Outcome of HIV-infected patients on peritoneal dialysis: experience in a center and literature review

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SUMMARY

Overall survival of HIV-infected has increased over the last ten years. In parallel a higher need for renal replacement therapy (RRT) in this population has been more observed. RRT associated complications and outcomes greatly varied since the introduction of highly active antiretroviral therapy (HAART) and scarce data is available regarding the outcome of peritoneal dialysis (PD) in HIV-infected patients under HAART. We described 8 HIV-infected patients who were admitted at the Peritoneal Dialysis Unit at our institution from november-95 to november-07. Mean age was 40.7 ± 5.3. Causes of end-stage renal disease were diabetes mellitus type 1 (2), focal and segmental glomerular sclerosis (2), IgA nephropathy (1) and unknown origin (3). High blood pressure was detected in 62,5 % of the patients. Mean follow-up was 41.2 ± 32.1 months (range 12-103). One, two and three year survival was 100, 62.5 and 50% respectively. Overall mortality was 62.5% and cardio-vascular events were the main cause of death (2 patients, 25%). Infective peritonitis rate was 0.36 IP/year, and Staphylococcus epidermidis was the most common pathogen identified. Hospital admission rate was 0.69 admission/year and the main cause of admission was respiratory tract infecction. All patients received HAART. Lamivudine, stavudine and nelfinavir were the most frequent treatment prescribed. During the first year in PD undetectable viral load and CD4% were not modified. A significant weight gain was observed during the first year of the study (60.6 kg vs 64.9 kg, p = 0.016). Our results suggest that PD is a suitable choice for RRT in HIV-infected. Compared to previous studies, an increase in overall survival and a decrease in PD-associated complications were seen. The significance of cardio-vascular risk factors in the outcome of PD in HIV-infected patients is not completely determined. A multidisciplinary aproach and a management of patients in individual basis remains mandatory.

Key words: *HIV. Peritoneal dialysis. Peritonitis. Antiretroviral therapy. Survival.*

RESUMEN

La supervivencia de los pacientes VIH ha mejorado en los últimos años. Secundariamente la necesidad de tratamiento renal sustitutivo en estos pacientes también ha aumentado. Su pronóstico en diálisis así como las complicaciones asociadas han mejorado desde los primeros casos descritos. Mostramos los pacientes VIH incluidos en nuestra unidad de diálisis peritoneal desde noviembre-95 hasta noviembre-07. Fueron 8 pacientes, con una edad media de 40,7 ± 5,3, con un tiempo de seguimiento de 41,2 ± 32,1 meses (rango 12-103). Las etiologías de la IRC fueron diabetes mellitus tipo 1 (2), glomérulo-esclerosis focal y segmentaria (2), nefropatía IgA (1) y no filiada (3). El 62,5% de los pacientes eran hipertensos. La supervivencia al año, dos y tres respectivamente fue de 100, 62,5 y 50%. La mortalidad total fue del 62,5% al finalizar el estudio. La causa principal de deceso fueron los eventos cardiovasculares (2 pacientes, 25%). La tasa de peritonitis y el número de admisiones fue de 0,36 paciente/año y de 0,69 ingresos/año respectivamente. El Estafilococo epidermidis fue la principal causa de peritonitis infecciosa y la infección respiratoria el motivo más frecuente de hospitalización. Todos los pacientes recibían tratamiento antirretroviral (TARV). La lamivudina, la estavudina y el nelfinavir fueron los más habituales en el tratamiento. Durante el primer año en diálisis peritoneal se pudo evidenciar que la carga viral y el porcentaje de CD4 no se modificaba. Al mismo tiempo se constató un aumento del peso en el primer año (60,6 kg *vs* 64,9 kg, p = 0,016). Nuestros resultados sugieren que la DP puede ser una técnica de elección en estos pacientes. La supervivencia ha aumentado y las complicaciones asociadas a la técnica de DP también son menores. La importancia de otros factores de riesgo, como los cardiovasculares no está definida. Por el momento la individualización de cada paciente y un trabajo multidisciplinario son obligados.

Palabras clave: VIH. Diálisis peritonel. Peritonitis. Antirretrovirales. Supervivencia.

INTRODUCTION

Current antiretroviral therapy has allowed for an increased survival of patients infected by the human immunodefi-

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ciency virus (HIV).[1] This increase has led to the occurrence of other associated complications that were less common 15 years ago.[2] From the nephrological perspective, an increase has occurred in HIV patients with renal involvement, and their prognosis in renal replacement therapy has changed favorably[3,4] as compared to the beginning of the 90s, when early studies reported high mortality and complication rates.[5,6] There is currently no controversy about inclusion of these patients in a hemodialysis (HD) or peritoneal dialysis (PD) program when they need it, The situation of these patients on PD has progressed over these years, and the most determinant factor today is the HIV disease itself.[7] The course over time and the characteristics of HIV-positive patients in our PD program from 1995 to date are reported.

