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Induction Therapy in Renal Transplantation

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Abstract

Induction therapy has become part of the standard therapeutic protocol in many kidney, simultaneous kidney-pancreas, and pancreas after kidney transplant patients. Monoclonal and polyclonal antibodies are available, both lymphocyte-depleting and non-lymphocyte-depleting. The aim of antibody induction is to intensify the immunosuppression in the early posttransplant period either to minimize the use of calcineurin inhibitors and steroids in patients with a low or moderate immunological risk, or to achieve an additional immunosuppressive effect in patients at high immunological risk. Interleukin-2 receptor antibody induction appears to be free of adverse events. All other induction agents are associated with an increased risk of infection and/or posttransplant malignancy. Therefore, a careful and individual risk/benefit analysis is necessary in order to decide if induction treatment is to be performed. **(Trends in Transplant. 2011;5:158-84)**

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Key words

Induction. Interleukin-2 receptor antagonist. Basiliximab. Antithymocyte globulin. Rituximab. Eculizumab. Alemtuzumab. Minimization. Calcineurin inhibitor. Steroid.

Introduction

The profile of the donor and the kidney recipient has changed drastically over the last decade. The shortage of organs to face the increasing transplant waiting list has led, on the one hand, to the use organs from donors with higher risk of failure, such as the expanded criteria donors (ECD), and donors after cardiac death, and, on the other hand, to promoting living donation. Considering the recipient, the improvement in the management of chronic renal failure and dialysis therapy has contributed to enrolling older patients on the waiting list. These patients have more cardiovascular comorbidity. On the other hand, there are an increased number of patients waiting for second or subsequent transplants.

Moreover, at present in renal transplantation the most effective immunosuppressive drugs for preventing acute rejection in the short and long term are calcineurin inhibitors (CNI). Due to their nephrotoxicity, lower doses and levels have been used, complementing this reduction, which would minimize efficacy of the prevention of acute rejection, with other antiproliferative or proliferation signal inhibitors drugs.

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Although *de novo* combinations of mammalian target of rapamycin (mTOR) inhibitors associated with CNI or with mycophenolic acid have been studied and have been effective in preventing acute rejection[1-3], they have not yet achieved widespread use in clinical practice, probably because of significant side effects such as wound healing problems. Nevertheless a recent publication indicates that wound healing complications are not affected by *de novo* everolimus[4]. However, there is an emerging tendency to minimize CNI, either from the time of transplantation adding biological induction therapy[5], or after a few weeks using concomitant therapy with proliferation signal inhibitors or high doses of antiproliferatives[6,7]. The intention is to improve renal function and long-term survival without worsening the incidence of acute and chronic rejection.

Another key point on current tendencies in immunosuppression is minimizing the use of steroids. They are responsible for high posttransplant cardiovascular comorbidity and can be removed without an increase in the incidence of acute rejection in many patients. There are reports on successful experiences with steroid avoidance from day zero, with the use of induction therapy and experiences with steroid withdrawal after a few posttransplant months using CNI and mycophenolate or mTOR inhibitors, without failures in the efficacy[8-11].

Donor and recipient characteristics are a key point when it comes to defining immunosuppression in order to guarantee good short- and long-term results.

Today the ideal transplant from a deceased donor, in other words the lowest risk transplant, is a first transplant in a recipient less than 60 years of age without extrarenal comorbidity, without anti-HLA antibodies, and with a kidney from a young donor who died of brain death caused by a head injury. On the contrary, higher risk renal transplants are those performed with kidneys from ECD who are 60 years or older or between 50 and 59 years and with two of the following criteria: having died of a cerebrovascular accident, having hypertension or serum creatinine at the time of extraction being > 1.5 mg/dl[12,13], and renal transplants performed with kidneys from donors after cardiac death or from donor with acute renal failure at the moment of extraction.

Immunosuppression in the ideal transplant may include induction therapy and in fact there are many studies in the literature supporting this practice in this type of transplant. However, this induction therapy is not absolutely necessary, unless there is a high immunological risk or a higher risk of delayed function or graft loss by the "precarious donor"[14-22].

In transplants performed with ECD, the risk of graft failure is higher, and then, we should try immunosuppression with lower possible nephrotoxic risk, but at the same time being effective, in order to avoid acute rejection. In these transplants it makes more sense to do induction therapy to minimize the CNI dose or to design therapies free of CNI *de novo*[23-25].

Transplants from donors after cardiac death increase ischemic stress, which leads to a longer time for recovery of renal function and a higher risk of primary non-function. Therefore, in renal transplant from donor after cardiac, induction therapy is important in order to avoid CNI during the first days posttransplantation, thus not adding the vasoconstrictive effects.

Transplantation in hyperimmunized recipients requires more intense immunosuppression from the beginning, and triple therapy consisting of a CNI combined with steroids and an antiproliferative drug is usually not enough in these patients: biological induction therapies should be added. Since the risk of humoral rejection is higher in these recipients, the use of anti-CD20 or eculizumab can be considered.

Living-donor renal transplants are also considered ideal transplants, however more and more older living donors are being used, thus justifying the minimization of CNI. In a low-risk transplant from a young living donor, induction therapy might not be necessary, although there are studies that demonstrate a reduction in the incidence of acute rejection.

Steroid-free immunosuppression or early steroid withdrawal might be advantageous in recipients with significant cardiovascular risk or risk of developing diabetes after transplantation[8-11].

Obviously, the biological agents used in clinical practice for induction have shown benefits in preventing acute rejection; however, the side effects associated with over-immunosuppression prevent them from being used universally. In this sense, anti-interleukin-2 receptor antibodies have a good safety profile with no short-term differences in infection and cancer compared with control groups not receiving this induction therapy[22]. However, lymphocyte-depleting antibodies present a higher complication rate, bacterial, viral, fungal and opportunistic infections in general, and a higher incidence of cancer, especially if the number of doses received are over 14 compared with those groups not receiving it[21,22,25,26].

For these reasons it is necessary to establish recommendations to guide the rational use of biological induction therapies to get the lowest rate of acute rejection and increased survival of transplants in the short, medium, and long term, with fewer side effects and with lowest morbidity and mortality.

The following sections will provide recommendations for the use of induction therapy in different modalities of renal transplantation based on the experiences published in the literature.

References

1. Groth CG, Bäckman L, Morales JM, et al. Sirolimus (rapamycin)-based therapy in human renal transplantation: similar efficacy and different toxicity compared with cyclosporine. Sirolimus European Renal Transplant Study Group. Transplantation. 1999;67:1036-42.
2. Kreis H, Cisterne JM, Land W, et al. Sirolimus in association with mycophenolate mofetil induction for the prevention of acute graft rejection in renal allograft recipients. Transplantation. 2000;69:1252-60.
3. Flechner SM, Goldfarb D, Modlin C, et al. Kidney transplantation without calcineurin inhibitor drugs: a prospective, randomized trial of sirolimus versus cyclosporine. Transplantation. 2002;74:1070-6.
4. Albano L, Berthoux F, Moal MC, et al. RAD A2420 Study Group. Incidence of Delayed Graft Function and Wound Healing Complications After Deceased-Donor Kidney Transplantation Is not Affected by De Novo Everolimus. Transplantation. 2009;88:69-76.
5. Ekberg H, Tedesco-Silva H, Demirbas A, et al. ELITE-Symphony Study. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med. 2007;357:2562-75.
6. Budde K, Becker T, Arns W, et al. ZEUS Study Investigators. Everolimus-based, calcineurin-inhibitor-free regimen in recipients of de-novo kidney transplants: an open-label, randomized, controlled trial. Lancet. 2011;377:837-47.
7. Nashan B, Curtis J, Ponticelli C, Mourad G, Jaffe J, Haas T. The 156 Study Group. Everolimus and reduced-exposure cyclosporine in de novo renal-transplant recipients: a three-year phase II, randomized, multicenter, open-label study. Transplantation. 2004;78:1332.
8. Vincenti F, Monaco A, Grinyo J, Kinkhabwala M, Roza A. Multicenter randomized prospective trial of steroid withdrawal in renal transplant recipients receiving basiliximab, cyclosporine microemulsion and mycophenolate mofetil. Am J Transplant. 2003;3:306-11.
9. Rostaing L, Cantarovich D, Mourad G, et al. CARMEN Study Group. Corticosteroid-free immunosuppression with tacrolimus, mycophenolate mofetil, and daclizumab induction in renal transplantation. Transplantation. 2005;79:807-14.
10. Woodle ES, Vincenti F, Lorber MI, et al. A multicenter pilot study of early (4-day) steroid cessation in renal transplant recipients under Simulect, tacrolimus and sirolimus. Am J Transplant. 2005;5:157-66.
11. ter Meulen CG, van Riemsdijk I, Hené RJ, et al. Steroid-withdrawal at 3 days after renal transplantation with anti-IL-2 receptor α therapy: a prospective, randomized, multicenter study. Am J Transplant. 2004;4:803-10.
12. Port FK, Bragg-Gresham JL, Metzger RA, et al. Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors. Transplantation. 2002;74:1281-6.
13. Metzger RA, Delmonico FL, Feng S, Port FK, Wynn JJ, Merion RM. Expanded criteria donors for kidney transplantation. Am J Transplant. 2003;3(Suppl 4):114-25.
14. Nashan B, Moore R, Amlot P, et al. CHIB 201 International Study group. Randomized trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients. Lancet. 1997;350:1193-8.
15. Kahan BD, Rajagopalan PR, Hall M. United States Simulect Renal Study Group. Reduction of the occurrence of acute cellular rejection among renal allograft recipients treated with basiliximab, a chimeric anti-interleukin-2-receptor monoclonal antibody. Transplantation. 1999;67:276-84.
16. Ponticelli C, Yussim C, Cambi V, et al. Simulect Phase IV Study Group. A randomized, double-blind trial of basiliximab immunoprophylaxis plus triple therapy in kidney transplant recipients. Transplantation. 2001;72:1261-7.
17. Nashan B, Light S, Hardie IR, Lin A, Johnson JR. Daclizumab Double Therapy Study Group. Reduction of acute renal allograft rejection by daclizumab. Transplantation. 1999;67:110-15.
18. Vincenti F, Kirkman R, Light S, et al. Daclizumab Triple Therapy Study Group. Interleukin-2-receptor blockade with daclizumab to prevent acute rejection in renal transplantation. N Engl J Med. 1998;338:161-5.
19. Lawen JG, Davies EA, Mourad G, et al. Simulect International Study Group. Randomized double-blind study of

