Daclizumab combined with mycophenolate mofetil and late onset of low dose tacrolimus as a therapeutic option for elderly donor-recipient pairs in kidney transplant

M. A. Gentil[1], A. Osuna[2], L. Capdevilla[3], C. Cantarell[3], P. Pereira[1], A. Mazuecos[4] and M. González Molina[5]

Spanish Study Group of Kidney Transplant from Elderly Donors. [1]Hospital Virgen del Rocío. Seville. [2]Hospital Virgen de las Nieves. Granada. [3]Hospital Vall d'Hebrón. Barcelona. [4]Hospital Puerta del Mar. Cádiz. [5]Hospital Carlos Haya. Málaga.

Nefrología 2008; 28 **(3)** 287-292

ABSTRACT

Background: *Nowadays, it is more frequent the use of kidneys from older donors in the renal transplantation. Moreover, it is also increasing the age of the recipients due to the ageing of the population treated with hemodialysis. This makes that recipients become older more commonly. This situation raises specific problems in the renal graft and in the recipient as well. In this manuscript we present the results of a multicenter study that analyzed an immunosuppressive strategy specifically designed to elderly renal transplant donor-recipients.*

Methods: *Patients ≥ 50 years were transplanted from donors ≥ 55 years. Immunosuppressive strategy consisted of daclizumab (2 doses of 1 mg/kg) in combination with steroids, mycophenolate mofetil (2 g/daily during the first 45 days and then adjusted according to local practice) and Tacrolimus. Tacrolimus was introduced between 5 and 7 day post-transplantation, adjusting the predose levels between 4-8 ng/mL. Mean follow-up was 12 months.*

Results: *A total of 133 patients were included in the study. Mean age of recipients and donors was 61.3 ± 6.2 years and 64.4 ± 5.3, respectively. 42.9% of patients needed dialysis during the first week (median 4 days). Between first month and first year, serum creatinine improved from 2.0 ± 1.0 mg/dl to 1.5 ± 0.4 mg/dl. Similar improvements were observed when creatinine clearance (Cockroft-Gault) was calculated. The survival of patient and renal graft at 12 months was 97.7% and 96.1%, respectively. The acute rejection rate was 13.5%. Security profile was good, as expected.*

Conclusions: *The Daclizumab and mycophenolate mofetil regimen with a late introduction of Tacrolimus at low doses is a good alternative in the elderly renal transplant recipients with a low immunologic risk.*

Key words: *Renal transplantation. Daclizumab. Tacrolimus. Mycophenolate mofetil. Older donor. Older recipient.*

Correspondence: *Miguel Á. Gentil Govantes*
Hospital Universitario Virgen del Rocío
Avda. Manuel Siurot, s/n
41013 Sevilla. España
mgentil@cica.es

RESUMEN

Antecedentes: **En la actualidad, es cada vez más común el uso de riñones procedentes de donantes añosos en el trasplante renal. También se incrementa la edad de los pacientes incluidos en las listas de espera, debido al envejecimiento progresivo de los pacientes sometidos a diálisis, por lo que con una frecuencia creciente, donante y receptor son ambos de edad avanzada. Esta situación plantea problemas específicos tanto en el órgano como en el receptor. Presentamos los resultados de un estudio multicéntrico que evalúa una pauta de inmunosupresión específicamente diseñada para la pareja donante-receptor añoso.**

Métodos: **Pacientes con edad ≥ 50 años fueron trasplantados con injertos de donantes ≥ de 55 años. El tratamiento inmunosupresor consistió en daclizumab (dos dosis de 1 mg/kg) en combinación con esteroides, Micofenolato Mofetil (2 g/día hasta el día 45, ajustándose después según la práctica de cada centro) y Tacrolimus. El Tacrolimus se introdujo entre el 5º y el 7º día posttrasplante, ajustado a niveles de predosis a 4-8 ng/mL. Se realizó un seguimiento de 12 meses.**

Resultados: **Se incluyeron 133 pacientes. La media de edad de los receptores fue de 61,3 ± 6,2 años y la de los donantes de 64,4 ± 5,3. El 42,9% de los pacientes requirieron diálisis en la primera semana con una mediana de duración de 4 días. Entre el primer mes y el primer año la creatinina mejoró desde 2,0 ± 1,0 mg/dl hasta 1,5 ± 0,4 mg/dl respectivamente. Los aclaramientos de creatinina calculados (Cockroft-Gault) evolucionaron en paralelo. La supervivencia del paciente y el injerto a los 12 meses fue del 97,7% y 96,1% respectivamente. La tasa de rechazo agudo fue del 13,5%. El perfil de seguridad fue bueno y se ajustó al esperado.**

Conclusiones: **La pauta Daclizumab y Micofenolato Mofetil con introducción tardía de Tacrolimus a dosis bajas es una buena opción terapéutica para receptores añosos de bajo riesgo inmunológico.**

Palabras clave: Trasplante renal. Daclizumab. Tacrolimus. Micofenolato Mofetil. Donante añoso. Receptor añoso.

