Update on potential medical treatments for encapsulating peritoneal sclerosis; human and experimental data

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Abstract Encapsulating peritoneal sclerosis (EPS) is an infrequent but serious complication of peritoneal dialysis (PD). The pathogenesis is unknown but speculation is ongoing. The current management of EPS focuses on prevention and treatment of the inflammatory and fibrotic changes at the level of the peritoneal membrane with immunosuppressive and antifibrotic agents, respectively. This article reviews the currently available human and animal data on potential agents to prevent and/or treat EPS. We propose a strategy for early diagnose EPS in an attempt to avoid the development of the full-blown and potentially life-threatening clinical syndrome of EPS. Future research should focus on studying potential prophylactic and therapeutic agents in humans in large, multicenter, randomized trials but also on early detection of EPS in the inflammatory phase by means of biomarkers and the establishment of a composite EPS score.

Keywords Peritoneal dialysis · Encapsulating peritoneal sclerosis · Prevention · Treatment

Introduction

Encapsulating peritoneal sclerosis (EPS) is a rare but potentially life-threatening complication of peritoneal dialysis (PD). After a period of 1–3 years on PD, all patients develop simple peritoneal sclerosis, but only few of them will progress to the syndrome of EPS that potentially consists of ultrafiltration failure with a high transport status, intermittent small-bowel obstruction and/or weight loss [1]. On abdominal imaging with computed tomography (CT), peritoneal thickening, adhesions of bowel loops, signs of obstruction and fluid collections are usually present [2]. The high morbidity and mortality of EPS is attributed to malnutrition and sepsis. The prevalence of EPS varies between 0.5 and 7.3% but may increase to as high as 15.2% in patients on PD for more than 15 years [3]. EPS frequently occurs after cessation of PD, perhaps because cessation of lavage may lead to accumulation of fibrin, cytokines and growth factors, leading to inflammation and fibrosis. EPS is also common in the post-transplant period [4], possibly because of the current tendency to decrease the dose of prednisone in transplantation together with the use of pro-fibrotic calcineurin inhibitors (CNI). The etiology of EPS is unclear but the speculation is a ‘two-hit’ hypothesis. The use of bio-incompatible solutions (containing glucose, glucose-degradation products and lactate in an acid solution) and exposure to toxins such as plasticizers and chlorhexidine leads to loss of normal mesothelial cell morphology,
expansion of the submesothelial subcompact zone (epithelial-to-mesenchymal transition) and also to neovascularization [5]. This is considered to be the ‘first hit’ in the development of EPS. The ‘second hit’ is often discontinuation of PD, an episode of severe PD peritonitis or any other peritoneal trauma such as abdominal surgery. A genetic predisposition to this second hit might put some patients at higher risk for developing EPS. Enhanced production of transforming growth factor beta (TGF-beta) and vascular endothelial growth factor (VEGF) plays a central role in fibrosis and neoangiogenesis, the two basic mechanisms in the pathogenesis of EPS [6].

The treatment of EPS is still controversial but is most often proposed to be a combination of cessation of PD as well as the use of immunosuppressive and antifibrotic agents together with nutritional support. Surgical intervention with enterolysis and decortication is common practice in Japan but less frequent in other parts of the world [7].

This review focuses on the reported use and benefits of immunosuppressive and antifibrotic agents in EPS. We reviewed through an extensive PubMed search the currently available human as well as animal data for the prevention and treatment of EPS.

**Human data on medical treatment for EPS**

**Tamoxifen**

Tamoxifen is a selective estrogen receptor modulator (SERM) that inhibits the production of TGF-beta by fibroblasts. It has been used in the past in several fibrosing syndromes such as retroperitoneal fibrosis and fibrosing mediastinitis [8].

