months | 20        |
| 9       | F   | 138                 | —                               | 8                          | Yes                    | Yes                | No                     | 10         | —                          | EVR                               | No                          | Improved; but tamoxifen and EVR started concomitantly resulted in no conclusion for EVR monotherapy effect | 21        |
| 10      | F   | 99                  | 8                               | —                          | Yes                    | Yes                | Yes                     | 10 before mTOR inhibitor administration | TAC + MMF                   | Yes at first but not after initiation of SIR | Improved | 22        |
| 11      | M   | 65                  | 1                               | —                          | Yes                    | Yes                | Yes                     | 20         | TAC + MMF                   | SIR                               | Yes                          | Died                 | 23        |
| 12      | M   | 72                  | 9                               | BD                         | Yes                    | Yes                | Yes                     | 20 BD      | TAC + MMF + AZA             | EVR                               | No                          | Improved, but after concomitant initiation of tamoxifen and another surgery after conversion to EVR | 24        |
| 13      | F   | 96                  | 14                              | —                          | Yes                    | Yes                | Yes                     | No         | EVR + CYC                   | No                                | Yes                          | Improved by increasing steroid dose later that he was transplanted | 25        |
| 14      | M   | ≈72                 | 6                               | —                          | Yes                    | Yes                | Yes                     | 10         | EVR (4 → 5–7)               | No                                | No, until 5 months later that he was transplanted | Improved | 25        |
| 15      | F   | 58                  | 5                               | —                          | No                     | Yes                | Yes                     | Yes        | TAC + MMF                   | SIR (4–6)                         | Yes                          | Improved                        | 26        |
| 16      | M   | 117                 | 17                              | —                          | No                     | Yes                | Yes                     | Yes        | TAC + MMF                   | SIR (4–6)                         | No                          | Improved                        | 26        |
| 17      | F   | 65                  | 4                               | —                          | Yes                    | No                 | Yes                     | Yes        | TAC + MMF                   | SIR (4–6)                         | No                          | Died due to cachexia              | 26        |
| 18      | F   | 58                  | 6                               | —                          | No                     | Yes                | Yes                     | No         | TAC + MMF                   | SIR (4–6)                         | No                          | Improved                        | 26        |
| 19      | F   | 82                  | 14                              | —                          | No                     | Yes                | Yes                     | Yes        | TAC + MMF                   | EVR (4–6)                         | No                          | Improved after changing to TAC | 27        |
| 20      | F   | 168                 | 36                              | —                          | No                     | Yes                | Yes                     | 10         | TAC + MMF/ AZA; TAC was switched to EVR due to nephrotoxicity | No, EPS developed while patient was on EVR; she was switched to TAC after EPS diagnosis | Yes                          | Improved | 27        |

AZA: azathioprine; CNI: calcineurin inhibitors; CYC: cyclosporine; Dx: diagnosis; EPS: encapsulating peritoneal sclerosis; EVR: everolimus; MMF: mycophenolate mofetil; mTORi: mTOR inhibitors; NI: not identified; SRL: sirolimus; TAC: tacrolimus; Tx: transplantation.
were not clearly defined. mTOR inhibitors mostly initiated with other treatment strategies including surgery, TPN and varying doses of steroids and tamoxifen. The administered doses of mTOR inhibitors and achieved whole blood levels differed between treated patients. All these confounding factors restrict precise conclusion on clinical efficacy of mTOR inhibitors in the management of EPS patients. Although the impact of mTOR inhibitors in ameliorating EPS remains unproven, however, it seems that in patients with post-kidney transplant EPS who do not have any contraindication for mTOR inhibitor administration, converting from CNIs to mTOR inhibitors in addition to other EPS treatments such as surgery, TPN and tamoxifen may result in improving EPS symptoms in approximately one-third of patients and decreasing patients’ mortality.

Disclosures statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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