immunoprophylaxis with basiliximab, a chimeric anti-interleukin-2 receptor monoclonal antibody, in combination with mycophenolate mofetil-containing triple therapy in renal transplantation. Transplantation. 2003;75:37-43.
20. Pescovitz MD, Bumgardner G, Gaston RS, et al. Pharmacokinetics of daclizumab and mycophenolate mofetil with cyclosporine and steroids in renal transplantation. Clin Transplant. 2003;17:511-17.
21. Vincenti F, de Andrés A, Becker T, et al. Interleukin-2 receptor antagonist induction in modern immunosuppression regimens for renal transplant recipients. Transpl Int. 2006;19:446-57.
22. Webster AC, Ruster LP, McGee R, et al. Interleukin 2 receptor antagonists for kidney transplant recipients. Cochrane Database Syst Rev. 2010;CD003897.
23. Andrés A, Marcén R, Valdés F, et al. NI2A StudyGroup. A randomized trial of basiliximab with three different patterns of cyclosporin A initiation in renal transplant from expanded criteria donors and at high risk of delayed graft function. Clin Transplant. 2009;23:23-32.
24. Andrés A, Budde K, Clavien PA, et al. SENIOR Study Team. A randomized trial comparing renal function in older kidney transplant patients following delayed versus immediate tacrolimus administration. Transplantation. 2009;88:1101-8.
25. Opelz G, Dohler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. Am J Transplant. 2004:4:222.
26. Swinnen LJ, Costanzo-Nordin MR, Fisher SG, et al. Increased incidence of lymphoproliferative disorder after immunosuppression with the monoclonal antibody OKT3 in cardiac-transplant recipients. N Engl J Med. 1990: 323:1723.
27. Nashan B, Luck R, Kliem V, et al. CMV in kidney transplantation: a single center experience over 22 years. Clin Transpl. 1999:181-8.

Induction Treatment in Kidney Transplantation in Living Donors

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Introduction

The recipient of a living donor kidney transplant (RLDT) obtains, as a rule, a graft that combines several advantages and it is often described as "the best transplant possible". The immunosuppressive therapy that is going to be offered to this recipient may have substantial differences from the therapy in a recipient of a transplant from a deceased donor. (See section "Donor Characteristics").

This means that we cannot talk about RLDT as a homogeneous entity, as there are a multitude of different situations that will require individualized immunosuppression including induction therapy.

Twins

In this type of transplant, compatibility is high, so there is unanimity that these patients should not receive any induction therapy. Some authors recommend not to do immunosuppressive therapy and others give a slight initial immunosuppression, which will then be suspended or minimized[1,2]. The RLDT between identical twins offers the best results.

HLA-identical siblings without being identical twins

Siblings who are HLA identical have inherited the same major histocompatibility system antigens from their parents. Due to the possibility of a certain degree of immunological incompatibility in other antigens, a basic immunosuppressive therapy is recommended. Some guidelines have recommended minimizing or suspending calcineurin inhibitors (CNI) and/or corticosteroids. If the recipient is not from a high immunological risk group, usually they are not given induction treatment[1]. However, some authors have made mild induction treatments for these patients preceding a planned withdrawal of CNI[1,3-6].

Non-HLA-identical living donor transplants

In these patients, there are greater disagreements among authors as to whether to

perform induction or not and, if so, how to do it. If donor and recipient are not HLA identical, if they do not have expanded criteria, and if there is no immunologic risk, the following options for induction treatment can be adopted:

– No induction therapy. Conventional triple immunosuppression (usually tacrolimus, mycophenolic acid, and prednisone) can be administered without polyclonal or monoclonal antibodies. The rejection rate is slightly higher, but reasonable.

– Administration of two doses of 20 mg basiliximab (day 0 and day 4) accompanying the abovementioned triple therapy. This regimen has excellent tolerance and the acute rejection rate decreases[7,8]. In our series of living donor transplants, this strategy offers a 5% reduction in acute rejection compared to standard triple therapy. Several authors advocate universal administration of basiliximab in RLDT except in high immunological risk cases[9]. Others, like Lim, et al.[8] in a study in a series of 1,106 transplants of the Australian Registry and New Zealand, showed that induction with basiliximab in living donor transplantation offered a reduction of the episodes of acute rejection and increased graft survival.

– Polyclonal antilymphocyte serum at low doses. There are several options:

  • Treatment of short duration (3-5 days and daily doses)[10,11]. This does not increase the risk of infections and/or neoplasias and decreases the incidence of acute rejection, while improving graft survival in the short to medium term.

  • Single bolus. Kaden, et al.[12] gave antithymocyte globulin (ATG) 9 mg/kg) on day 0, and described improvements in terms of acute rejection and graft survival. The described safety profile is excellent. Other authors have also used ATG for a living donor program recently, with good tolerance and decreased initial acute rejection[13,14]. In addition, thymoglobulin has also been used as low-dose single bolus (1.5 mg/kg) in living donor programs with the same good results[15].

Living donor with expanded criteria

Living donors over 60 years are increasingly common. The results obtained from these donors have been described as very good[16-18]. In the experience of our center, in the last 200 living donor kidney transplants, 20% of donors were over 60 years. Of these, 38% were over 65 years and 12% over 70 years. Since kidneys from these donors have a certain degree of aging, immunosuppression provided should try to minimize nephrotoxic drug effects as far as possible[19]. Therefore, although triple conventional immunosuppression would not be wrong, there is a marked tendency towards induction therapy with basiliximab or polyclonal antilymphocyte serum to allow the initial use and minimization of CNI, somewhat similar to in brain dead donors of older age[1,20].

Living donor in high immunological risk recipients

This situation will occur mainly in three different circumstances:

– ABO incompatibility;

– Transplantation with previous positive crossmatch;

– Hypersensitized recipient.

Since in all three situations there is a high risk of acute humoral rejection, a strong

immunosuppression is required. The transplant process is conducted in two phases:

1. Reduction of antibody titres (isoagglutinin and/or anti-HLA), and

2. Powerful immunosuppression.

Various methods have been used to reduce antibody titres:

Splenectomy

Splenectomy has been used routinely in most desensitization protocols in case of ABO-incompatible transplantation with good results, especially by the Japanese groups[21]. However, after the introduction of rituximab, splenectomy is no longer considered an essential procedure and it has been withdrawn from desensitization protocols, avoiding the morbidity and mortality associated to it[22].

Plasmapheresis and immunoglobulin infusion

This has been widely used by Japanese groups and with successful results in ABO-incompatible transplants. The number of both depends on the evolution of isoagglutinin titers. The transplant is not performed until the titer is less than 1:8 or 1:16 depending on the transplant group. Sessions are usually done between 4-5 pretransplant sessions and between 3-5 posttransplant sessions. The infusion of immunoglobulins is usually 100 mg/kg after each session of plasmapheresis[23]. It is also used in transplants with a previous positive crossmatch in order to become negative.