METHODS

From November 1995 to November 2007, data were retrospectively collected from all HIV-infected patients who had started renal replacement therapy using peritoneal dialysis at our center. Demographic and laboratory data of all patients were reviewed. The survival curve was calculated using the Kaplan-Meier method. Patients who were switched to another replacement treatment modality (HD or kidney transplant) were considered lost for outcome purposes. Outcomes were compared using a Student's t test for paired data. Means and medians are given with their standard deviation and range respectively. A value of $p < 0.05$ was considered statistically significant.

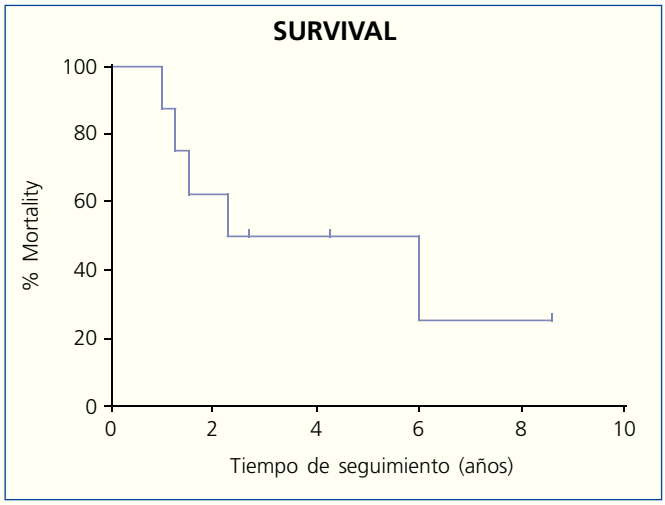

Figure 1. Kaplan-Meier. Survival of HIV patients in our PD program. Marks are censored (alive) patients.

RESULTS

Eight patients, seven males and one female, were included in this period. All patients were Caucasian. Mean patient age was 40,7 ± 5,3 years. The different underlying diseases are given in Table 1. Six patients had stage C3 HIV infection, one stage B3, and the other stage B2 HIV infection. Serological testing for HCV was positive in all patients, but only one patient had data suggesting chronic liver disease. They all were former intravenous drug users.

Table I. Demographic data and characteristics of HIV patients on PD

Patient	Sex	Age	ESRD etiology	Time on PD (months)	Status at study end	Cause	No. of peritonitis	No. of admissions	HBP	TBC
1	M	35	DM	15	Dead	AMI	1	1	YES	YES
2	M	45	IgAN	72	Dead	Sclerosing peritonitis	6	3	YES	YES
3	M	35	U	51	Alive	HD	1	2	YES	YES
4	M	37	FSGS	103	Alive	KT	0	4	YES	NO
5	M	38	U	12	Dead	LL gangrene	0	2	NO	NO
6	M	47	U	27	Dead	AMI	1	1	NO	YES
7	M	41	FSGS	32	Alive	PD	0	3	YES	YES
8	F	48	DM	18	Dead	Unknown	1	3	NO	NO

DM: Diabetes mellitus; U: Unknown; IgAN: IgAN; FSGS: Focal segmental glomeruloesclerosis; AMI: Acute myocardial infarction; HD: Hemodialysis; KT: Kidney transplant; PD: Peritoneal dialysis.
All patients were former IDUs and tested positive for HCV.

Table II. Survival, hospitalization, and peritonitis in different studies

	No. of patients on PD	Survival: 1-2-3 years	Mean survival (months)	Hospitalization rate	Peritonitis rate
Tebben, 1993 (1987-1992)	39	58-54-32	10	53.4 days/year	3.9 episodes/year
Kimmel, 1993 (1984-1992)	8	ND	17.9 ± 10.7	NA	2.4 episodes/year
Khana, 2005	53	ND	29.28 ± 34.4	3.59 admissions/year	1.4 episodes/year
Soleymanian, 2006 (1989-2004)	7	100-83-50	48.5 (13.5-77.1)	1.01 admissions/year	NA
Rivera, 2008 (1995-2007)	8	100-62.5-50	41.25 (12-103)	0.69 admissions/year	0.3 episodes/year

NA: Not available.