Guest recently summarized the available clinical data for the usage of tamoxifen in EPS [9]. Between 1992 and 2007, 14 different groups have reported on their experience with tamoxifen therapy for EPS. The number of patients varied between 1 and 14 in each group. In total, 36 patients were studied. Twenty-one patients received tamoxifen as sole therapy, 8 patients were also treated with steroids (of which 1 patient also received azathioprine), 2 patients received rapamycin together with tamoxifen and 5 patients underwent surgery in conjunction with tamoxifen treatment. Doses of tamoxifen varied between 10 and 80 mg per day. In 2 patients, the outcome was reported as ‘resolved’, 20 patients ‘improved’, 14 patients remained ‘stable’, 4 patients died and in 1 patient the outcome was not reported.

Del Peso extended the use of tamoxifen to patients with pre-EPS changes in a non-randomized study [10]. A total of 23 PD patients with peritoneal sclerosis, who had ultrafiltration failure and a high transport status but without the typical CT findings for EPS, were studied for a period of 47 (tamoxifen group) and 29 (control group) months. None of the 9 patients in the ‘tamoxifen as prophylaxis’ arm did progress to full-blown EPS. However, 4 of the 14 patients in the control group who did not receive tamoxifen developed EPS and died. Tamoxifen dose in this study was 40 mg per day; steroids were not used.

Tamoxifen is generally well tolerated. Potential side effects include hot flushes, nausea, fatigue, endometrial carcinoma and deep venous thrombosis. Evidently, randomized, controlled trials are necessary to assess the efficacy of tamoxifen for prophylactic and therapeutic management of EPS. Particularly interesting is indeed the idea to start treating EPS in the early stages with tamoxifen. This could be applied to patients on long-standing PD, who develop ultrafiltration failure with a high transport status but who do not have the typical imaging changes as expected in EPS.

**Glucocorticoids**

In 1997, Mori and colleagues reported for the first time on the successful use of steroids alone in one patient with EPS [11]. In 1999, Martins and colleagues also reported on one patient who was successfully treated for EPS with prednisone 100 mg per day, tapered to be stopped over 4.5 months [12]. The patient responded excellently with recovery of lost weight, normalization of serum albumin and disappearance of the ‘cocooning’ on CT of his abdomen. This patient also received azathioprine 50 mg per day for 2.5 months. In 2001, Kuriyama and Tomonori reported on their experience in the treatment of EPS before and after 1997, the year wherein the decision was made to treat all EPS patients with prednisolone 0.5 mg/kg per day [13]. All 6 patients before 1997 died as a consequence of EPS, and all 5 patients treated after 1997 were alive and doing well. The use of steroids for the treatment of EPS was subsequently confirmed as a successful strategy in a rat model.
model [14]. In this study, peritoneal fibrosis was induced in 20 rats by an acid dialysis solution. Glucocorticoid treatment prevented the progression of peritoneal fibrosis and adhesion of peritoneum. Dejagere and colleagues presented a patient who developed EPS after renal transplantation and who was successfully treated with high doses of corticosteroids [15]. A subsequent relapse, most likely due to fast tapering of the steroid dose, responded well to an increase in the steroid dose.

The pharmacological mode of corticosteroid action on EPS is still unknown. However, the speculation is that it may be via both the anti-inflammatory effect and the immunosuppressive effect of it. Matsuo et al. [16] recently showed, in a rat model, that prednisolone inhibits the glucose-mediated induction of monocyte chemoattractant protein-1 (MCP-1), which is important in recruiting monocytes and promoting fibrosis in peritoneal sclerosis. Glucose is supposed to upregulate MCP-1 through hyperosmolarity by activating protein kinase C (PKC) and its downstream NF-kappa B signaling.

Azathioprine

Azathioprine (AZA) has shown advantages in anecdotal case reports in humans. Wong and colleagues reported on two patients with EPS who were treated with AZA [17]. The first patient was started on AZA 125 mg per day (1.5 mg/kg/day) and prednisolone 30 mg per day. Gastro-intestinal symptoms improved quickly, and his body weight and serum albumin normalized, and subsequently, AZA was gradually tapered to 75 mg per day and prednisolone to 20 mg per day. The second patient reported by Wong et al. made a full recovery within 4 weeks of starting the dual immunosuppressive treatment. Junor et al. [18] suggested the beneficial role of AZA in EPS from the finding that five PD patients who developed EPS after renal transplant had a prolonged survival with or without functioning graft, when compared to twelve PD patients who were not on immunosuppression and died within a year after developing EPS. He attributed the benign EPS course of the renal transplant patients to AZA being part of the immunosuppressive regime.

