See original article on page 446

Importance of elderly donors as a source of valid organs for renal transplantation: where is the limit?

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In the current issue of Nefrología, Dr Gonzalez Roncero et al,[1] all of whom are members of a study group of thirteen transplant hospitals, present their results regarding the long-term evolution of 133 kidney grafts from expanded criteria donors.

In this study, immunosuppression was used with two doses of daclizumab, mycophenolate mofetil, normal steroid doses, and late introduction of tacrolimus. They present the 5-year evolution of patients that reached one year of graft survival in a study that initially used a prospective design, whose results were published in 2008 in this same journal. The continuation of follow-up with these patients is of great interest, since it is a multi-centre study with an originally prospective study design and shows 5-year results, information that is not commonly presented in the medical literature for these types of donors.

In addition, this article is of special application in Spain, where the age and comorbidity of donors has increased substantially in the past two decades, donor age increasing from 34 years in 1992 to 57 years in 2010. Currently, more than 50% of donors are older than 60 years, and many of them have associated comorbidity, such as diabetes or arterial hypertension.[2]

As a consequence of these changes in donor characteristics, the scenario surrounding kidney transplants has shifted notably in recent decades.

At the end of the 1990's and the start of the new millennium, published studies focused primarily on two different aspects: the indications for transplants in elderly recipients, and the evolution of grafts in elderly recipients regardless of the age of the donor.

The indications for kidney transplants in elderly renal failure patients on dialysis was established in a study (among others) by Wolfe et al,[3] which compared the mortality of recipients of standard organs, those receiving marginal organs, and those who remained on the kidney waiting list. In their statistical analysis, the authors concluded that the mean expected survival rate was 5 years higher in transplant recipients as compared to those who remained on the wait list.[3-5]

In the analysis of the evolution of kidney transplants in elderly recipients, regardless of the type of donor, the article published by Waiser et al is especially interesting. They evaluated the 8-year survival of 1269 patients, 176 of which received kidneys from donors older than 55 years (132 were placed in elderly recipients and 44 in young recipients). The relative risk of graft loss after 8 years was 1.97 times higher in young recipients than in recipients >55 years.[6] The cause of graft loss in young patients was primarily acute rejection (33.7%) and chronic rejection (24%).

Once the safety and efficacy of transplants in elderly recipients was established, and it was shown that the primary cause of graft loss in these patients was death with a functioning transplant, the majority of transplant teams expanded their criteria for organ donors under the "old for old" policy, in which elderly recipients received organs from expanded criteria donors. This policy is reasonable, since organ survival is not so important in elderly recipients as in young recipients.[7-12]

Graft survival rates are worse in expanded criteria kidneys due to structural changes in kidneys that come with age. These alterations include glomerulosclerosis, interstitial fibrosis, tubular atrophy, and vascular damage,

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which make them more sensitive to ischaemia and reperfusion damage. In addition, they have a higher rate of acute tubular necrosis (ATN) than those of young donors, and higher sensitivity to calcineurin inhibitor-related nephrotoxicity. Furthermore, these kidneys have worse renal function one month following transplantation, donor age being the main risk factor for decreased glomerular filtration rate.[10-12]

Experimental studies performed in rats have suggested that acute failure is more probable in older kidney transplants; however, these experimental data have produced contradictory results in human studies.[13-15]

Other characteristics of elderly recipients include metabolic changes that can induce differences in the pharmacokinetics of immunosuppressants and other drugs, more cardiovascular risk factors and immune system alterations, making patients more susceptible to infections and tumours.[16,17] In fact, in the study by Gonzalez-Roncero et al[1] previously mentioned, 7 of the 10 deaths were due to tumours.

All of these physiological changes in elderly donors and recipients have generated substantial interest in achieving optimal immunosuppression when organs are derived from elderly donors in all transplant recipient groups.

In the majority of these studies, induction therapy is used with early introduction of calcineurin inhibitors at lower doses than in standard donors, or, as in the case we are focusing on, with calcineurin inhibitors starting a few days after transplantation.[1,15,18-26]

Other groups have opted to avoid calcineurin inhibitors altogether, using instead high induction doses with proliferation signal inhibitors or mycophenolate mofetil directly following transplantation.[27,28]

Unfortunately, we lack prospective randomised studies that might definitively establish an optimal immunosuppression regimen in this group of donors/recipients, who require such a delicate equilibrium between immunosuppression and immunocompetence. This is due to the fact that the majority of clinical trials have excluded elderly recipients in order to avoid the side effects associated with the characteristics of these recipients.