INTRODUCTION

Kidney transplant (KT) is the treatment of choice for patients with end-stage chronic renal failure because it improves survival and quality of life in both young and older patients.[1,2]

The proportion of patients aged > 50 years in waiting lists for kidney transplant has gradually increased due to both aging of the population on dialysis and the results obtained with transplant in elderly recipients, with patient survival of 80%-90% and 70% and organ survival of 80% and 55%-60% at 1 and 5 years respectively.[3] The increase in organ demand, combined with a stagnant number of patients and an increase in the mean age of donors, has led to a growing acceptance of organs from elderly donors.[4]

Reluctance to use kidneys from elderly donors were based on age-related structural and functional changes that make them more susceptible to ischemia-reperfusion damage, resulting in a greater proneness to delayed graft function and acute interstitial rejection.[3] Moreover, once the acute rejection episode has occurred, the capacity to develop a reparative response to lesions is decreased.

In addition, the lower metabolic demand characterizing elderly recipients allows for the decreased mass of kidneys from elderly donors to be sufficient to meet their needs, while their decreased immunological response reduces the risk of acute rejection.[5,6] Because of this, kidneys from elderly donors tend to be used in elderly recipients. A better survival has also been attributed to elderly kidneys when implanted into older recipients, though this finding has not been confirmed.[7]

Calcineurin inhibitors (CNIs) currently used as the basis of immunosuppressant therapy at full doses and from treatment start may worsen the incidence and duration of delayed renal function and increase the risk of acute nephrotoxicity.[8] Regimens with low doses of these drugs or even without them are therefore being under continued research,[9-11] and have shown acceptable acute rejection rates and a good preservation of kidney function. Such regimens with no CNIs or CNIs at reduced doses mainly rely on use of induction with antibodies[12,13] and/or use of full doses of MMF[14] and/or sirolimus.[15]

While a great interest exists in establishing which is the most adequate immunosuppression for KTs from elderly donors to recipients, little information is currently available. This article reports the final results of a prospective, multicenter, open label, uncontrolled study conducted in 13 Spanish centers to assess whether use of anti-IL-2R antibodies combined with MMF could provide adequate protection to delay CNI start and reduce their dose levels as an immunosuppression regimen specifically proposed for the elderly donor-elderly recipient pair. This study supports the previously published preliminary analyses.[16,17]

MATERIALS AND METHODS

The purpose of the study was to assess the efficacy of immunosuppressive treatment both in terms of kidney function and acute rejection rate. The safety profile of treatment was also assessed.

Enrolled patients should have ≥ 50 years of age and be recipients of a single organ (kidney) from a donor aged ≥ 55 years. Recipients from living donors or organs with a cold ischemia time > 30 hours, and patients with a RAP > 25% within 6 months of entry were excluded. Patients with leukocyte counts < 2.5 x 10^9/L, platelet counts < 100 x10^9/L, or hemoglobin values < 6 g/dL were also excluded. Patients who got over the first early postoperative days were finally enrolled. Nine scheduled visits were performed in a 12-month follow-up period.

Pre-transplant assessment included donor and recipient demographic data, patient clinical history, histocompatibility, cold ischemia, complete laboratory tests, and vital signs. The same clinical and laboratory parameters were monitored at the nine visits after transplant. Adverse effects, immunosuppression and dose used, tacrolimus trough levels, and MPA levels (if their measurement was a standard practice at the center) were also recorded. Kidney function was estimated based on serum creatinine and creatinine clearance (Cockcroft-Gault). If no medical contraindications existed, all acute rejection episodes had to be confirmed by biopsy, and treatment was administered according to the standard practice at each center.

Delayed kidney function was defined as the need for dialysis within one week of transplant.