They hypothesized that immunosuppression suppresses the uncontrollable fibrogenesis and the inflammatory infiltrate of the peritoneal membrane that causes EPS.

A recent animal study with 52 non-uremic rats with EPS, however, could not show any benefit of AZA for the treatment of EPS [19]. In the steroid group on the other hand, there was a lower fibrosis score and less peritoneal thickness when compared to the control animals.

Mycophenolate mofetil

Mycophenolate mofetil (MMF) has been shown to be efficacious for EPS treatment in three patients reported by Lafrance et al. [20]. The first patient received colchicine 0.6 mg per day, prednisone 50 mg per day for 2 weeks with progressive tapering to 25 mg per day and MMF 500 mg twice a day. Her general condition improved dramatically together with resolution of the abdominal pain syndrome and normalization of the serum albumin. A repeat CT abdomen showed less thickening of the peritoneal membrane and normal bowel loops. This patient underwent living donor kidney transplantation 1 year later. The second patient was treated with prednisone 25 mg per day tapered over 2 months to 15 mg per day together with MMF 500 mg twice a day. Abdominal symptoms and fever resolved rapidly, and both prednisone and MMF were stopped after 6 months of treatment. The third patient was treated with prednisone 50 mg per day and MMF 500 mg twice per day with rapid clinical and radiological improvement. Both prednisone and MMF were held 2 months after initiation of the treatment because of disseminated herpes zoster.

All three patients showed significant improvement within a month after MMF was started in combination with steroids, and all three patients were still alive more than 2 years after EPS was diagnosed. None of them experienced a relapse. We question, however, whether it was the MMF or the concomitant use of steroids that had the greatest impact on the EPS course. No other data on the use of MMF in the treatment of EPS are available.

Conclusion on human data

Human data suggest that tamoxifen and steroids might be useful in the prevention and/or treatment of EPS. Data on AZA and MMF are scarce and weak.
The reason why transplant recipients may be at higher risk to develop EPS, although being treated with steroids and AZA or MMF, lies, as stated before, in the use of lower steroid dose and in the use of CNI in current immunosuppressive regimes.

**Experimental data on medical treatment for EPS**

**Rosiglitazone**

Rosiglitazone is a peroxisome proliferator-activated receptor (PPAR) agonist. PPARs are the major regulators of key metabolic pathways of various inflammatory responses in fibrosing processes in most tissues. PPAR gamma receptors are expressed in mesothelial cells [21]. PPAR gamma plays a significant role in cell differentiation as well as in anti-inflammatory and antiangiogenic responses. They might therefore have a potential role in peritoneal defense. Bozkurt et al. [22] investigated the effect of rosiglitazone on progression and regression of EPS in 53 non-uremic rats with EPS. They found that rosiglitazone was more effective than peritoneal resting (leaving peritoneal cavity empty for 3 weeks till time of analysis after intraperitoneal chlorhexidine administration for initial 3 weeks) for almost all of the functional and structural peritoneal parameters, including an improvement in dialysate over plasma urea concentration (D/P urea) and ultrafiltration (UF) capacity and a decrease in inflammatory cell count and neoangiogenesis. These authors suggest that rosiglitazone may have a role in the prevention of EPS by inhibiting inflammation and neovascularization, especially in diabetes.

**N-acetylcysteine**

The well-known antioxidant N-acetylcysteine (NAC) is a capable reactive oxygen species (ROS) scavenger. Generation of ROS, as for instance by the presence of bio-incompatible PD solutions, might be responsible for progressive peritoneal membrane dysfunction and fibrosis. NAC also inhibits VEGF and decreases the activity of angiotensin II and TGF-beta1 in human peritoneal mesothelial cells [23].