Treatment protocols that do not include calcineurin inhibitors, such as that described by Abrogast and Guba,[27,28] may cause an excessive rate of acute rejection, higher than 50%. This study's protocol was based on high initial induction doses of thymoglobulin at 4mg/kg/day on day zero and two doses of basiliximab followed by high steroid and mycophenolate doses, which did not reduce the rate of ATN or provide benefits in terms of mid-term patient or graft survival.[28]

In protocols involving late introduction of calcineurin inhibitors (which range between 3 and 7 days), the rate of acute rejection is acceptable, and graft and patient survival rates are adequate.[19,20,22,25] In the study published in this issue,[1] the acute rejection rate was 13%, and patient and graft survival rates adjusted for patient death after one year of follow-up were 97.7% and 96.1%, respectively, some of the highest rates published in the medical literature.[20]

One particularly interesting result of this study was the low rate of acute rejection when using two doses of daclizumab, a drug that was initially designed for use in five doses, which without a doubt has considerably decreased the initial costs of treatment for this condition, without increasing the rate of acute rejection.

In this study, the results after 5 years were also good, with patient survival at 93.3% and graft survival at 93.8% (adjusted for patient death). This could be due to close follow-up of patients in this study, with a very strict control of cardiovascular risk factors, since at the end of the follow-up period, 92% of patients received antihypertensive drugs, 63% statins, 18.4% erythropoietin, and 15% oral anti-diabetics or insulin. This very close clinical surveillance, along with low doses and low blood levels of tacrolimus over the 5-year follow-up period, undoubtedly contributed to the good results obtained.

In our hospital, we use a regimen based on induction with basiliximab in two doses, early introduction of calcineurin inhibitors (day +1 post-transplant) at one-half the normal dose, and low target levels. We analysed graft and patient survival in especially elderly donors (older than 70 years). These data were published by Galeano et al[26] and showed an acute rejection rate (8.5%) and ATN of 38.5%. Compared with donors aged 50-70 years, very elderly donors do not show a higher rate of acute rejection or ATN. Graft survival rates without adjusting for death are similar between recipients from donors aged 50-70 years and recipients from donors older than 70 years, with evidently higher mortality rates in the group of older recipients.[26]

The Table summarises the initial immunosuppression treatment, donor and recipient age, incidence of ATN, incidence of acute rejection, and patient and graft survival after 1 and 5 years in elderly recipients in selected articles. It is evident in articles published in recent years that donor and recipient age is very advanced, and is notably higher than in the article published in this issue.[1]

In the studies by Foss, Collini, Favi, and Galeano,[23-26] taking into account the advanced age of both donors and recipients, patient and graft survival rates were adequate and, in comparison to articles published at the start of the new millennium, the mean age of donors and recipients has increased without having established an age limit for donors or recipients.

Tabla 1. Immunosuppression and evolution of organs from elderly donors

Author, year, reference	N Age D/R	IS	Ci	LI	AR (%)	ATN (%)	PS 1 year (%)	GS 1 years (%)	PS 5 years (%)	SI 5 years (%)
Arbogast 2005[27]	30 66.8 63.8	ATG MMF Esteroids	No		23.6				69.8	87.9[a]
Emparan C 2004[19]	15 72 67	Basiliximab Cs	Yes	Cr < 3	6		100	100		
Gentil MA 2008[20]	133 61.3 64.4	Daclizumab MMF Tacrolimus	Yes	Yes 5-7 days	13	42.9	97.7	96[a]		
Smits 2002[21]	227 70 -	Variable	-	-	40	41	86	79		50
Frei 2008[29]	1406 70.2 -	Variable	-	-	37	29.7	86	79	60	
Palomar 2002[30]	88 - > 60		Yes		33.4	29	96	78		
Fritsche 2003[9]	69 67.9 71.2	ATG (71%) Cs/Tacrolimus Aza/MMF	93%	No	43		85	83		
Stratta 2006[22]	37 DCE 65	Timoglobulina or alentuzumab Tacrolimus MMF	Yes	Yes			89[b]	84[b]		
Bodingbauer 2006[15]	56 DCE	Timoglobulin or basiliximab MMF Esteroids	Yes						71	52
Guba 2008[28]	56 DCE	ATG 4 mg/kg day 0 Basiliximab days 0 and 4 MMF Esteroids	No		53.6	44.6	89.3	85.4		
Foss 2009[23]	54 77.5 70.1	Baxiliximab Tacrolimus MMF Esteroids	Yes	No		57.9	81	87[c]	59	83[c]
Collini 2009[24]	38 > 75 22 double tx	Baxiliximab Ac + MMF o sirolimus	Yes	No			81.2	73.7		
Favi 2010[25]	20 >75	Baxiliximab + Timoglobulin 200 + Ac[a] Esteroids	Yes	Yes Day 4	0		95[d]	95[d]		
Galeano 2010[26]	70 > 70 65.7	Baxiliximab Tacrolimus MMF Esteroids	Yes	No	8.5	38.5	90	81	86	70