The immunosuppressive treatment of the study consisted of daclizumab combined with MMF, tacrolimus, and steroids. Patients were given two doses of daclizumab 1.0 mg/kg (maximum 100 mg). The first dose was administered within 6 hours of the start of transplant surgery (study day 0), and the second dose on day 14. The MMF dose was 2 g daily by the oral route (1 g every 12 hours) up to day 45 of the study, after which it was adjusted based on the clinical judgment of each center. The initial dose of tacrolimus was 0.1 mg/kg/day, and was administered between days 5 and 7 after transplant in the event of stabilization of kidney function (creatinine levels under 3.0 mg/dL or creatinine clearance > 10 mL/min), and never later than 7 days after the transplant. Dosage was adjusted to achieve target trough levels ranging from ≥ 4 and ≤ 8 ng/mL. Tacrolimus was administered twice daily. As regards steroids, methylprednisolone 250 mg was administered at the time of surgery, and its dose was tapered as follows: day 1: 125 mg IV/24 hours; days 2-14: 20 mg/24 hours; days 15-30: 15 mg/24 hours; days 31-90: 5-10 mg; and days 91-360: according to the practice at each center. Prophylactic treatment against cytomegalovirus and *Pneumocystis carinii* using the regimen established at each center was recommended.

Statistical analysis

SPSS version 11.0 software was used for descriptive and inferential data analyses. An intention-to-treat analysis was performed.

The main endpoint (rate of acute rejection episodes) was analyzed using absolute and relative frequencies. Mean rejection-free time was calculated using the Kaplan-Meier model. All other variables were described using absolute and relative frequencies for qualitative parameters and mean, standard deviation, median, and interquartile range for quantitative parameters.

For statistical tests between different variables studied at two different times (at baseline and one year after transplant), a two-sided Student's t test for related samples was used. A value of $p < 0.05$ was considered statistically significant.

RESULTS

A total of 133 patients were enrolled into the study. Sixty-four percent of donors and 60% of recipients were males. Mean age of recipients and donors was 61.3 ± 6.2 years and 64.4 ± 5.3 years respectively. The cause of death of donors was vascular in 88% of cases. High blood pressure (HBP) and diabetes were found in 35.3% and 11.3% of donors respectively, while the corresponding proportions in recipients were 61.7% and 6.1%.

Mean creatinine before patient death was 1.1 ± 0.5 mg/dL. Mean cold ischemia time was 18.2 ± 5.7 hours. Twelve recipients had ischemic or peripheral heart disease or had undergone revascularization procedures, and 22 patients had other clinical heart diseases. Eight patients had a history of cancer.

No donor was positive for the hepatitis B and C viruses. A single recipient was positive for the hepatitis B virus (0.8%), and 9 recipients were positive for the hepatitis C virus (6.7%). Ninety-one percent of recipients had a positive serology for cytomegalovirus, and 9% of grafts were from donors with positive serology to recipients negative for cytomegalovirus.

Among the 133 patients enrolled, 123 completed the year of follow-up scheduled in the study. Four deaths (1 due to pyelonephritis, 2 sudden deaths, and 1 from an unknown cause), 2 graft losses (1 from primary renal failure and 1 from acute rejection), and 4 dropouts for other reasons occurred during follow-up.

Twelve-month survival was 97.7% for patients, 96.1% for grafts, and 98.5% in the case of graft survival censored for death.

Compliance with the immunosuppression protocol was very high in the case of daclizumab. Patients received two administrations, with a mean interval of 14.0 ± 0.9 days. Both the pre-transplant and the second doses were of 1.0 ± 0.1 mg/kg.

For MMF, the mean dose on day 7 was virtually 2 g/day (1.96 ± 0.18 g/day), but dose was reduced in many cases, so that at the end of the first study month only 53 patients (of the 130 patients who continued in the study at that time) continued to receive 2 g daily of MMF, while the mean dose in the overall population was 1.5 g/day. Dose reduction continued over the rest of the year, so that 12 months after the transplant no patient received 2 g/day, 14 patients were given a dose higher than 1 g/day, 65 patients 1 g/day, and lower doses were administered to all other patients. MPA levels were available in 71 patients. Mean levels were 4.3 ± 2.9 µg/mL on post-transplant day 7 and 3.6 ± 2.0 at one month, and mean levels ranging from 2.87 ± 1.6 (month 2) and 2.63 ± 1.7 (month 12) were found for the rest of the year.

A good compliance was found as regards time of start of tacrolimus, with a time to administration of the first dose of 5.5 ± 1.4 days. The initial dose was 6.3 ± 2.4 mg. At the time tacrolimus was started, mean serum creatinine levels were 5.3 ± 2.9 mg/dL, and creatinine clearance 19.9 ± 13.3 mL/min. A poorer compliance was seen with regard to maintenance of target levels during the study. There was a trend throughout the study to exceed the established range of trough levels, but with a tendency to range adjustment towards the end of the year (fig. 1). One month after transplant, 56 patients (44%) maintained ranges within the study objectives, but this number increased up to 78 patients at 12 months (66%). Tacrolimus was not discontinued in any case.

At the end of first year, 93.9% of patients were taking steroids at a mean dose of 5.1 ± 1.2 mg/day.