The group of Bozkurt studied 39 non-uremic rats to assess the prophylactic and therapeutic effect of NAC in EPS [24]. NAC significantly improved peritoneal UF failure and neovascularization when compared with peritoneal resting. Surprisingly, there was no protective effect of NAC on fibrosis. However, the authors considered the decreased inflammation and vascularity to be promising for peritoneal membrane protection.

**Colchicine**

Colchicine is a well-known anti-inflammatory and antifibrotic agent. It also decreases the TGF-beta1 mRNA expression in idiopathic pulmonary fibrosis [25]. In a study of 48 non-uremic rats with EPS, colchicine resulted in significantly better UF volume when compared to the peritoneal resting group [26]. In the colchicine-regression group (intraperitoneal chlorhexidine for 3 weeks followed by colchicine in drinking water for 3 weeks), colchicine significantly improved peritoneal thickness and neovascularization compared to the resting group. In the colchicine-progression group (in which intraperitoneal chlorhexidine and oral colchicine were administered together during 3 weeks), there was a more pronounced effect of colchicine on fibrosis compared to the regression model. This finding might be compatible with the suggestion of an early inflammatory phase in the course of EPS and possibly confirms the need for early intervention before irreversible changes take place. In conclusion, colchicine was shown to have protective effects on membrane integrity via decreased inflammation, cell infiltration and vascularity.

**Renin–angiotensin system inhibition**

Angiotensin II promotes fibrosis and inflammation in various tissues via the enhanced gene expression of TGF-beta1, VEGF, epidermal growth factor (EGF), plasminogen activator inhibitor and pro-inflammatory cytokines. It plays an important role in fibrotic disease processes such as diabetic nephropathy, cardiac remodeling and hypertensive vasculopathy. The role of angiotensin II in peritoneal fibrosis has also been well described [27].

Sawada et al. [28] studied the antifibrotic effects of quinapril, an ACE inhibitor, on mice with EPS. Macroscopic examination revealed that fibrotic changes in the parietal peritoneum were statistically
more significant in the group of animals in which EPS was induced with intraperitoneal chlorhexidine and ethanol compared to the animals in which intraperitoneal chlorhexidine and ethanol were administered together with oral quinapril. Histological examination demonstrated that peritoneal thickening was clearly improved in the quinapril group.

Kyuden et al. [29] showed, in a cultured human peritoneal mesothelial cell model, that perindopril and candesartan attenuated the increased production of TGF-beta1 and that they reduced cell proliferation caused by exposure to high glucose. These effects were greater with the combination of both drugs.

Nakamoto et al. [30] studied the effects of the orally administered angiotensin receptor blocker olmesartan versus the calcium channel blocker amlodipine on peritoneal fibrosis in 40 hypertensive rats in which EPS was induced by a glucose-containing acid dialysis solution. Treatment with olmesartan prevented the progression of peritoneal fibrosis and adhesions, on which amlodipine did not have an impact.

In another non-uremic EPS rat model, the advantages of renin–angiotensin system (RAS) blockade in regression of EPS were studied [31]. The enalapril and valsartan group had better results with respect to UF volume and D/P urea when compared to the resting group. Surprisingly, these improvements were not present in the enalapril–valsartan combination group. Structural changes (peritoneal thickness and number of vessels) were ameliorated in all treatment groups compared to the resting group. In summary, RAS blockade seemed more effective than peritoneal resting with respect to ultrafiltration volume, vascularity and peritoneal thickness. Interestingly, dual blockade with enalapril and valsartan had no additional beneficial effects and even made some functional improvements disappear.

