

Implementation of peritoneal dialysis after loss of renal transplant function*

International medical literature contains a little information on peritoneal dialysis (PD) modality in patients who need dialysis due to loss of renal transplant function (LRTF). This paper presents the current status of knowledge about the prevalence of PD after LRTF and therapeutic problems arising after returning to PD or hemodialysis (HD) in such cases. The overall survival rate is similar independently on dialysis modality (PD, HD) started after allograft failure. However, the utilization of PD after LRTF is only about 2 - 18%. This suggests under-usage of PD after LRTF.

(NEPROL. DIAL. POL. 2014, 18, 210-212)

Dializa otrzewnowa u chorych po utracie czynności przeszczepionej nerki

W światowym piśmiennictwie przedmiotu istnieje niewiele informacji na temat stosowania dializy otrzewnowej (PD) u chorych, którzy wymagają leczenia nerkozastępczego (RRT) po utracie czynności przeszczepionej nerki (LRTF). W pracy przedstawiono dotychczasowy stan wiedzy na temat częstości stosowania PD po LRTF oraz problemy terapeutyczne po powrocie do leczenia PD lub hemodializą (HD) w takich przypadkach. Wskaźnik przeżycia wśród chorych leczonych HD lub PD po LRTF jest podobny, ale wykorzystanie PD po LRTF wynosi tylko ok. 2 – 18%, co przemawia za niedostatecznym wykorzystaniem tej opcji leczenia.

(NEFROL. DIAL. POL. 2014, 18, 210-212)

The number of individuals after renal transplantation is increasing. Therefore, the quantity of patients returning to dialysis after loss of renal transplant function (LRTF) also increases commensurately. Patients returning to dialysis after LRTF represent about 12% of the population starting dialysis each year [1]. The American [2] or European [3,4] guidelines for renal transplantation do not mention about the care of patients who have lost their allografts. Similarly, the American and European dialysis guidelines did not establish clear recommendations when patients with LRTF have to restart dialysis [5,6]. Furthermore, at the conference held in Lisbon in 2007 on the care of renal transplant recipients in which specialists from three continents took part, no aspects related with graft failure patients were considered [7]. In 2009, the working group of the Spanish Society of Nephrology reviewed each clinical aspect of care of kidney transplant patients with renal failure returning to dialysis and drew up a consensus document to optimize management [8]. These recommendations state that dialysis should be started when the glomerular filtration rate is below 15 ml/min/1.73 m². However, the best modality of dialysis - peritoneal dialysis (PD) or hemodialysis (HD) - for patients who lost renal transplant function was not clearly defined. Therefore, whether PD or HD would be the best treatment option for these patients is a question that still has to be answered.

It is well known that renal allograft recipients are younger than patients undergoing dialysis [9]. The former generally experienced an increased quality of life during their renal transplant period, free from regular dialysis treatment. Hence, after

LRTF they might prefer PD at home instead of HD in dialysis centers. However, patients with LRTF who are starting or re-starting PD treatment need special consideration. They are at increased risk of death after allograft loss compared to patients with a functioning graft [10] and constitute a unique group with specific risk factors that include a longer duration of end-stage renal disease (i.e. a longer duration between first renal replacement therapy of any type and starting PD), concomitant immunosuppression, increased susceptibility for dialysis-related infections, and possibly more rapid loss of residual renal function in comparison to patients with native kidneys who started dialysis for the first time [11,12]. In view of the foregoing and based on the available data, it is difficult to draw firm conclusions or to recommend whether PD or HD is preferable for starting dialysis in patients with LRTF [12-15].

The aim of this review is to evaluate the prevalence, management and outcome of patients treated with PD after LRTF. Papers for this analysis were extracted in response to "peritoneal dialysis, failed renal transplant" catchwords using *PubMed* tools.

Prevalence and survival of PD patients with failed allografts

A failed renal allograft is becoming one of the most frequent causes of dialysis initiation or re-initiation. Until now, studies concerning effects of a failed renal transplant on outcomes of re-started dialysis treatment have reported conflicting findings [1,16,17]. Studies, in which PD patients with LRTF are compared with PD ones who have never received a transplant, are limited. Sasal

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Key words:

- graft failure
- hemodialysis
- immunosuppression
- loss of renal transplant function
- peritoneal dialysis

Słowa kluczowe:

- dializa otrzewnowa
- hemodializa
- leczenie immunosupresyjne
- niewydolność przeszczepionej nerki
- utrata funkcji przeszczepionej nerki

**Pracę dedykujemy Panu Profesorowi Bolesławowi Rutkowskiemu w podziękowaniu za nieoceniony wkład w rozwój dializoterapii polskiej*