Fifty-seven patients required dialysis during the first week (42.86%). Median functional delay time was 4 days, and only 7 patients required hemodialysis for longer than two weeks (fig. 2).

Creatinine levels improved to 2.0 ± 1.0 mg/dL at month 1 and 1.7 ± 0.6 mg/dL at month 2. No functional impairment was seen during the first year, and there was even a slight improvement to 1.57 ± 0.4 mg/dL at the end of the year (fig. 3). Creatinine clearance, estimated using the Cockcroft-Gault formula, followed a parallel course: 42.8 ± 15.0 and 46.5 ± 14.5 mL/min at 1 and 2 months, with an increase to 52.6 ± 16.4 mL/min at the end of the year.

Nineteen acute rejection episodes occurred in 18 patients (13.5%). Fourteen of these episodes were confirmed by biopsy (9.8% of all patients). According to Banff-97 classification, rejection severity was borderline in 1 patient, grade 1A in 5, grade 1B in 5, and grade 2A in 3 patients. Complete and partial treatment responses were seen in 3 and 2 respectively of the 5 clinically diagnosed cases (in which no biopsy was performed due to technical problems). Antibodies (thymoglobulin) were only used in one patient. The rejection-free (confirmed by biopsy) survival curve was 90% at 12 months.

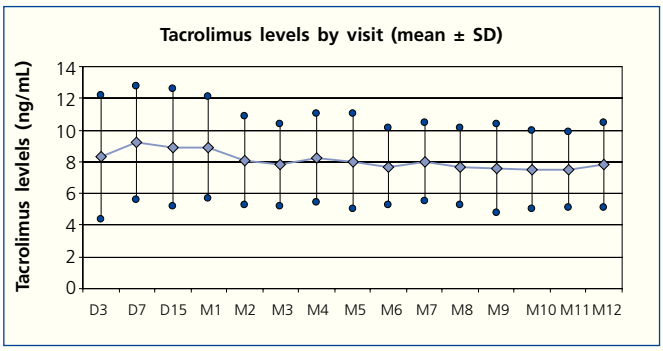

Figure 1. Graph of tacrolimus levels by visit.

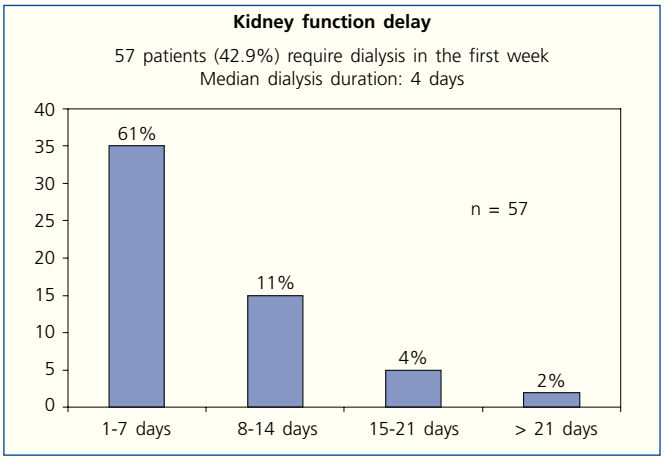

Figure 2. Delay in kidney function.