Ci: calcineurin inhibitors; Aza: azathioprine; Cr: creatinine (mg/dl); Cs: cyclosporine; D: donor; ECD: expanded criteria donor; IS: immunosuppression; LI: late introduction; MMF: mycophenolate mofetil; No.: number; ATN: acute tubular necrosis; R: recipient; AR: acute rejection; GS: graft survival; PS: patient survival; Tx: transplant.
[a] Adjusted for deaths; [b] Survival at 6 years; [c] Survival at 3 years; [d] Survival and 6 months.

The results from the three-year BENEFIT EXT study[31] were published recently, in which belatacept administered with cyclosporine and mycophenolate mofetil resulted especially beneficial for improving glomerular filtration rates in recipients of organs from elderly donors. There were no significant differences in the rate of acute rejection as compared to the control group, which received cyclosporine, mycophenolate, and steroids.

Without a doubt, organ transplants from elderly donors require special treatment in the immediate postoperative period, including minimal cold ischaemia time, immunosuppression adjusted for donor/recipient characteristics, the highest possible number of HLA compatibilities, and minimal use of calcineurin inhibitors. This study shows the vital importance of continuing optimal treatment over time, minimising the use of calcineurin inhibitors, and proper control of cardiovascular risk factors. The long-term benefits of belatacept in these patients remain to be established.