Mean follow-up time on PD was 41.2 ± 32,1 months, with a median of 29,5 months (range: 12-103). Survival rates at one, two, and three years were 100%, 62.5%, and 50% respectively, as may be seen in Figure 1, with an overall mortality at study end of 62.5%. Five patients died, two from ischemic heart disease, a third patient from fulminant gangrene in his right leg caused by *Pseudomonas aeruginosa*, a fourth patient died at home for an unknown reason, and the final patient died from sclerosing peritonitis after six years on PD. A patient was switched to HD after peritonitis induced by *Mycobacterium fortuitum*, another patient received a kidney transplant after 9 years on dialysis, and a final patient continued on PD at study completion (table I). Table II compares the survival rates reported by studies involving HIV patients on peritoneal dialysis, showing an increased survival and a decrease in complications over the years.

Complications of the procedure

The infectious peritonitis (IP) rate and the number of hospitalizations were 0.36 IP/year and 0.69 admissions/year respectively. *Staphylococcus epidermidis* was the most common causative organism, but was only found in two patients. A patient experienced six IP episodes (two from *Klebsiella pneumoniae*, two from *Staphylococcus epidermidis*, one sterile peritonitis, and one from *Pseudomonas fluorescens*). Another patient experienced an IP by *Mycobacterium fortuitum* that required removal of his peritoneal catheter and switching to HD. In another case with a good outcome, the identified germ was *Escherichia coli*, and IP induced by *Candida albicans* occurred in a single case. Three patients suffered no peritonitis during this study period, one of them probably because of his short time on PD (12 months). A second patient continues on PD after 32 months, and the remaining patient received a kidney transplant after almost nine years on PD. Only 15.7% of hospital admissions were caused by an infectious peritonitis. The most common reason for admission was respiratory tract infection.

Course of HIV infection

All patients were on antiretroviral therapy. Although different schemes were used, all patients but one were on triple therapy. Among nucleoside reverse transcriptase inhibitors (NRTIs), the most commonly used drug was lamivudine (Epivir®) taken by 75% of patients. Thus, the most usual combination consisted of lamivudine plus stavudine (Zerit®), found in half the cases. These drugs were normally associated to a protease inhibitor (PI). Both stavudine and abacavir (Ziagen®) were taken by 62.5% of patients. The most commonly used PI was nelfinavir (Viracept®), received by 37.5% of patients. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) were scarcely used, and only one patient received efavirenz (Sustiva®) in his treatment. From the clinical viewpoint, patients maintained a good viral response. None of the five patients with an undetectable viral load experienced any changes in viral load, that decreased to undetectable levels in the other three patients. CD4 levels increased in all patients but one. Mean CD4 percentage was 20.2% at baseline and 23.5% at one year, but this increase was not statistically significant. Another aspect assessed was weight gain (net weight), based

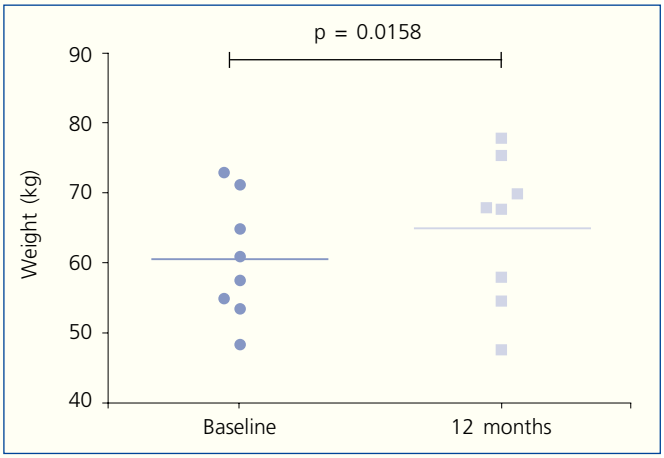

Figure 2. Weight values at baseline and after 12 months of renal replacement therapy with PD.

on the assumedly greater malnutrition in PD due to protein loss in peritoneal fluid. No differences were found in our patients in serum albumin levels or nPCR, but a significant weight gain was seen in the first year. Mean patient weight was 60.6 ± 8 kg at baseline and 64.9 ± 10 kg at one year, p = 0.016 (fig. 2).

DISCUSSION

Our study confirms an increased survival of HIV patients on peritoneal dialysis. Survival rates at one, two, and three years were similar to another recent study[3] and higher than the rates reported by Tebben and Kimmel.[5,6] Early studies on HIV patients with end-stage renal disease (ESRD) and renal replacement therapy by Ortiz,[8] Perinbasekar,[9] and Feinfeild[10] reported a poor outcome. New highly active antiretroviral therapy (HAART) has led, particularly since 1995, to a marked increase in life expectation[1] which has allowed for survival rates in peritoneal dialysis longer than 5 years, and up to 9 years in our experience.[3] However, mortality continues to be high in these patients despite more effective treatments.[3,4] Survival of HIV-infected patients has improved,[1] and does not change irrespective of the renal replacement therapy used.[7] Rodríguez et al, in their study on 100 HIV-infected patients, showed that those who started dialysis in the pre-HAART era survived 9.4 months, while patients starting dialysis in the HAART era survived 16.1 months. However, the corresponding figures for all HIV-positive patients not on dialysis were 16 and 81 months.[11] Other studies suggested an inadequate antiretroviral treatment in patients on renal replacement therapy.[12] However, an analysis of the different studies involving HIV-infected patients on PD showed an improved survival, particularly when the two pre-HAART studies were compared to studies conducted in the HAART era, from a mean survival of 17.9 months to longer than 40 months (table II).