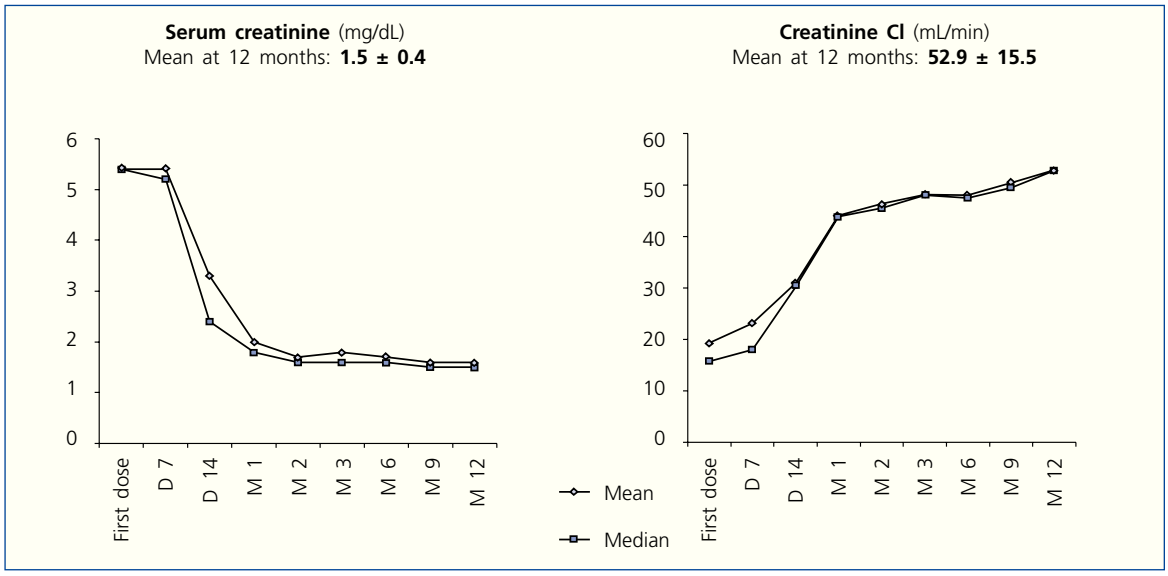

Figure 3. Kidney function over time.

No significant changes occurred in glucose levels during the study year. Mean glucose levels were 111.6 ± 56.2 mg/dL at baseline and 106.1 ± 40.6 mg/dL after the year of follow-up. Variables related to lipid profile showed a slight impairment in total cholesterol values from baseline to one year after treatment (182.9 ± 55.6 *vs* 199.9 ± 41.3 mg/dL, p < 0.01). Increases were also seen in LDL cholesterol (109.3 ± 44.0 *vs* 120.1 ± 37.9 mg/dL, p = NS) and HDL cholesterol levels (47.0 ± 16.3 mg/dL *vs* 57.7 ± 17.7, p < 0.001). There was a non-significant reduction in triglyceride levels (145.7 ± 81.6 *vs* 132.0 ± 62.4 mg/dL). Hemoglobin values increased from baseline to one year after transplant (12.5 ± 2.4 *vs* 13.7 ± 2.9 mg/dL, p < 0.05), as did leukocyte count (7.1 ± 1.9-7.7 ± 2.6 x 10^3/mm^3, p < 0,05).

Adverse events occurring in > 5% of patients included diarrhea (7.1%), anemia (6.5%), edema (4.8%), and leukopenia (4.5%). Event severity was mild in 54% of cases, moderate in 35.5%, and severe in 8.1%, while the event was life-threatening in 1.7% of cases. No severity data were available for 0.7% of cases.

Some infection occurred in 79.7% of patients, with a mean of 3 ± 2.3 infections per patient. Urinary tract infections (49.2%) and respiratory infections (17.1%) were most common. Among infections, 58.6% were bacterial in origin, 14% viral (of which approximately a half were caused by cytomegalovirus), and 3.1% fungal. No information was available about the origin of 24% of infections. Fourteen patients experienced a total of 23 severe infections.

No cases of cancer were reported. Fifteen patients (12%) developed diabetes *de novo* after the transplant, and another 8 patients (7.2%) showed at any time altered glucose levels.

DISCUSSION

The increased mean age of both donors and recipients of kidney transplants has required the development of specific approaches.[18] Attempts have therefore been made to find new approaches in immunosuppressive therapy having an adequate intensity to prevent acute rejection episodes associated to delayed kidney function (characteristics in older kidneys), but avoiding the risk of overimmunosuppression and nephrotoxicity, which is increased in these patients.

The Eurotransplant Senior Programme developed a scheme for allocating organs from donors aged > 65 years to recipients aged > 65 years. The 5-year results of this scheme support its success[19,20] by showing a 43% increase in the availability of elderly donors and a reduction in waiting times for elderly recipients, with graft survival rates at 3 years of transplant as good as for HLA-matched transplants (64% *vs* 67%).

However, the type of immunosuppression plays an essential role in the success of transplants of grafts from elderly donors into elderly recipients. Use of anti-CD25 has been shown to be highly effective for reducing acute rejection, improving graft survival without impairing the safety profile.[13] In particular, daclizumab has been shown to be able to allow for use of regimens with reduced CNI or corticosteroid dosages[21] after the initial attempt by Vincenti et al to administer it for allowing use of a CNI-free regimen.[22] In our study, a two-dose regimen was used because of the long half-life of the drug (approximately 20 days). Vincenti et al[23] found that two daclizumab doses maintained drug levels higher than 1 µg/mL until day 59 after transplant. In a study in pancreas-kidney transplant, use of two daclizumab doses was seen to be associated to the lowest acute rejection rates, the highest rejection-free survival rate, and the lowest graft loss.[24]

As regards combination of daclizumab with low doses of tacrolimus, Kuypers et al,[25] using a very similar regimen to the one used in our study, found similar results in terms of acute rejection, renal function, and patient and graft survival. However, as these authors did not apply any restriction on transplant donor and/or recipient age, their data about frequency of patients with delayed kidney function were different from those found in our study. Our results in terms of

kidney function delay are much more in agreement with those reported by Pallet et al[26] in a retrospective study conducted in patients who received kidneys based on expanded donation criteria[27] and were treated with immunosuppression consisting of antibodies (ATG or basiliximab), high MMF doses (3 g/day), Csa, and steroids.