Specific immunoadsorption

This consists of polycarbonate columns filled with sepharose with trisaccharides of group A or B attached to its surface (Glycosorb®) or with the above and proteins of the HLA system (Therasorb®). The removal of antibodies by this technique avoids plasmapheresis. The number of immunoadsorption sessions will depend on the previous antibodies titres. If they are initially very high, a poor response to treatment can be expected.

– Rituximab: This is a humanized murine monoclonal type that binds to CD20, which is expressed on most B-cells. The addition of rituximab to desensitization protocols has led to the eradication of the practice of splenectomy and improvement of results in recent years. Since most plasma cells do not express CD20, its use must be completed with the removal of antibody by plasmapheresis or immunoabsorption[24-26]. Usually, the patient receives one or two doses of rituximab 375 mg/m^2. European protocols based on specific immunoadsorption and rituximab state that treatment should begin one to four weeks before the estimated date of transplantation.

– Powerful immunosuppression. The immunomodulation process is completed with the administration of an immunosuppressive scheme that includes tacrolimus, mycophenolic acid, corticosteroids, and polyclonal or monoclonal antilymphocyte antibodies.

References

1. Pascual SJ, Hernandez MD. [Immunosuppression for living donor renal allograft recipients]. Nefrologia. 2010;30(Suppl 2):80-4.
2. Kessaris N, Mukherjee D, Chandak P, Mamode N. Renal transplantation in identical twins in United States and United Kingdom. Transplantation. 2008;86:1572-7.
3. Venot M, Abboud I, Duboust A, et al. Calcineurin inhibitor-free monotherapy in human leukocyte antigen-identical live donor renal transplantation. Transplantation. 2011;91:330-3.
4. Afaneh C, Halpern J, Cheng E, et al. Steroid avoidance in two-haplotype-matched living donor renal transplants with basiliximab induction therapy. Transplant Proc. 2010;42: 4526-9.
5. van de WJ, Gerrits JH, van Besouw NM, Ijzermans JN, Weimar W. Successful tapering of immunosuppression to low-dose monotherapy steroids after living-related human leukocyte antigen-identical renal transplantation. Transplantation. 2009;87:740-4.
6. Walker JK, Alloway RR, Roy-Chaudhury P, et al. A prospective trial of a steroid-free/calcineurin inhibitor minimization

regimen in human leukocyte antigen (HLA)-identical live donor renal transplantation. Transplantation. 2009;87:408-14.
7. Gralla J, Wiseman AC. The impact of IL2ra induction therapy in kidney transplantation using tacrolimus- and mycophenolate-based immunosuppression. Transplantation. 2010;90: 639-44.
8. Lim WH, Chang SH, Chadban SJ, et al. Interleukin-2 receptor antibody reduces rejection rates and graft loss in live-donor kidney transplant recipients. Transplantation. 2009;88:1208-13.
9. Hourmant M. [Immunosuppressor treatment in kidney transplantation from a live donor]. Nephrol Ther. 2008;4(Suppl 3):S170-3.
10. Hardinger KL, Schnitzler MA, Koch MJ, et al. Thymoglobulin induction is safe and effective in live-donor renal transplantation: a single center experience. Transplantation. 2006;81: 1285-9.
11. Woodle ES, Peddi VR, Tomlanovich S, Mulgaonkar S, Kuo PC. A prospective, randomized, multicenter study evaluating early corticosteroid withdrawal with Thymoglobulin in living-donor kidney transplantation. Clin Transplant. 2010;24: 73-83.
12. Kaden J, May G, Volp A, Wesslau C. Improved long-term survival after intra-operative single high-dose ATG-Fresenius induction in renal transplantation: a single centre experience. Ann Transplant. 2009;14:7-17.
13. Sheashaa HA, Hamdy AF, Bakr MA, Abdelbaset SF, Ghoneim MA. Long-term evaluation of single bolus high dose ATG induction therapy for prophylaxis of rejection in live donor kidney transplantation. Int Urol Nephrol. 2008;40:515-20.
14. Bou-Jaoude MM, Almawi WY. Intraoperative anti-thymocyte globulin-Fresenius (ATG-F) administration as induction immunosuppressive therapy in kidney transplantation. Mol Immunol. 2003;39:1089-94.
15. Schenker P, Ozturk A, Vonend O, et al. Single-dose thymoglobulin induction in living-donor renal transplantation. Ann Transplant. 2011;16:50-8.
16. Iordanous Y, Seymour N, Young A. et al. Recipient outcomes for expanded criteria living kidney donors: the disconnect between current evidence and practice. Am J Transplant. 2009;9:1558-73.
17. Nanovic L, Kaplan B. The advantage of live-donor kidney transplantation in older recipients. Nat Clin Pract Nephrol. 2009;5:18-19.
18. Gill J, Bunnapradist S, Danovitch GM, Gjertson D, Gill JS, Cecka M. Outcomes of kidney transplantation from older living donors to older recipients. Am J Kidney Dis. 2008; 52:541-52.
19. Bulatova N, Yousef AM, Al-Khayyat G, Qosa H. Adverse effects of tacrolimus in renal transplant patients from living donors. Curr Drug Saf. 2011;6:3-11.
20. Sola R, Guirado L, Lopez NA, et al. Renal transplantation with limit donors: to what should the good results obtained be attributed? Transplantation. 1998;66:1159-63.
21. Ishida H, Koyama I, Sawada T, et al. Anti-AB titer changes in patients with ABO incompatibility after living related kidney transplantations: survey of 101 cases to determine whether splenectomies are necessary for successful transplantation. Transplantation. 2000;70:681-5.
22. Gloor JM, Lager DJ, Fidler ME, et al. A Comparison of splenectomy versus intensive posttransplant antidonor blood group antibody monitoring without splenectomy in ABO-incompatible kidney transplantation. Transplantation. 2005; 80:1572-7.
23. Sonnenday CJ, Warren DS, Cooper M, et al. Plasmapheresis, CMV hyperimmune globulin, and anti-CD20 allow ABO-incompatible renal transplantation without splenectomy. Am J Transplant. 2004;4:1315-22.
24. Sawada T, Fuchinoue S, Teraoka S. Successful A1-to-O ABO-incompatible kidney transplantation after a preconditioning regimen consisting of anti-CD20 monoclonal antibody infusions, splenectomy, and double-filtration plasmapheresis. Transplantation. 2002;74:1207-10.
25. Sawada T, Fuchinoue S, Kawase T, Kubota K, Teraoka S. Preconditioning regimen consisting of anti-CD20 monoclonal antibody infusions, splenectomy and DFPP-enabled nonresponders to undergo ABO-incompatible kidney transplantation. Clin Transplant. 2004;18:254-60.
26. Toki D, Ishida H, Horita S, Setoguchi K, Yamaguchi Y, Tanabe K. Impact of low-dose rituximab on splenic B cells in ABO-incompatible renal transplant recipients. Transpl Int. 2009;22:447-54.

Induction Therapy in High-Risk Kidney Transplant Patients

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Introduction

Graft survival and acute rejection are influenced by the presence of anti-HLA antibodies. Patients can be immunized by previous transplants or pregnancies and by blood transfusions. Currently, a high percentage of patients in the waiting list for kidney transplantation are hypersensitized, showing a high rate of anti-HLA antibodies. The waiting time is longer for these patients and their management is more complicated after transplantation, needing more intensive immunosuppressive therapy and plasmapheresis or immunoadsorption to remove these anti-HLA antibodies. The use of induction therapy in kidney transplant recipients with a high percentage of anti-HLA antibodies is a common practice, but there is no consensus either on the best induction drug to be used or on the definition of high-risk patients.

Evidence

Different trials have defined this population by different ways. Noël, et al. defined

high-risk patients as those with current panel reactive antibodies (PRA) > 30%, peak PRA > 50%, loss of a first kidney graft from rejection within two years of transplantation, or two or three previous grafts[1]. A recent report by Hanaway, et al. defined high-risk patients by a repeat transplant, a peak or current value of PRA ≥ 20%, or black race[2]. Brennan, et al. enrolled patients considering donor, recipient, and transplant procedure factors, which put the recipient at high risk for acute rejection (PRA > 20%, multiple transplantations, at least one donor HLA mismatch, and black race) or delayed graft function such as cold ischemia time > 24 hours, donor aged > 50 years or who had acute tubular necrosis, high inotropic support, or donors after cardiac death[3]. A registry study defined high-immunologic risk recipients as those with peak PRA > 20%, prior kidney transplantation, or black race[4]. So, it is not possible to consider "high-immunologic risk" patients as a homogeneous population. Moreover, the new available methods to determine anti-HLA antibodies are more sensitive and are changing our ability to know how a recipient will respond to a specific donor[5]. New immunologic tools are being developed to analyze which patients are or are not responders[6]. Interferon-gamma enzyme-linked immunosorbent spot (ELISPOT) has been successfully used to identify those patients in whom induction drugs must be used. As induction therapy is directed at alloreactive T-cells, antibody induction therapy preferentially benefits kidney transplant candidates with strong pretransplant donor-reactive cellular immunity estimated by ELISPOT[7].