From the therapeutic viewpoint, there are studies and guidelines with recommendations for antiretroviral therapy in ESRD and dialysis, but ART in PD is not clearly defined.[13] Szczech reviewed this aspect in 89 HIV-positive patients, five of them on PD, and found that the most commonly used drug was lamivudine, in 36 patients, followed by stavudine in 33 patients and nelfinavir in 21 patients. These results were similar to those seen by our study group. These data are consistent with the widespread use of stavudine and nelfinavir during the final 90s and the beginning of the 2000 decade, the period mostly described in our study. These drugs are now used as first-line treatment because of their low potency (nelfinavir) or high associated toxicity (stavudine).[14,15] Currently, and until studies providing new indications are available, it appears reasonable to take the same measures as in hemodialysis, considering the special characteristics of these patients on PD.[16,17]

Complications of the procedure have decreased in parallel to the increase in survival. Thus, infectious peritonitis rates in HIV patients have decreased from 3.9 and 2.4 episodes/year in early studies to 1.4 episodes/year in the Khana study or 0.3 episodes/year in our study,[4,6] though some studies have reported conflicting results. Thus, Tebben et al[6] found in a group of 39 patients a higher number of peritonitis in HIV-infected patients, and Scholoth[18] also noted in 9 similar patients a higher rate of infectious peritonitis, as did Khana.[4] Other authors showed no differences between both groups.[5,19] In our study, peritonitis rate was not different from the rate seen in non-HIV-infected population in our unit.

Although opportunistic infections have been reported in HIV patients treated with PD, Gram-positive cocci are the most common cause of infectious peritonitis.[6,20-22] Our results are very similar to those of the Kimmel group, with a case each of IP caused by *Pseudomonas* and *Mycobacterium*. Fungal involvement was seen in a single patient, and there were no cases of polymicrobial peritonitis. [23] It should be noted that 6 of the 10 episodes of peritonitis occurred in the same patient, and three patients experienced no IP while on peritoneal dialysis, in contrast to other studies where 100% of patients experienced some episode of IP.[5] Course of peritonitis in our study was usually favorable, and removal of peritoneal catheter was only required in two cases. Hospitalization rate was also low as compared to previous studies.[3-4]

These results are possibly conditioned by advances in antiretroviral therapy, a decreased viral load, and an improved immune status, which are known good prognostic factors.[24-26] In our study, all patients were on HAART, viral load was low or undetectable in most cases, and the CD4 percentage was adequate. Although higher serum albumin levels[3] and an increased risk of peritonitis associated to them[27] have been reported in PD, this does not appear to result in a lower survival in HIV patients.[5] While no changes in serum albumin levels or nPCR were found in our patients, an increase in net weight was shown, at least during the first year. However, 62% of patients were hypertensive at PD start, and two patients died from coronary disease. Some drugs, such as lopinavir, have been associated to an increase in systolic blood pressure,[28] other drugs such as fosamprenavir[29] to a lipid-lowering effect, and still others such as ritonavir have been associated to both effects.[30] NNRTIs and PIs usually have a poorer lipid profile and a higher risk of associated coronary disease.[31-33] Association of risk factors may be determinant for a decreased overall survival in these patients.

On the other hand, increased prevalence of these patients raises therapeutic alternatives that were unthinkable not long ago. Thus, kidney transplant is a valid option if the following requirements are met: HAART, undetectable viral load, CD4 count above 200 cells/mm^3, and absence of recent opportunistic infections.[25,34,35] In our case, a patient meeting the above criteria received a kidney transplant with an excellent outcome. Long-term outcome in these kidney transplant patients is unknown, but short and mid-term course appears safe, or at least with a similar survival to other risk groups.[36,37]

In conclusion, while our study has the limitations inherent to a retrospective study on a small patient sample, it showed an improved survival and low rates of infectious peritonitis and hospitalization. Adequate treatment of HIV infection and other associated diseases conditions the current outcome of the procedure, which is similar to the non-HIV population in our study. Immune status does not appear to change in PD, and adequate nutrition is possible. PD is therefore a treatment of choice for these patients. Until greater experience and additional studies are available, individualized and multidisciplinary control appears reasonable in these patients.

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