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et al. [11] have found that patients starting PD after LRTF were at increased risk of complications than never-transplanted PD patients. However, these investigations were limited by small sample sizes. Sasal et al. [11] compared 42 patients starting PD after LRTF with 43 randomly selected never-transplanted PD patients. They found that patients starting PD after a failed allograft showed significantly higher morbidity defined as time to the first peritonitis, more frequent subsequent episodes of peritonitis, catheter exchange, need for transfer to HD, and higher mortality rates (12 deaths vs 3 deaths during the seven years of study) compared with never-transplanted PD patients. The mean age at death was only 47 years, and the causes of mortality were equally divided between cardiovascular events and infections. Time to the first peritonitis episode was also shorter in PD patients after LRTF, although the overall peritonitis rate was not different. The proportion of patients with diabetes was similar between the failed transplant patients and the new PD patients, but a prevalence of other risk factors (steroid administration, higher low-density lipoprotein cholesterol) was greater. The authors concluded that the high mortality was due to increased cardiovascular risk, and a failed allograft should be considered an adverse prognostic factor for patients commencing PD. On the other hand, in the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry [18], which included 11,979 patients who started PD treatment, about 2% started dialysis after LRTF, and patients commencing PD after renal allograft failure experienced outcomes comparable to those with native renal failure. The peritonitis-free survival was similar, and the mortality was determined predominantly by age and comorbid conditions. Authors concluded that PD appears to be a safe and viable option for the patients returning to dialysis after a failed allograft. These findings are in line with two previous smaller single-center studies [12,13]. Duman et al. [13] compared 34 PD patients with a failed renal transplant with 82 PD patients who had never received a renal transplant or HD treatment. The groups were similar regarding to age, gender, residual renal function; none of them was diabetic. Authors showed that previous renal transplantation did not adversely affect patients survival. They did not observe earlier loss of peritoneal functions in the post-transplant patients. Davies [12] similarly showed that patient survival rate was not significantly different for the patients returning to PD with failed allograft and never transplanted PD patients.

A very important and significant for the evaluation of a therapeutic modality are studies in which the two procedures - PD and HD - are compared in patients with failed allografts. Davies [12] identified 45 patients who returned to dialysis after failure of an allograft that functioned for more than 6 months. Among them, 28 patients returned to PD and 17 patients returned to HD. Survival rate of patients with LRTF was not different for the group commencing PD as compared with the group commencing HD, although the median survival tended to be longer in the PD patient group. Author conc-

luded that there is no difference in outcome between patients returning to PD or to HD after LRTF and that the principal risk factor for patients returning to dialysis is accrued comorbidity and not the specific dialysis modality. In retrospective single-center study by Jonge et al. [14], 60 patients returning to dialysis after LRTF were identified. Twenty one of these patients commenced PD and 39 commenced HD. As in the former study [12], they found no inferiority of PD as compared to HD with regard to the outcome. Survival did not differ significantly between the two groups in a Kaplan-Meier analysis and related statistics. Moreover, they found one death every 82.9 patient month in the HD post-transplant group and only one death every 132.6 patient months in the PD post-transplant group. Authors concluded that it might suggest a survival benefit in the PD post-transplant group. Perl et al. [19] identified 2,110 patients from the Canadian Organ Replacement Register who initiated dialysis after first renal transplant failure between January 1991 and December 2005. The strength of this study lies in its large sample size. They were used a multivariable Cox proportional hazard model to evaluate the impact of initial dialysis modality (PD vs HD) on early (2 years) and late (after 2 years) mortality. Compared to HD patients, PD patients were younger but they had more comorbidities such as diabetes mellitus. After adjustment, they found no difference between the modalities and similar results in the early and late survival analysis.

Recommendations for the PD patients with a failed renal allograft

There are no prospective and only a limited number of retrospective studies addressing the management of patients with a failed renal transplant who return to PD. Failed renal allografts are sometimes left *in situ* as long as residual diuresis reduces the need for fluid restriction. The management of patients returning to dialysis (PD or HD) after LRTF with a renal allograft *in situ* depends on clinical experience of the dialysis centres. Renal transplant recipients are on immunosuppressive therapy. In the case of early allograft failure and nephrectomy, immunosuppressive therapy is interrupted immediately. In the case of late failure, there are two main alternatives if the allograft is left in place. One of them favours early discontinuation of immunosuppressant drugs [20-22] or removal of the failed renal allograft [23]. The other clinicians prefer continuation of low-dose maintenance immunosuppressive medication to avoid rejection symptoms [24,25]. However, there are no data about either the effect of maintaining immunosuppression on the preservation of allograft function or which immunosuppressive regimen is the best. The reasons for maintaining immunosuppression are to preserve renal function, to prevent allograft rejection, or to avoid a rise in panel reactive antibodies (PRA) that could occur after discontinuation of maintenance immunosuppression without allograftectomy [26]. The clinicians have to choose the type and the dose of immunosuppression. If immunosuppression is continued, then allograft function