Nowadays, rabbit antithymocyte globulin (rATG), interleukin-2 receptor antibody (IL2-RAb), and alemtuzumab are being used to prevent acute rejection in high-risk kidney transplant patients[8]. These drugs were better than placebo or no induction therapy in different trials. Meier-Kriesche, et al. reported a lower rate of acute rejection with IL2-RAb versus no induction (26 vs. 49%) in a high-risk population defined by race[9]. The incidence of first-year acute rejection was lower in African American patients receiving rATG than placebo (18 vs. 47%; $p < 0.05$)[10]. Although most centers use an induction drug in high-risk patients, it is not known which drug is the best to be used in these patients.

There are only three randomized controlled trials comparing rATG versus IL2-RAb in high-risk transplants. Brennan, et al. compared rATG (141 patients) versus basiliximab (137 patients) in patients at risk of acute rejection or delayed graft function under a regimen based on cyclosporine, mycophenolate mofetil, and prednisone. The rATG group had a lower incidence of acute rejection (15.6 vs. 25.5%; $p = 0.02$) and of acute rejection requiring antibody therapy (1.4 vs. 8.0%; $p = 0.005$). At 12 months there were no differences in graft loss (9.2 vs. 10.2) and death (4.3 vs. 4.4%)[3]. After five years of follow-up, a composite endpoint of acute rejection, graft loss, or death was lower in the rATG group than in the basiliximab group (37 vs. 51%; $p = 0.04$). The rate of acute rejection remained lower in the rATG group (15 vs. 27%; $p = 0.03$). There were no differences in five-year graft and patient survival[11].

Noël, et al. compared daclizumab (114 patients) versus rATG (113 patients) in a high-immunologic risk population under tacrolimus, mycophenolate mofetil, and steroids. Patients treated with rATG had a lower incidence of biopsy-proven acute rejection (15.0 vs. 27.2%; $p = 0.016$) and steroid-resistant rejection (2.7 vs. 14.9%; $p = 0.002$), but without differences in one-year graft (82.3 vs. 86.0%; $p = 0.47$) and patient survival (95.6 vs. 96.5%; $p = 0.42$)[1]. Last, in a study published in abstract form, Locke, et al. randomized 41 patients with donor-specific anti-HLA antibodies to receive rATG or daclizumab. Patients treated with rATG suffered less episodes of acute rejection (66.7 vs. 95.0%; $p = 0.02$), but without differences in patient and graft survival[12]. The results of these three studies are very similar (Fig. 1),

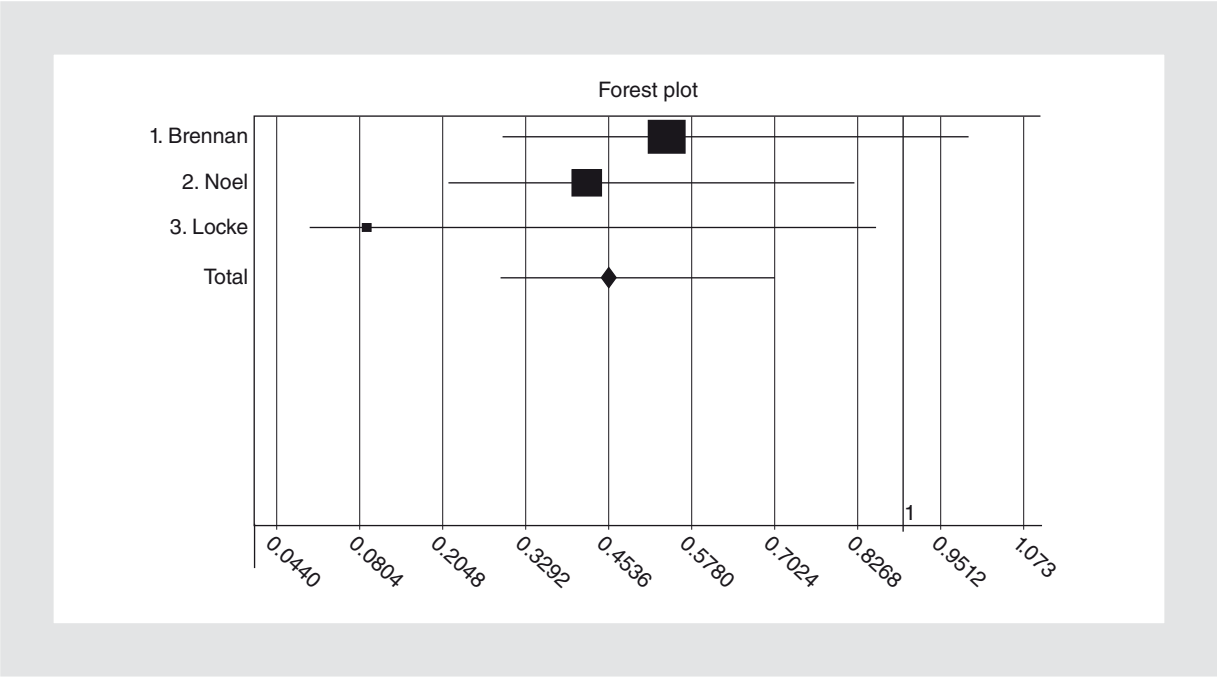

Figure 1. *Forest plot to show the overall risk (OR) of acute rejection of the three reports of induction use comparing antithymocyte globulin versus interleukin-2 receptor antibody in high-risk kidney transplant recipients (Synergy 3.2). OR: 0.508; 95% CI: 0.328-0.787; p = 0.002.*

concluding that rATG is better than IL2-RAb to prevent acute rejection in high-immunologic risk patients, but without differences in graft and patient survival in the time of follow-up.

Retrospective and registry studies can overcome the limitations in number of patients included and time of follow-up of randomized controlled trials. Two single-center retrospective analyses found that rATG therapy reduces acute rejection rates more than IL2-RAb in high-risk patients. Using rATG in high-risk patients and IL2-RAb in low-risk patients, Weng, et al. reported an even lower rate of acute rejection with rATG than with IL2-RAb (6.7 vs. 23.5%; $p < 0.05$), without differences in graft and patient survival in spite of there being a higher risk[13]. Similarly, kidney transplant recipients with a PRA > 50% under rATG suffered acute rejection less frequently than IL2-RAb-treated patients (12 vs. 50%; $p = 0.02$)[14]. In a larger retrospective study with data of the Organ Procurement Transplantation Network (OPTN), high-risk deceased transplant recipients over 60 years have a higher risk of acute rejection and first-year graft loss (HR: 1.27; 95% CI: 1.02-1.60) with IL2-RAb than with rATG, but not beyond this point[4]. The Kidney Disease: Improving Global Outcomes (KDIGO) recommends "using a lymphocyte-depleting agent, rather than an IL2-RAb, for kidney transplants at high immunologic risk"[15].

Alemtuzumab is the third most used induction agent in the USA[16]. Until 2011, few small randomized controlled trials examined the use of alemtuzumab as an induction agent in kidney transplantation[15]. In 21 high-immunologic risk kidney transplant patients randomized to alemtuzumab plus tacrolimus vs. four doses of polyclonal antibodies plus tacrolimus, mycophenolate and steroids, there were two vs. three acute rejections, respectively[17]. Two recent trials compared alemtuzumab versus rATG in high-risk kidney transplant recipients. Hanaway, et al. included 139 high-risk patients treated with alemtuzumab or rATG under a regimen of tacrolimus, mycophenolate, and early (five day) glucocorticoid withdrawal. No significant difference was

seen between alemtuzumab and rATG in biopsy-proven acute rejection rates (18 vs. 15%; p = 0.63). There were also no differences in three-year patient survival (99 vs. 91%; p = 0.07), three-year graft survival (91 vs. 84%; p = 0.32), and overall rate of adverse events, although the rate of infectious adverse events with alemtuzumab was slightly lower than with rATG (60 vs. 81%; p = 0.009)[2]. Similar findings have been reported by a smaller trial with only minor, not significant, differences between alemtuzumab and rATG in the cumulative graft survival at two years (90.9 vs. 81.8%; p > 0.05) and two-year freedom from rejection (81.8 vs. 72.7%; p > 0.05)[18]. More prospective long-term studies are necessary to know the exact role of alemtuzumab as induction therapy in kidney transplant patients at high immunologic risk. A large retrospective study with data of OPTN high-risk deceased transplant recipients over 60 years of age showed that high-risk transplantations treated with alemtuzumab suffered a greater risk of graft loss and death compared with rATG[4].