As is known, reduction in CNI doses is an objective in the general population of transplant patients and particularly in elderly subjects, in whom, as established by Land et al,[28] use of CNIs should be avoided because they induce oxidative stress, while use of inhibitors of inosine monophosphate dehydrogenase such as MMF, that decrease oxidative stress, should be promoted. In addition, long-term use of CNIs impairs some cardiovascular risk factors such as HBP, diabetes, or hyperlipidemia, and increases the risk of tumor development (particularly lymphoma and skin cancer).[29,30]

In the general population, early randomized studies aimed at CNI reduction and/or discontinuation, relying on use of MMF, demonstrated the benefits of Csa reduction/discontinuation on patient kidney function.[31,32] The five-year results of the study proposing Csa discontinuation in patients with triple Csa+MMF+steroid therapy[33] showed how definitive withdrawal of the CNI was associated to higher acute rejection rates and slightly lower survival figures, though kidney function was better in the group not receiving CNI.

Land et al recently reported the results of a study in 89 elderly recipients of kidneys from elderly donors in whom a CNI-free regimen was used.[34] A higher rejection rate was found as compared to our study, but very good results were reported in terms of both kidney function and patient and graft survival. It appears obvious that the benefits of use of reduced CNI doses supported by use of antibodies and MMF are superior to total CNI withdrawal, and new regimens are therefore based on quadruple therapy using reduced doses of CNIs: antibodies + MMF + low CNI doses + steroids, or in addition of sirolimus as a new potentially non-nephrotoxic immunosuppressive agent.

In the search for regimens with a reduced nephrotoxicity, an increasing number of studies have been published in which sirolimus is added to the regimen, in all cases combined with MMF and steroids.[35,36] Data relating to use of sirolimus in recipients of organs from marginal donors have been reported in two small studies.[37,38] The fact that sirolimus has been little investigated in elderly patients could be related to the fear of its impact on recovery from ischemia-reperfusion damage, established in animal models and confirmed in small clinical studies.[39] Virtually all studies using sirolimus and MMF concluded that better results are obtained in terms of kidney function, with acceptable acute rejection rates and a similar or better safety profile, though the recently reported data from the Symphony study[40] showed results that significantly qualify the conclusions of prior studies.

Based on the data discussed and in our study result, it appears that our selected immunosuppressive regimen, consisting of two 1 mg/kg doses of daclizumab combined with MMF 2 g/day and steroids, late onset of tacrolimus (days 5-7), and maintenance of low levels during follow-up (trough levels of 4-8 ng/mL) represents a good option for immunosuppression in the elderly donor-elderly recipient pair, despite the difficult for maintaining full doses of MMF (2 g/day) and low doses of tacrolimus (with an existing trend to lower the MMF dose and increase CNI levels, possibly out of conservatism). This partial success in treatment compliance —the objective of low tacrolimus levels was only maintained over time in a fraction of the group— is a limitation shared by other minimization studies, such as Symphony. On the other hand, it should be agreed that our study has clear methodological limitations, particularly its uncontrolled, open nature, that prevented an adequate comparative assessment *versus* immediate start of CNIs. Moreover, the form of recruitment may have excluded cases of intraoperative thrombosis, which are not exceptional in this type of donor-recipient pairs. Despite these limitations, however, our study achieved good mean survival and kidney function results considering the characteristics of donors (advanced mean age, death from predominantly cardiovascular causes, and a high frequency of HBP and diabetes) and recipients (elderly subjects also, representing a higher risk population as compared to the general transplant patient population), but it should not be forgotten that relatively low rates of diabetes and vascular nephropathy could suggest a positive selection among dialysis patients of this age group. While a high incidence of delayed graft function was found, it should be noted that the delay tended to be short in duration, with a median delay of 4 days, thus minimizing its negative impact on patient management. Finally, safety data were as expected. Particular mention should be made of the low incidence of adverse effects traditionally related to the tacrolimus + MMF combination: *de novo* diabetes after transplant in 12% of patients, diarrhea in 7.1%, anemia in 6.5%, and CMV infection in 7.5% or patients.