Human data on the effect of RAS inhibition on the peritoneal membrane are scarce. Kolesnyk and colleagues retrospectively analyzed data from 66 patients treated with PD for at least 2 years, during which at least 2 standard peritoneal permeability analyses (SPA) were performed [32]. Thirty-six patients were treated with an ACE inhibitor and/or ARB, 30 patients did not receive any of these agents. In the ACE-inhibitor/ARB group, small solute transport had decreased, while it increased in the control group during the time on PD. The same group from the Netherlands studied data from 217 long-term PD patients, of whom 120 were treated with an ACE inhibitor/ARB, 87 were not and 10 who had them for less than 25% of their time on PD [33]. The value of the 24-h D/P creatinine was correlated with PD duration ($P = 0.01$), but the slope of the rise of D/P creatinine over time was less steep in the group treated with RAS inhibition ($P = 0.05$). Increase in small solute transport due to peritoneal inflammation and/or fibrosis is a well-known early sign of EPS. The presented human data suggest that RAS inhibition may play a role in preventing EPS in PD patients. Wong et al. [34] showed that ACE activity is independently associated with mortality in diabetic PD patients. Apart from its role in macroangiopathy, increased ACE activity might also be associated with the development of EPS and hence explain its association with mortality in PD patients. This is also compatible with data from Fang et al. [35], showing that treatment with ACE inhibitor and/or ARB in PD patients was associated with a dramatically reduced mortality independent of blood pressure and other clinical and demographic variables.

**Thalidomide**

Thalidomide suppresses the production of tumor necrosis factor (TNF) alpha by macrophages and T cells, and based on its immunomodulatory, anti-inflammatory and antiangiogenic effects, it may have a role in the treatment of EPS [36].

Based on this rationale, Mondello and colleagues induced EPS in 40 rats by intraperitoneal administration of chlorhexidine, and thalidomide was given orally [37]. Thalidomide reduced the extent and severity of histological signs of peritoneal injury as well as the degree of polymorphonuclear cell infiltration in injured peritoneum. It also resulted in reduction of the expression in the tissue of TNF-alpha, TGF-beta, VEGF and NF-kappa B activation.

**Everolimus**

Everolimus is a macrolide immunosuppressive agent that inhibits the activity of mammalian target of rapamycin (mTOR), a cellular enzyme that plays a key role in cell growth and proliferation. The antifibrotic effects of mTOR inhibitors are well described [38–40].
Duman studied the effects of everolimus in a non-uremic EPS rat model [41]. Everolimus was more effective than peritoneal rest with regard to vascularity and peritoneal thickness. It had beneficial effects on UF failure, inflammation and fibrosis.

Other experimental agents

More experimental data are available for the treatment of EPS. However, none of these agents are currently used in clinical practice to treat other diseases. This is in contrast to the previously described agents. An excellent review of all these experimental data for the treatment of EPS was written by Park and colleagues [6]. Agents such as pirfenidone (inhibits the expression of TGF-beta 1 and TNF-alpha and scavenges reactive oxygen species) [42], antiangiogenic strategies with anti-VEGF neutralizing antibodies [43], TPN-470 [44] and endostatin peptide [45] as well as oligonucleotides against the collagen accumulating heat shock protein 47 (HSP-47) [46], ONO 487 (reduces the expression of MMP-2, TGF-beta and VEGF and subsequent accumulation of type I collagen) [47], chimeric DNA–RNA hammerhead ribozyme targeting TGF-beta mRNA [48] and hepatocyte growth factor [49] are discussed.

Stabilization of D/P creatinine over time on PD has also been reported in a PD patient with metastatic renal cell carcinoma treated with the tyrosine kinase inhibitor sunitinib that also has anti-VEGF effects [50].

Biocompatible PD solutions

Numerous factors related to the composition of standard peritoneal dialysis solutions possibly contribute to the pathogenesis of peritoneal fibrosis during PD, including glucose, glucose-degradation products [51], high osmolarity, low PH, lactate and plasticizers released from the PD bags.

Garosi showed in a rabbit model that PD solutions containing amino acids did not cause mesothelial damage as opposed to solutions containing glucose [52]. Submesothelial edema was worse in rabbits dialyzed with glucose solution when compared to amino acid solution, and within the glucose-containing dialysate group, the edema was worst in the highest glucose group. No difference in submesothelial infiltration was found between the groups.