New perspectives of induction therapy in high-risk patients could be developed from different combinations of drugs or new immunosuppressive drugs[19]. Ruggenenti, et al. reported an effective experience by adding basiliximab to low-dose rATG, while Bächler, et al. combined rATG and intravenous immunoglobulins in patients with low-level donor-specific HLA antibodies reducing the development of antibody-mediated rejection[20,21].

Pancreas transplantation

As pointed out by Meier-Kriesche, et al., the use of antibody induction remains higher for pancreas recipients than for any other solid organ. The rate of induction use increased from near 65% in 1999 to over 80% in 2004 in all categories of pancreas transplants in the USA. Over the last years, the most commonly used antibody was rATG (about 50%). Alemtuzumab was the second most used agent (19% of simultaneous pancreas/kidney recipients) and IL2-RAb was the third most used group[16,22]. There are scarce data of induction use in pancreas transplantation in other countries.

The 2005 International Pancreas Transplant Registry showed that graft survival in all categories was higher when antibodies were used[23]. Three randomized controlled trials have demonstrated the advantages of using induction therapy in pancreas transplantation. Cantarovich, et al. randomized 50 simultaneous pancreas/kidney (SPK) transplants to rATG versus non-induction in patients under a regimen of cyclosporine, azathioprine, and corticosteroids. Patients receiving rATG suffered a lower incidence (36 vs. 76%; p < 0.01) and number (13 vs. 29; p < 0.05) of acute renal rejection episodes, but without differences in patient, pancreas, and renal survival rates between groups with an average follow-up of 36 months. Adverse events were more frequent in the rATG group[24]. Burke, et al. enrolled 174 SPK recipients, randomizing non-induction versus induction based on the institutional standard agent used in each center. All patients received tacrolimus, mycophenolate, and corticosteroids. Three-year cumulative incidence of biopsy-confirmed treated acute kidney rejection was lower in the induction group, but without reaching statistical significance (19.5 vs. 27.5%; p = 0.14). Three-year pancreas and patient survival was similar between both groups. Kidney graft survival was better in the induction group at three years (92 vs. 81.6%; p = 0.04)[25]. The greater study was reported by Stratta, et al., who included 297 SPK patients, randomized to two different daclizumab doses or no induction. The incidence of composite events (acute rejection, graft loss, or death) at one year was significantly higher in the group without induction (36.4, 32.7 vs. 48.7%; p < 0.05). Acute rejection was higher in the group with no induction (22.4, 22.1 vs. 34.6%; p < 0.05) and the

adverse event profiles were comparable among the three groups[26]. In a further report of the same trial with a follow-up of three years, the benefits of using IL2-RAb progressively disappeared[27]. In a recent review of immunosuppression in SPK transplantation, Heilman, et al. highlight the fact that no induction studies under a regimen of tacrolimus, mycophenolate, and corticosteroids reported higher acute rejection rates than induction studies, but with similar short-term graft survival rates[22].

Few randomized controlled trials have compared different immunosuppressive therapies in pancreas transplantation. Cantarovich, et al. reported a small trial in 1993 including 40 SPK recipients, finding no significant differences in patient, pancreas, and kidney survival and similar rates of acute rejection and cytomegalovirus (CMV) infection in groups treated with rATG and IL2-RAb[28]. In the prospective study carried out by Burke, et al. in which induction drug was based on the institutional protocol, patients treated with a lymphocyte-depleting agent showed lower rejection rate compared to IL2-RAb (11.1 vs. 23.5%; p = 0.14), but without significant differences. By contrast, CMV viremia was significantly more frequent in patients who received lymphocyte-depleting agents compared to the IL2-RAb-treated and non-induction group (36.1, 2.0 vs. 8.1%, respectively; p = 0.001)[25]. Alemtuzumab has been compared to rATG in 36 SPK transplants with similar kidney graft survival (88 vs. 86%; p > 0.2) and pancreas graft survival (88 vs. 93%; p > 0.2). Alemtuzumab recipients suffered less biopsy-proven acute rejection (13 vs. 36%; p = 0.07) and CMV infection (8 vs. 17%; p = 0.07), but without significant differences[29]. None of the three induction agents currently in use for pancreas transplantation has demonstrated superiority over the others. The rATG increases the risk of CMV infection compared both with IL2-RAb and alemtuzumab in the randomized controlled trials[25,29,30]. Stronger short-term efficacy of rATG to prevent acute rejection in pancreas transplantation can be compensated for its higher risk for viral infection. Prospective long-term studies are necessary to know which induction drug is the best in pancreas transplantation. Retrospective studies showed similar results. Changing induction drug from IL2-RAb to rATG improved short-term outcome by reducing pancreas rejection from 24 to 5.4% (p = 0.032) and kidney rejection from 24 to 2.7% (p = 0.009) in a single-center US retrospective study, while long-term (up to 10 years) pancreas graft survival was better with basiliximab, reducing CMV infection in a single European center[31,32].

In the setting of pancreas transplantation, steroid withdrawal or avoidance is very important to decrease toxicity and prolong graft survival. The efficacy of IL2-RAb to allow steroid withdrawal in pancreas transplantation is unproven[22]. By contrast, five studies with alemtuzumab and six studies with rATG have reported the efficacy of both agents in preventing acute rejection and allowing steroid withdrawal, with excellent graft survival and low rejection rates[22]. In pancreas transplantation under a steroid withdrawal/avoidance regimen, alemtuzumab or rATG induction must be added in order to reduce acute rejection rates. Long-term randomized trials are mandatory to know the best induction therapy in these patients.

References

1. Noël C, Abramowicz D, Durand D, et al. Daclizumab versus antithymocyte globulin in high-immunological-risk renal transplant recipients. J Am Soc Nephrol. 2009;20:1385-92.
2. Hanaway MJ, Woodle SE, Mulgaonkar S, et al. Alemtuzumab induction in renal transplantation. N Engl J Med. 2011;364: 1909-19.
3. Brennan DC, Daller JA, Lake KD, et al. Rabbit antithymocyte globulin versus basiliximab in renal transplantation. N Engl J Med. 2006;355:1967-77.
4. Gill J, Sampaio M, Gill JS, et al. Induction immunosuppressive therapy in the elderly kidney transplant recipients in the United States. Clin J Am Soc Nephrol. 2011;6:1168-78.
5. López-Hoyos M, Fernández-Fresnedo G, Pastor JM, Arias M. Anti HLA post-transplant antibodies. A new method of monitorization. Nefrologia. 2004;24(Suppl 4):62-6.
6. Rodrigo E, Arias M. A practical approach to immune monitoring in kidney transplantation. Minerva Urol Nefrol. 2007;59: 337-52.
7. Augustine JJ, Poggio ED, Heeger PS, Hricik DE. Preferential benefit of antibody induction therapy in kidney recipients with high pretransplant frequencies of donor-reactive interferon-gamma enzyme-linked immunosorbent spots. Transplantation. 2008;86:529-34.