may be optimized, but the risk of infection is potentially higher [12]. Andrews et al. [27] showed that immunosuppressed patients had more episodes of peritonitis, required more frequent hospital admissions, had more days off dialysis, and required more laparotomies to remove infected catheters. They presumed that in PD patients immunosuppression is an important risk factor for PD-related peritonitis. In addition, Puttinger et al. [28] found that PD immunosuppressed patients with chronic renal allograft failure have a higher risk of Gram-negative peritonitis, a shorter interval between start of dialysis and first episode of peritonitis, and a higher risk of catheter infections with *Staphylococcus aureus* than PD patients without maintained grafts. Gregoor et al. [29] compared the morbidity and mortality due to infections between PD and HD patients with or without low-dose immunosuppression. They found that the increase in serious and life-threatening infections is associated with even low-dose immunosuppression. On the other hand, Jassal et al. [30] found that continued transplant immunosuppression may prolong survival after return to PD. They have shown that life expectancy was prolonged from 5.3 years to 5.8 years when immunosuppression was continued and a benefit from continued immunosuppressive therapy was seen for all values of additional glomerular filtration rate greater than 15 L/week.

There are many ways of tapering of immunosuppression in graft failure patients who returned to dialysis [14,26,29,30] but no data which immunosuppressive regimen is the best. In some studies, patients were kept on low-dose immunosuppression that included steroids and cyclosporine or tacrolimus [14]. Some authors advocate avoidance of calcineurinic inhibitors [30] and tacrolimus [2] because of their nephrotoxic effect. The detection of nephrotoxicity may prompt changes in immunosuppressive regimens. However, it is worthy to note that even small changes in the doses of immunosuppressive medications may cause changes in graft function [2]. Thus, it seems that we should aimed for optimize the dose of immunosuppressive medications. However, there is no consensus about the effect of low-doses of immunosuppression. The very low doses of immunosuppression might not be sufficient even to suppress PRA. On the other hand, maintaining high immunosuppression is not without a risk of higher morbidity and mortality [26,29]. There are many ways of stopping immunosuppression [31]. However, no clear protocol has been devised how to reduce or withdraw the immunosuppressive treatment. In general, steroids are withdrawn over a period of weeks to months, azathioprine is discontinued, and variable quantities of calcineurinic inhibitors are prescribed. Marcén et al. [26], in patients on triple therapy, abruptly stopped the administration of azathioprine and mycophenolate mofetil as well as reduced the dose of anticalcineurinic by one half. They maintained anticalcineurinic for 6 to 8 weeks before stopping their administration. After withdrawal of anticalcineurinic, the steroids were tapered by 2.5 mg each month until their complete discontinuation.

Since the more widespread use of the lower doses of steroids, graft nephrectomy has become a safe procedure and can be prepared according to planned schedule. The role of allograft nephrectomy in the management of renal transplant recipients with LRTF remains controversial. When graft failure occurs early after transplantation, the graft will be removed immediately in most cases. When graft failure occurs later, the policy is much less restricted [21]. Advocates of nephrectomy contend that the failed allograft may be an ongoing source of sepsis or chronic inflammation that could lead to complications, such as infection, erythropoietin resistance, or immune activation. In addition, the failed allograft could become a source of difficult to control hypertension. There is common agreement that allograft nephrectomy must be performed in case of hyperacute rejection, vascular thrombosis, and other technical complications of transplant surgery. Leaving the allograft *in situ* has advantages such as erythropoietin production, hydroxylation of calcidol, maintenance of some residual diuresis, and lower risk of sensitization. In some centers [26], allograft nephrectomy is systematically performed in the case of early allograft failure, but the allograft is left in place when the loss of allograft function is slow, and immunosuppression is tapered until complete withdrawal within a few months [14,32]. In the case of slow allograft loss, nephrectomy is only performed when there is allograft intolerance syndrome [26]. It should be noted that the surgical procedure is not without morbidity or mortality, and patients may become sensitized post nephrectomy either because of removal of the allograft or the need for perioperative transfusions, or both [33].

In the summary of the issue discussed above we can conclude that early transplant failure needs allograftectomy and discontinuation of immunosuppression. In late failure, a allograft is frequently kept *in situ*, usually on low immunosuppressive therapy. When allograft intolerance syndrome or unclear inflammatory state appear, prompt allograftectomy is necessary. PD patients, even on low-dose immunosuppression, may have higher peritonitis rate and more severe course of infections, thereby re-education in prophylaxis and quick reaction on early symptoms of infection are necessary. Systematic allograft nephrectomy can be used as an option of treatment, and can help to ameliorate patient outcome, but prospective studies are needed to confirm its beneficial effects [26].

Thus, the problems with maintenance of immunosuppression after failed renal transplantation and the best time for graft

nephrectomy are equally unsolved for post-transplant PD and HD patients.

In summary, the use of PD or HD is associated with similar early and overall survival among patients initiating dialysis after LRTF. However, despite similar outcomes of PD or HD patients with failed renal allografts, utilization of PD after LRTF is less frequent than HD, similarly to the overall PD under-usage in RRT, and seems to be underused in failed transplant patients. In accordance with some studies [12-14,19], increased use of PD among patient returning to dialysis after LRTF may improve survival in this group.

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