REFERENCES

1. González-Roncero FM, Gentil-Govantes MA, González-Molina M, Rivero M, Cantarell C, Alarcón A, et al. Evolución tardía del trasplante renal de donante y receptor añosos con una inmunosupresión inicial con daclizumab, mofetil-micofenolato e introducción retrasada de tacrolimus. Nefrologia 2012;32(4):446-54.
2. Organización Nacional de Trasplantes. Memorias - Datos de donación y trasplante renal de la ONT [varios años]. Available at: http://www.ont.es/infesp/Paginas/Memorias.aspx
3. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation and recipients of a first cadaveric transplant. N Engl J Med 1999;341:1725-30.
4. Ojo AO, Hanson JA, Meier-Kriesche H, Okechukwu CN, Wolfe RA, Leichtman AB, et al. Survival in recipients of marginal cadaveric donor kidney compared with other recipients and wait-listed transplant canditates. J Am Soc Nephrol 2001;12:589-97.
5. McDonald S, Russ G. Survival of recipients of cadaveric kidney transplant with those receiving dialysis treatment in Austria and New Zeland, 1991-2001. Nephrol Dial Transplant 2002,17:2212-9.
6. Waiser J, Schreiber M, Budde K, Fritsche L, Böhler T, Hauser I, et al. Age-matching in renal tansplantation. Nephrol Dial Transplant 2000;15:696-700.
7. Cohen B, Smits JM, Hase B, Persijn G, Vanrenterghem Y, Frei U. Expanding the donor pool to increase renal transplantation. Nephrol Dial Transplant 2005;20:34-41.
8. Beckurts UTA, Stippel D, Pollok M, Arns W, Weber M, Hölscher AH. Single center experience with the old for old program for renal transplantation. Transplant Proc 2001;33:3779-80.
9. Fritsche L, Hörstrup J, Budde K, Reinke P, Giessing M, Tullius S, et al. Old for old kidney allocation allows successful expansion of the donor and recipients pool. Am J Transplant 2003;3:1434-9.
10. Zhou XJ, Rakheja D, Yu X, Saxena R, Vaziri ND, Silva FG. Te ageing kidney. Kidney Int 2008;74:710-20.
11. Feinfeld DA, Guzik H, Cavournis C, Lynn RI, Somer B, Aronson MK, et al. Sequential changes in renal fuction tests on the old: results from de Bronx Longitudinal Aging Study. J Am Geriatr Soc 1995;43:412-4.
12. Siddidi N, McBride MA, Hariaharan S. Similar risk profiles for postransplant dysfunction and long term graft faillure: UNOS/OPTN database analysis. Kidney Int 2004;65:1906-13.
13. Reutzel-Selke A, Filatenov A, Jurische A, Denecke C, Martins PN, Pascher A, et al. Grafts from elderly donors elict a stronger immune response in the early period postransplantation. A study in a rat model. Transplant Proc 2005;37(1):382-3.
14. Lim WH, Ghang S, Chadban S, Campbell S, Dent H, Russ GR, et al. Donor-recipient age matching improves years of graft function in deceased donor kidney transplantation. Nephrol Dial Transplant 2010;25(9):3082-9.
15. Bodingbauer M, Pakrah B, Steininger R, Berlakovich G, Rockenschaub S, Wekerle T, et al. The advantage of allocating kidney from old cadaveric donors to old recipients. A single center experience. Clin Transplant 2006;20:471-5.
16. Meier-Kriesche HU, Ojo A, Hanson J, Cibrik D, Lake K, Agodoa LY, et al. Increased immunosuppressive vulnerability in the elderly renal transplant recipients. Transplantation 2000;69:885-9.
17. Trouillet I, Benito N, Cervera C, Rivas P, Cofán F, Almela M, et al. Infuence of age in renal transplant infections. Cases and control study. Transplantation 2005;80:989-92.
18. Daniovicht GM, Gill J, Bunnapradist S. Immunosupression of the elderly kidney transplant recipient. Transplantation 2007;84(3):285-91.
19. Emparan C, Wolters H, Laukotter M, Senninger N. Long term results of calcineurion free protocols with basiliximab induction in old to old programs. Transplant Proc 2004;36:2646-8.
20. Gentil MA, Osuna A, Capdevilla L, Cantarell C, Pereira P, Mazuecos A, et al. Daclizumab en combinación con micofenolato mofetilo e introducción tardía de tacrolimus a dosis bajas, como opción terapéutica en la pareja donante-receptor añoso en trasplante renal. Nefrologia 2008;28(3):287-92.
21. 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;2:664-70.
22. Stratta RJ, Sudberg AK, Rohr R, Farney AC, Hartmann EL, Roskopf JA, el al. Optimal use the old donors and recipients in kidney transplantation. Surgery 2006;139:324-33.
23. Foss A, Heldal K, Scott H, Foss S, Leivestad T, Jørgensen PF, et al. Kidneys from deceased donors more than 75 years perform acceptably after transplantation. Transplantation 2009;87:1437-41.
24. Collini A, Kalmar P, Damo A, Ruggieri G, Carmellini M. Renal transplantation from very old donors. How far can we go? Transplantation 2009;87:1437-41.
25. Favi E, Gargiulo A, Spagnoletti G, Salerno MP, Silvestrini N, Valente I, et al. Induction with basiliximab plus thymoglobulin is effective and safe in old for old renal transplantation: Six months results of a prospective clinical study. Transplant Proc 2010;42(4):1114-7.
26. Galeano C, Marcén R, Jimenez S, Fernández Rodríguez A, Sosa H, Villafruela JJ, et al. Utilization of elderly kidney donors (>70 years) does not affect graf survival in medium term. Transplant Proc 2010;42:3935-7.

27. Arbogast H, Huckelheim H, Shneeberger H, Illner WD, Tarabichi A, Fertmann J, et al. A calcineurin antagonist free induction/maintenance strategy for inmunossupresión in elderly recipients of renal allograft from elderly cadaver donors. Clin Transplant 2005;19:309-15.
28. Guba M, Rentsch M, Wimmer CD, Uemueksuez A, Illner WD, Schönermarck U, et al. Calcineurin inhibitor avoidance in elderly renal allograft recipients using ATG y basiliximab combined with mycofenolate mofetil. Transpl Int 2008;21:637-45.
29. Frei U, Noeldeke J, Machold-Fabrizzi V, Arbogast H, Margreiter R, Fricke L, et al. Prospective age maching in elderly kidney transplant recipients. A 5 years analysis of the Eurotransplant Senior Program. Am J Transplant 2008;8:50-7.
30. Palomar R, Ruiz JC, Zubimendi JA, Cotorruelo JG, de Francisco AL, Rodrigo E, et al. Acute rejection in the early recipient: Influence of age in the outcome of kideny transplantation. Int Urol Nephrol 2002;33:145-8.
31. Pestana JO, Griñó JM, Varenterghem Y, Becker T, Campistol JM, Florman S, et al. Three-year outcomes from Benefit-ext: a phase III study of belatacept versus cyclosporine in recipients of extended criteria donor kidneys. Am J Transplant 2012;12(3):630-9.

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