8. Morris PJ, Russell NK. Alemtuzumab (Campath-1H): a systematic review in organ transplantation. Transplantation. 2006;81:1361-7.
9. Meier-Kriesche H-U, Kaza H, Palekar SS, et al. The effect of daclizumab in a high-risk renal transplant population. Clin Transplant. 2000;14:509-13.
10. Hammond EB, Taber DJ, Weimert NA, et al. Efficacy of induction therapy on acute rejection and graft outcomes in African American kidney transplantation: Clin Transplant. 2010;24:40-7.
11. Brennan DC, Schnitzler MA. Long-term results of rabbit antithymocyte globulin and basiliximab induction. N Engl J Med. 2008;359:1736-8.
12. Locke JE, Simpkins CE, Leffell MS, et al. Induction immunosuppression in crossmatch positive renal transplant recipients: results of a randomised controlled clinical trial. Am J Transplant. 2009;9(Suppl 2):176A.
13. Weng RR, Piper M, Foster CE, et al. Rabbit antithymocyte globulin versus basiliximab in deceased donor renal transplants using a risk-adjusted protocol. Am J Transplant. 2009;9(Suppl 2):1758A.
14. Castro MCR, Araujo LMP; Nahas WC, et al. Induction versus noninduction therapy in kidney transplantation: considering different PARA levels and different induction therapies. Transplant Proc. 2004;36:874-6.
15. KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients. Chapter 1: Induction therapy. Am J Transplant. 2009;9:S6-9.
16. Meier-Kriesche H-U, Li S, Gruessner RWG, et al. Immunosuppression: Evolution in practice and trends, 1994-2004. Am J Transplant. 2006;6:1111-31.
17. Thomas PG, Woodside KJ; Lappin JA, et al. Alemtuzumab (Campath 1H) induction with tacrolimus monotherapy is safe for high immunological risk renal transplantation. Transplantation. 2007;83:1509-12.
18. Lü T, Yang S,Wu W, et al. Alemtuzumab induction therapy in highly sensitised kidney transplant recipients. Chin Med J. 2011;124:664-8.
19. Cruzado JM, Bestard O, Grinyó JM. New Immunosuppressive protocols with the advent of novel biological drugs. Transplantation. 2009;88:S20-3.
20. Ruggenenti P, Codreanu I, Cravedi P, et al. Basiliximab combined with low-dose rabbit anti-human thymocyte globulin: a possible further step toward effective and minimally toxic T cell-targeted therapy in kidney transplantation. Clin J Am Soc Nephrol. 2006;1:546-54.
21. Bächler K, Amico P, Hönger G, et al. Efficacy of induction therapy with ATG and intravenous immunoglobulins in patients with low-level donor-specific HLA-antibodies. Am J Transplant. 2010;10:1254-62.
22. Heilman RL, Mazur MJ, Reddy S. Immunosuppression in simultaneous pancreas-kidney transplantation. Drugs. 2010; 70:793-804.
23. Gruessner AC, Sutherland DE. Pancreas transplant outcomes for United States (US) and non-US cases as reported to the United Network for Organ Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR) as of June 2004. Clin Transplant. 2005;19:433-55.
24. Cantarovich D, Karam G, Giral-Classe M, et al. Randomized comparison of triple therapy and antithymocyte globulin induction treatment after simultaneous pancreas-kidney transplantation. Kidney Int. 1998;54:1351-6.
25. Burke GW, Kaufman DB, Millis JM, et al. Prospective, randomised trial of the effect of antibody induction in simultaneous pancreas and kidney transplantation: three years results. Transplantation. 2004;77:1269-75.
26. Stratta RJ, Alloway RR, Lo A, et al. One-year outcomes in simultaneous kidney-pancreas transplant recipients receiving an alternative dosing regimen of daclizumab. Transplant Proc. 2004;36:1080-1.
27. Stratta RJ, Alloway RR, Lo A, Hodge EE. A prospective, randomised, multicenter study evaluating the safety and efficacy of two dose regimens of daclizumab compared to no antibody induction in simultaneous kidney-pancreas transplantation: results at 3 years. Transplant Proc. 2005;37:3531-4.
28. Cantarovich D, Hourmant M, Dantal J, et al. Anti-interleukin 2 monoclonal antibody following simultaneous pancreatic and kidney transplantation: a randomised trial vs rabbit antithymocyte globulin. Transplant Proc. 1993;25:1366.
29. Farney AC, Doares W, Rogers J, et al. A randomised trial of alemtuzumab versus antithymocyte globulin induction in renal and pancreas transplantation. Transplantation. 2009;88: 810-19.
30. Huurman VA, Kalpoe JS, van de Linde P, et al. Choice of antibody immunotherapy influences cytomegalovirus viremia in simultaneous pancreas-kidney transplant recipients. Diabetes Care. 2006;29:842-7.
31. Shen L, Turgeon N, Tso P, et al. A single center comparison between basiliximab and rabbit antithymocyte globulin induction therapy for simultaneous pancreas and kidney transplantation. Am J Transplant. 2009;9(Suppl 2):1274A.
32. Yamamoto S, Tufveson G, Wahlberg J, et al. Factors influencing outcome of simultaneous kidney and pancreas transplantation: a 23-year single-center clinical experience. Transplant Proc. 2010;42:4197-201.

Induction Therapy Use in Deceased Donor Standard-Risk Renal Transplants

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Which kidney transplants must receive induction therapy?

Induction therapy is the administration of antibodies against specific or multiple antigenic targets of immune cells in the immediate perioperative period to lower the incidence of acute rejection or to allow a reduction of other components of the regimen, such as calcineurin inhibitors (CNI) in order to treat delayed graft function, or corticosteroids[1,2]. Induction use steadily increased in the USA from 46% in 1995 to 83% in 2006[3]. To a lesser degree, induction use increased in Spain from 27.8% in 1990 to 40.0% in 2002[4]. There are great disparities in the utilization of induction between countries and centers. Reported

induction in the Collaborative Transplant Study was 37%, while it reached 62% in the Australian registry and only 18% in an Asian registry[5-7]. These data highlighted the lack of consensus in induction therapy indication in renal transplantation.

The lack of common indications for induction therapy would suggest that it is not well known which patients should receive it and which induction drug must be prescribed. Commonly, induction is used in patients with a higher rejection risk (African Americans, highly sensitized patients, patients undergoing retransplantation), a higher delayed graft function risk (longer cold ischemia time, expanded criteria donors, donors after cardiac death, diabetic recipients), or in patients under minimization immunosuppressive strategies[8]. In a Spanish retrospective cohort study with 4,861 adult kidney allograft recipients over four different years (1990, 1994, 1998 and 2002), patients who received induction more frequently were those older than 60 years (RR: 1.28; 95% CI: 1.03-1.58; p = 0.0211), with panel reactive antibodies (PRA) > 15% (RR: 1.74; 95% CI: 1.32-2.30; p = 0.0001), receiving a second or more transplant (RR: 1.47; 95% CI: 1.11-1.95; p = 0.0061), with more mismatches (RR: 1.20; 95% CI: 1.12-1.28; p < 0.001), and diabetics (RR: 1.54; 95% CI: 1.13-2.09; p = 0.0055). But not all patients with these characteristics received induction and even some low-risk recipients (without any of these features) were treated with induction antibodies. Moreover, there was great variability in the use of induction therapy among the different Spanish transplant centers[4].

In order to solve this issue, the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for the care of kidney transplant recipients recommended "including induction therapy with a biologic agent as part of the initial immunosuppressive regimen" in all kidney transplant recipients[2]. This recommendation is based on several meta-analyses and registry studies that have demonstrated that induction use reduces acute rejection rates and increases both short- and long-term graft survival. Renal transplant recipients receiving antilymphocyte antibodies had a lower risk of allograft failure at two years (OR: 0.66; 95% CI: 0.45-0.97; p = 0.03) compared with patients not receiving induction in a meta-analysis including seven reports[9]. In a Spanish registry study, after adjusting for delayed graft function, acute rejection, first year creatinine, pretransplant PRA, first year hypertension, and recipient age, the use of any kind of induction therapy remained significant as a protective factor for long-term graft survival beyond the first year (HR: 0.686; 95% CI: 0.587-0.801; p < 0.001)[4]. A meta-analysis of 25,000 kidney transplant recipients in the United Network for Organ Sharing (UNOS) database showed that the use of antibody induction was independently associated with a lower risk of rejection, fewer graft losses, and improved survival compared to no induction at one year[10]. Another meta-analysis including more than 112,000 deceased donor kidney recipients with a three-year follow-up showed that graft loss was improved with the use of both monoclonal anti-interleukin-2 receptor antibodies (IL2-RAb) (RR: 0.78; 95% CI: 0.72-0.84) and rabbit antithymocyte globulin (rATG) (RR: 0.74; 95% CI: 0.68-0.81) compared to no induction[11]. In a recent Cochrane review, Webster, et al. have shown that IL2-RAb use reduces graft loss at one year by 25% (24 studies; RR: 0.75; 95% CI: 0.62-0.90) and first-year biopsy-proven acute rejection (BPAR) by 28% (14 studies; RR 0.72: 95% CI: 0.64-0.81) compared with placebo[12]. Nine recipients would need therapy with IL2-RAb to prevent one recipient having acute rejection and 42 to prevent one graft loss[12]. The use of IL2-RAb has also been found to be cost-effective compared to placebo[13]. Among others, all these studies support the KDIGO recommendation that all kidney transplant recipients must be treated with a biological