ABBREVIATIONS

CNI: *Calcineurin inhibitor.* Csa: *Cyclosporin.* HBP: *High blood pressure.* KT: *Kidney transplant.* MMF: *Mycophenolate mofetil.* RAP: *Reactive antibody panel.*

REFERENCES

1. Morrissey PE, Yango AF. Renal transplantation: older recipients and donors. *Clin Geriatr Med 2006;* 22 (3): 687-707.
2. Danovitch G, Savransky E. Challenges in the counseling and management of older kidney transplant candidates. *Am J Kidney Dis* 2006; 47 (4 Supl. 2): S86-97.
3. Fijter JW. The impact of Age on rejection in kidney transplantation. Review article. *Drugs aging* 2005; 22 (5): 433-49.
4. Faenza A, Sestigliani E, Zanbianchi L, Ridolfi l. Utilization of suboptimal kidney donors. *Transplantation proceedings* 2004; 36 (3): 485-487.
5. Selke-AR, Filatekov A, Jurisch A, Denecke C, Martins PNA, Pascher A. Grafts from elderly donors elicit a stronger Immune Response in the early period post transplantation: a study in a rat model. *Transplantation proceedings* 2005; 37 (1): 382-83.
6. Bradley BA. Rejection and recipient age. *Transpl Immunol* 2002; 10 (2-3): 125-32.
7. Registre de malalts renals de Catalunya. Informe stadístic 2004. Servei Català de la Salut. ISBN 84-393-7171-3, 2006.
8. Olyaei AJ, De Mattos AM, Bennett WM. Nephrotoxicity of immunosuppressive drugs: new insight and preventive strategies. *Curr Opin Crit Care* 2001; 7 (6): 384-89.
9. Grinyo JM, Cruzado JM. Steroid or calcineurin inhibitor-sparing immunosuppressive protocols. *Contrib Nephrol* 2006; 146: 30-42.