The use of biocompatible solutions has been advocated for in an attempt to prevent the development of EPS [53]. However, to date, no definitive human data are available to support the use of biocompatible solutions for this purpose.

Recently, Yao and colleagues studied conventional and biocompatible PD solutions in a rat model [54]. Twenty-eight rats were dialyzed three times daily for 4 weeks with a conventional or biocompatible solution each with various glucose concentrations. The use of conventional solutions, especially the highest glucose-containing ones, resulted in the expansion of the submesothelial compact zone, loss of mesothelial cell layer integrity, hypercellularity, accumulation of collagen, increased vessel numbers and increased TGF-beta1 expression, but this did not significantly change fluid and solute peritoneal transport characteristics.

Van Westrhenen et al. [55] investigated in a rat model whether a filter-sterilized pyruvate-buffered dialysis solution, made by combination of low concentrations of amino acids, glycerol and glucose (PYRAGG), would induce less peritoneal abnormality than glucose/lactate-based peritoneal solutions. No differences with respect to peritoneal transport were found between the different groups. However, histological assessment of the peritoneum revealed that the PYRAGG group had lower degree of fibrosis and neoangiogenesis than the 2 other groups. They concluded that a combination of osmotic agents (each in lower concentration) rather than the use of glucose alone (in high concentration) might help in the prevention of neoangiogenesis and fibrosis and therefore EPS.

Whether the use of biocompatible solutions could prevent the development of EPS is unclear as stated before. Prolonged (longer than 3 years), large, randomized trials are lacking to address this question. In a recent editorial, Tejde et al. [56] reported on 2 patients who developed EPS even though they were treated only with biocompatible solutions. However, both patients had multiple episodes of PD peritonitis possibly explaining why they developed EPS, even in the presence of biocompatible solutions in the peritoneal cavity.

Conclusions

Encapsulating peritoneal sclerosis (EPS) is a rare but potentially dangerous complication in PD patients. The exact pathogenesis is unfortunately not well
Sampimon and colleagues analyzed the time course of CA-125 and IL-6 preceding the diagnosis of EPS [63, 64]. They showed that an appearance rate of CA-125 lower than 33 U per minute and of IL-6 higher than 350 pg per minute in patients with ultrafiltration failure had a sensitivity of 70% and a specificity of 89% for the diagnosis of EPS. They suggest that peritoneal samples should be taken regularly in PD patients to detect early peritoneal membrane inflammation. However, larger, randomized studies are necessary to look further into the detection and validation of these novel biomarkers for EPS.

In an attempt to facilitate the early diagnosis of EPS, we suggest that the nephrology community should aim at developing an EPS score. This EPS score could potentially consist of a combination of clinical, laboratory and radiological features (Table 1). Ideally, this EPS score should be monitored, for example, every 3–6 months and PD patients should be started on prophylactic EPS treatment with 20–40 mg of tamoxifen per day and low-dose prednisone once the EPS score reaches a specific threshold. Large, randomized trials are obviously necessary to validate this strategy, and these trials should be initiated once the nephrology community agrees on the EPS score.

This proposed and hypothesized strategy of early detection of EPS in the inflammatory phase by means of an EPS score in combination with early treatment of EPS offers an alternative to the idea of an ‘expiry date’ for PD, which is propagated by some nephrologists as an attempt to try to prevent EPS from developing. Opposed to the principle of discontinuing PD according to pre-specified timing even before EPS is suspected, we strongly believe that individual evaluation of each PD patient based on clinical,
laboratory and radiological characteristics is a more valid approach to patients on long-standing PD treatment. Large, registry-based multicenter prospective studies are required to better understand and delineate the genetic, demographic and treatment-related risk factors contributing to the development of EPS. Awaiting the results of these studies, measures such as early use of tamoxifen, mTOR-inhibitor-based immunosuppressive regimes in transplantation, the use of biocompatible solutions and promoting the use of RAS inhibition in PD patients, should be the cornerstones in the prevention of the fibrotic phase of EPS rather than the systematic prescription of an ‘expiry date’ [65, 66].

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