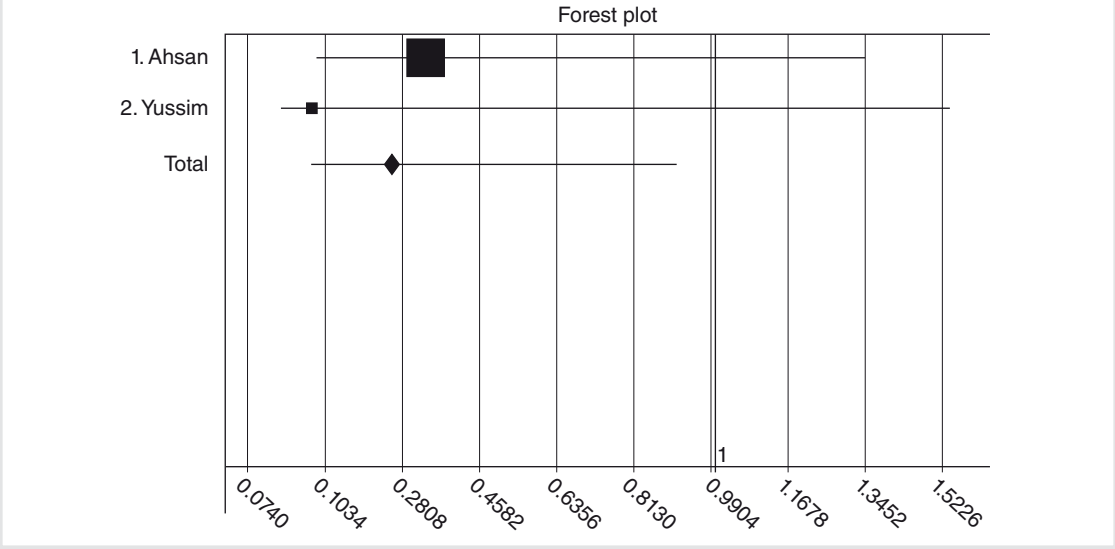

Figure 2. *Forest plot to show the overall risk (OR) of acute rejection of two reports of induction use with interleukin-2 receptor antibody in patients under a tacrolimus plus mycophenolate regimen. OR: 0.258; 95% CI: 0.072-0.912; p = 0.035 (Sinergy 2.3. soft).*

agent as induction therapy as part of the initial immunosuppressive regimen[2].

The main concern about this statement is that a high rate of patients included in these studies were not receiving the currently most frequently used immunosuppressive regimen based on tacrolimus and mycophenolate mofetil (MMF) or mycophenolic acid (MPA). Under this regimen, the acute rejection rate of standard recipients is so low that the benefits of induction with IL2-RAb could be too small to outweigh costs and minor adverse effects[2] and the risks for infection or posttransplant lymphoproliferative disease (PTLD) of using antilymphocyte antibody induction therapy could be too high[14,15]. Therefore, not using induction in low-risk recipients under a tacrolimus-MMF/MPA regimen would be reasonable. A recent retrospective analysis from the Scientific Renal Transplant Registry (SRTR) of 28,686 adult primary kidney transplant recipients with initial immunosuppression of tacrolimus/mycophenolate-based therapy tried to solve this question. Although one- and three-year graft and patient survival was not different between those receiving IL2-RAb and no-induction therapy, IL2-RAb remained as reducing the risk of acute rejection (RR: 0.90; 95% CI: 0.85-0.96; p = 0.001) on multivariate analysis. Some 70 patients would need to be treated with IL2-RAb to prevent one episode of acute rejection in kidney graft recipients on a tacrolimus/mycophenolate-based therapy. So the use of IL2-RAb induction therapy has a cost-effective and significant impact on acute rejection when used with tacrolimus/mycophenolate, but is of smaller absolute benefit than when used in cyclosporin A (CsA)-based regimens[16]. There are only two prospective randomized control trials comparing induction with IL2-RAb versus no induction in adult kidney transplant recipients under tacrolimus/mycophenolate therapy. There were no significant differences in graft survival, but acute rejection rates were lower in patients receiving IL2-RAb induction (Fig. 2)[17,18]. In order to know the role of IL2-RAb induction in kidney graft recipients under a tacrolimus/mycophenolate regimen, it is mandatory to carry out larger and longer randomized control trials.

Which induction drug must be used in standard kidney transplant recipients: basiliximab, rabbit antithymocyte globulin, or alemtuzumab?

Nowadays, no standard induction immunosuppressive regimen exists for patients undergoing renal transplantation. The most commonly used agent in USA is rATG, but not in Europe or in Asia and Australia where IL2-RAb are the preferred induction drugs[3-7]. The choice of regimen depends on the preferences of clinicians and institutions, with great differences even in the same country[4,19]. In general, rATG is used in circumstances of heightened immunologic risk, whereas IL2-RAb is primarily used in the setting of lower immunologic risk[16] and rATG is the most used lymphocyte-depleting antibody (37% in 2004 in US patients). Alemtuzumab induction increased up to 7% of patients in 2004 in the USA[3], but, except for the UK, it is not currently in use in Europe in kidney transplantation. Although basiliximab and daclizumab were equally safe and efficient as immunosuppressive drugs[20], the only IL2-RAb induction agent that can be prescribed at present is basiliximab. Next, we will analyze the information comparing rATG and basiliximab with placebo and between them and the reported data about alemtuzumab.

Compared to no antibody induction, rATG is associated with a lower incidence of acute rejection episodes in low-immunologic risk kidney transplant recipients. In a randomized controlled trial including 555 renal transplant patients mainly with a low immunologic risk, the rate of six-month BPAR was significantly lower using rATG with a tacrolimus triple regimen than without this induction therapy (15.1 vs. 25.4%; $p = 0.004$)[21]. A meta-analysis of four randomized controlled trials including 892 patients has shown that induction with antithymocyte globulin reduces the incidence of six-month (RR: 0.68; 95% CI: 0.49-0.96) and one-year acute rejection (RR: 0.67; 95% CI; 0.50-0.89) and chronic rejection (RR: 0.70; 95% CI: 0.57-0.84)[22]. But the use of antithymocyte globulin was also related to an increased incidence of cytomegalovirus (CMV) infection (RR: 1.61; 95% CI: 1.27-2.04), leukopenia (RR: 3.88; 95% CI: 2.80-5.38) and thrombocytopenia (RR: 2.92; 95% CI: 1.77-4.04)[22]. Retrospective registry analyses have clearly demonstrated that antilymphocyte antibodies increased the risk of death due to infection (RR: 1.32; $p < 0.001$), the risk of PTLD (RR: 1.78; $p < 0.001$) and bradykinin virus nephropathy (RR: 1.42; $p < 0.0001$)[14,15,23]. In the current era of immunosuppression, it seems reasonable not to use antithymocyte globulins as induction drugs in standard kidney graft recipients with a low risk of acute rejection unless patients were under a regimen with a delayed introduction or avoidance of CNI or with early steroid withdrawal.

By contrast, the main advantages of using IL2-RAb as induction drugs have been shown in standard kidney graft recipients with a low immunologic risk. A recent meta-analysis from the Cochrane Library included 32 randomized trials (5,784 patients) comparing IL2-RAb with placebo or no treatment. The use of IL2-RAb reduced the BPAR by 28% (RR: 0.72; 95% CI: 0.64-0.81) and graft loss by 25% at six months (RR: 0.75; 95% CI: 0.58-0.98) and at one year (RR: 0.75; 95% CI: 0.62-0.90), but not beyond this. Moreover, there was a 19% reduction in CMV disease (RR: 0.81; 95% CI: 0.68-0.97) and a 64% reduction in early malignancy within six months (RR: 0.36; 95% CI: 0.15-0.86). So, compared with no induction therapy, nine recipients would need treatment with IL2-RAb to prevent one recipient having acute rejection, 42 to prevent one graft loss, and 38 to prevent having CMV disease over the first year posttransplantation[12]. As pointed out above, most of the patients included in this meta-analysis were not under the currently most frequently used immunosuppressive regimen based on tacrolimus

plus MMF/MPA. However, although the benefit is smaller than with cyclosporine, a retrospective analysis has shown that adding IL2-RAb induction to tacrolimus plus MMF/MPA contributes to reducing acute rejection rates in a cost-effective way[16]. Further prospective randomized trials must clarify the role of IL2-RAb in kidney transplant recipients receiving tacrolimus plus MMF/MPA therapy. Current evidence supports the KDIGO recommendation that an IL2-RAb must be the first-line induction therapy[2].

The Cochrane meta-analysis including 16 studies (2,211 participants) also compared IL2-RAb to polyclonal antithymocyte antibodies. There was no difference in graft loss at any time point. There was a benefit of polyclonal antithymocyte antibodies over IL2-RAb for BPAR at one year (RR: 1.30; 95% CI: 1.01-1.67), but at the cost of a 75% increase in malignancy (RR: 0.25; 95% CI: 0.07-0.87) and a 32% increase in CMV disease (RR: 0.68; 95% CI: 0.50-0.93)[12]. The risks of using polyclonal antithymocyte antibodies outweigh the benefit over the acute rejection rate without improving graft survival in low-immunologic risk patients. Lymphocyte-depleting agents must be reserved for kidney transplant recipients at high immunologic risk[2].