10. Lo A. Strategies to prevent chronic allograft nephropathy in kidney transplantation: focus on calcineurin inhibitors. *Prog Transplant* 2004; 14 (2): 157-64.
11. Fischereder M, Kretzler M. New immunosuppressive strategies in renal transplant recipients. *J Nephrol* 2004; 17 (1): 9-18.
12. Carswell CI, Plosker GL, Wagstaff AJ. Daclizumab: a review of its use in the management of organ transplantation. *BioDrugs* 2001; 15 (11): 745-73.
13. Nashan B. Antibody induction therapy in renal transplant patients receiving calcineurin-inhibitor immunosuppressive regimens: a comparative review. *BioDrugs* 2005; 19 (1): 39-46.
14. Titte R Srinivas, Jesse D Schold and Herwig- Ulf Meier- Kriesche. Mycophenolate mofetil: long-term outcomes in solid organ transplantation. *Expert Rev Clin Immunol* 2006; 2 (4): 495-518.
15. Kuypers DR. Benefit-risk assessment of sirolimus in renal transplantation. *Drug Saf* 2005; 28 (2): 153-81.
16. Osuna A, Gentil MA, Capdevila L, Cantarell C, Mazuecos A, Pereira P et al. Two doses of daclizumab with delayed introduction of low-dose tacrolimus in elderly recipients of cadaveric renal transplants from donors > 55 years of age. *Transplant Proc* 2005; 37 (3): 1438-40.
17. Gentil MA, Osuna A, Capdevila L, Rodríguez-Algarra G, Cantarell C, Pereira P et al. Safety and efficacy of delayed introduction of low-dose tacrolimus in elderly recipients of cadaveric renal transplants from donors over 55 years of age. *Transplant Proc* 2003; 35 (5): 1706-08.
18. Meier-Kriesche HU, Kaplan B. Immunosuppression in elderly renal transplant recipients: are current regimens too aggressive? *Drugs Aging* 2001; 18 (10): 751-59.
19. Smits JM, Persijn GG, Van Houwelingen HC, Claas FH, Frei U. Evaluation of the Eurotransplant Senior Program. The results of the first year. *Am J Transplant* 2002; 2 (7): 664-70.
20. Prospective age-matching in elderly kidney transplant recipients- A 5-year analysis of the Eurotransplant Senior Program. *Transplantation* 2006; 15; 82 (1 Supl. 2): 141.
21. Carswell CI, Plosker GL, Wagstaff AJ. Daclizumab: a review of its use in the management of organ transplantation. *BioDrugs* 2001; 15 (11): 745-73.
22. Vincenti F, Ramos E, Brattstrom C, Cho S, Ekberg H, Grinyo J et al. Multicenter trial exploring calcineurin inhibitors avoidance in renal transplantation. *Transplantation* 2001; 71 (9): 1282-87.
23. Vincenti F, Pace D, Birnbaum J, Lantz M. Pharmacokinetic and pharmacodynamic studies of one or two doses of daclizumab in renal transplantation. *Am J Transplant* 2003; 3 (1): 50-52.
24. Stratta RJ, Alloway RR, Hodge E, Lo A. A multicenter, open-label, comparative trial of two daclizumab dosing strategies *vs* no antibody induction in combination with tacrolimus, mycophenolate mofetil, and steroids for the prevention of acute rejection in simultaneous kidney-pancreas transplant recipients: interim analysis. *Clin Transplant* 2002; 16 (1): 60-68.
25. Kuypers DRJ, Evenepoel P, Maes B, Coosemans W, Pirenne J, Vanrenterghem Y. The use of an anti-CD25 monoclonal antibody and mycophenolate mofetil enables the use of a low dose tacrolimus and early withdrawal of steroid in renal transplant patients. *Clin transplant* 2003; 17 (3): 234-41.
26. Pallet N, Anglicheau D, Martínez F, Mamer MF, Legrendre C, Thervet E. Comparison of sequential protocol using basiliximab *versus* antithymocyte globulin with High dose Mycophenolate Mofetil in recipients of a kidney graft from an expanded criteria donor. *Transplantation* 2006; 81 (6): 949-52.
27. Ojo AO, Heinrichs D, Emond JC, McGowan JJ, Guidinger MK, Delmonico FL et al. Organ donation and utilization in the USA. *Am J Transplant* 2004; 4 Supl. 9: 27-37.
28. Land WG. Ageing and immunosuppression in kidney transplantation. *Exp Clin Transpant* 2004; 2 (2): 229-37.
29. Flechner SM. Minimizing Calcineurin Inhibitor Drugs in Renal Transplantation. *Transplantation proceedings* 2003; 35 (Supl. 3A): S118-S21.
30. Herwig-Ulf-Meier-Krische. Mycophenolate mofetil- based immunosuppressive minimization and withdrawal strategies in renal transplantation: possible risks and benefits. *Curr Opin Nephrol Hypertens* 2006; 15 (Clinical Updates): S1-S5.
31. Abramowicz D, Manas D, Lao M, Vanderenterghem Y, Del Castillo D, Wijngaard P et al. Cyclosporine withdrawal from a mycophenolate mofetil containing immunosuppressive regimen in stable kidney transplant recipients: a randomized controlled study. *Transplantation* 2002; 74 (12): 1725-34.
32. Dudley C, Pohanka E, RIAD H, Dedochova J, Wijngaard P, Sutter C et al. Mycophenolate Mofetil Creeping creatinine Study group. *Transplantation* 2005; 79 (4): 466-75.
33. Abramowicz D, Del Carmen Rial M, Vitro S, Del Castillo D, Manas D, Lao M et al. Cyclosporine withdrawal from a mycophenolate mofetil containing immunosuppressive regimen. Results of a prospective randomized study. *Transplantation* 2003; 75 (12): 2159.
34. Arbogast H, Huckelheim H, Schneeberger H, Illner WD, Tarabichi A, Fertmann J et al. A calcineurin antagonist-free induction/ maintenance strategy for immunosuppression in elderly recipients of renal allografts from elderly cadaver donors: long-term results from a prospective single centre trial. *Clin Transplant* 2005; 19 (3): 309-15.
35. Flechner SM, Kurian SM, Solez K, Cook DJ, Burke JT, Rollin H et al. De novo kidney transplantation without use of calcineurin inhibitors preserves renal structure and function at two years. *Am J Transplant* 2004; 4 (11): 1776-85.
36. Lo A, Egidi MF, Gaber LW, Amiri HS, Vera S, Nezakatgoo N et al. Comparison of sirolimus-based calcineurin inhibitor-sparing and calcineurin inhibitor-free regimens in cadaveric renal transplantation. *Transplantation* 2004; 77 (8): 1228-35.
37. Pisani F, Buonomo O, Iaria G, Iorio B, Rizzello A, Pollicita S et al. Sirolimus in kidney transplantation from marginal donors. *Transplant Proc* 2004; 36 (3): 495-96.
38. Shaffer D, Langone A, Nylander WA, Goral S, Kizilisik AT, Helderman JH. A pilot protocol of a calcineurin-inhibitor free regimen for kidney transplant recipients of marginal donor kidneys or with delayed graft function. *Clin Transplant* 2003; 17 Supl. 9: 31-34.
39. Knight RJ, Kahan BD. The place of sirolimus in kidney transplantation: can we reduce calcineurin inhibitor renal toxicity? *Kidney Int* 2006; 70 (6): 994-99.
40. Ekberg H, Tedesco-Silva H, Demirbas A, Vitko S, Nashan B, Gurkan A y cols.; ELITE-Symphony Study. Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med* 2007; 357 (25): 2562-75.