After rATG and IL2-RAb, alemtuzumab is the third most used induction drug in the USA[3]. Although initially introduced to kidney transplantation in the 1990s with the hope of establishing tolerance, subsequent studies alone or in monotherapy demonstrated high acute-rejection rates with occasional humoral components that lead to abandoning the concept of achieving tolerance with alemtuzumab. After that, several institutions modified their immunosuppressive regimen using low-dose tacrolimus together with alemtuzumab with acceptable acute rejection rates and low incidences of viral infection and PTLD[24]. However, there are few prospective and randomized studies analyzing the role of alemtuzumab as an induction drug in kidney transplantation. Vathsala, et al. reported the results of a randomized controlled trial including 30 patients comparing alemtuzumab induction and low-dose cyclosporine maintenance with triple therapy. Acute rejection rates were 25 and 20% in the alemtuzumab and control group, respectively. Six-month graft and patient survival were comparable[25]. A randomized prospective trial demonstrated that alemtuzumab with low-dose tacrolimus and MMF and steroid avoidance was less effective than either thymoglobulin or daclizumab with higher maintenance immunosuppression, with a trend towards worse death-censored graft survival and higher chronic allograft nephropathy in the alemtuzumab group, but allowing a high rate (80%) of steroid-free patients[26]. A recently published trial with early steroid withdrawal has shown that alemtuzumab reduces the BPAR rate more than IL2-RAb (10 vs. 22%: $p = 0.003$) in low-risk patients, but without differences in graft survival and with a higher rate of infectious adverse events (22 vs. 35%; $p = 0.02$)[27].

Although, at this moment, there are no demonstrated differences either in acute rejection or in graft survival comparing alemtuzumab, thymoglobulin, and IL2-RAb, one of the main advantages of alemtuzumab is its low cost. A typical course of alemtuzumab can be five to six times cheaper than a course of thymoglobulin and IL2-RAb[28]. Long-term prospective randomized studies with alemtuzumab will be necessary to determine their role as induction therapy[24].

Is induction therapy useful to delay calcineurin inhibitor introduction in patients at risk of delayed graft function?

In an effort to reduce CNI exposure and thus reduce the potential for nephrotoxicity, without increasing the risk of rejection, induction

therapy has been added to various CNI-minimization protocols. These protocols avoid completely the use of CNI, delay their introduction, or minimize dosing. Calcineurin inhibitor avoidance or withdrawal protocols increase the risk of acute rejection in spite of using induction. The CAESAR trial compared cyclosporine withdrawal, low-dose and standard-dose with mycophenolate and steroids and with IL2-RAb in the groups of minimization and withdrawal. Despite induction use, the withdrawal group experienced a higher incidence of acute rejection (38 vs. 25, vs. 28%)[29]. So, minimization is better than total withdrawal in terms of acute rejection.

A delayed CNI introduction can reduce the rate of delayed graft function (DGF) or can limit its length by avoiding its nephrotoxic effect[30]. Several prospective randomized trials have analyzed whether induction therapy can help to diminish acute rejection rates in patients at DGF risk under a CNI delayed introduction protocol. Both antithymocyte globulin and IL2-RAb drugs safely allow a delayed CNI start in kidney transplant patients. The use of rATG and a nine-day delay in CNI administration was associated with a lower rate of BPAR, a similar DGF rate, and comparable evolution of renal function compared to no induction therapy and immediate CNI administration[31]. Similarly, IL2-RAb induction with a six- to 10-day delay in tacrolimus and cyclosporine administration have shown comparable BPAR and DGF rates than a no induction group with immediate CNI introduction[32-34]. Thus, induction therapy can help to delay CNI administration without increasing the acute rejection risk, although delayed CNI introduction seems not to improve either the DGF rate or renal function. As there are no prospective randomized trials comparing the efficacy of rATG and IL2-RAb induction in a CNI-delayed protocol, it is not possible to recommend any of these drugs, although the higher rate of infection and PTLD with rATG can limit its use in this instance.

Which induction therapy must be used to withdraw corticosteroids?

Steroid minimization or avoidance regimens attempt to reduce cardiovascular risk, the leading cause of death with a functioning graft, and chronic allograft nephropathy favored by hyperlipidemia, hypertension, and diabetes. However, any advantage seen in cardiovascular risk must be balanced against the risk of acute rejection and further allograft loss[35]. Steroid withdrawal was initially attempted at three to six months posttransplantation, but, progressively, more aggressive strategies were adopted by withdrawing steroids within the first week posttransplantation[36]. Induction therapy can make steroid minimization or avoidance easy, increasing the global immunosuppressive level, but which induction agent is the best to achieve this goal is an issue for discussion. In a meta-analysis of 34 studies (5,637 patients) comparing steroid avoidance or withdrawal, the type of antibody induction was not related with the relative risk of acute rejection[35].

Several trials have analyzed the role of antithymocyte agents or IL2-RAb in steroid withdrawal or avoidance regimens separately. Six trials using IL2-RAb randomized patients to early steroid withdrawal (by day 7) or to standard steroid therapy. Four of these trials found a similar incidence of acute rejection in the steroid withdrawal groups[37-40], while only in two trials, the group with early steroid withdrawal suffered more acute rejection rates, but without reaching statistical significance[41,42]. Large randomized controlled trials have shown that in a regimen including IL2-RAb induction with CNI-based therapy, steroid withdrawal within the first posttransplant week is possible without a significant increase in risk of rejection[36].

Similar data was shown with antithymocyte globulin. In a randomized trial in 500 patients receiving cyclosporine and mycophenolate

comparing steroids versus low-dose steroid and steroid cessation at three months, the group of steroid withdrawal suffered more acute rejections (23 vs. 14%; p = 0.008) only in patients who did not receive induction with antithymocyte globulin. Acute rejection was similar in the cohort of patients who received antithymocyte antibodies (13.4 vs. 11.5%; p = ns), suggesting that steroid withdrawal can also be carried out safely when including antithymocyte globulins[43].

Only two prospective trials compared IL2-RAb with rATG avoiding steroids within the first week. Heilman, et al. used induction with basiliximab in 17 patients and rATG in 72 patients to withdraw steroids at day 4. At six months posttransplantation, acute rejection-free survival was 93% for rATG and 65% for basiliximab. There were no differences between groups in the percentage of patients who continued to be steroid-free at last follow-up (90% with rATG vs. 88% with IL2-RAb)[44]. Woodle, et al. recently published the five-year results of a prospective randomized controlled trial comparing seven-day steroid cessation versus long-term steroid therapy. Induction use was not randomized. About one-third of patients received IL2-RAb and two-thirds rATG. The BPAR rate was higher in the steroid-withdrawal group, without reaching statistic significance (18 vs. 11%; p = 0.06). Interestingly, the BPAR was higher with IL2-RAb than with rATG (24 vs. 14%; p = 0.09) in steroid-withdrawal patients[45].

In registry and retrospective studies, antithymocyte globulins are more useful to reduce acute rejection rates in steroid avoidance or withdrawal regimens than IL2-RAb. Data of 19,137 kidney transplant recipients of the Organ Procurement and Transplantation Network (OPTN) showed that when steroids are absent at discharge, the risk reduction for a composite endpoint of rejection, graft failure, or death at six months in thymoglobulin-treated compared with basiliximab-treated patients (OR: 0.66; 95% CI: 0.44-1.00) and with patients without induction (OR: 0.36; 95% CI: 0.25-0.52) was significant[46]. A recent retrospective single-center study including 167 patients receiving tacrolimus, mycophenolate and induction drugs with steroid withdrawal within the first week showed a lower rate of acute rejection episodes throughout the first year with rATG versus IL2-RAb (11.4 vs. 25.6%; p = 0.01), a higher rate of CMV infection (27.9 vs. 7.9%; p = 0.001) and a lower proportion of a combined endpoint of death and graft loss (4.5 vs. 16.5%; p = 0.01)[47].

So, studies that directly compared antithymocyte globulins versus IL2-RAb pointed out that antithymocyte globulin could be a better induction drug when patients are included in a steroid withdrawal or avoidance regimen. Due to its higher toxicity, further randomized controlled trials must be carried out to determine which induction drug should be used in order to avoid or withdraw steroids more safely.

References

1. Padiyar A, Augustine JJ, HRIcik DE. Induction antibody therapy in kidney transplantation. Am J Kidney Dis. 2009;54: 935-44.
2. KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients. Chapter 1: Induction therapy. Am J Transplant. 2009;9:S6-9.
3. Meier-Kriesche H-U, Li S, Gruessner RWG, et al. Immunosuppression: Evolution in practice and trends, 1994-2004. Am J Transplant. 2006;6:1111-31.
4. Rodrigo E, Fernández-Fresnedo G, Robledo C, et al. Heterogeneity of induction therapy in Spain. Changing patterns according to year, centre, indications and results. NDT Plus. 2010;3(Suppl 2):ii9-14.
5. Opelz G, Döhler B. Collaborative Transplant Study. Influence of immunosuppressive regimens on graft survival and secondary outcomes after kidney transplantation. Transplantation. 2009;87:795-802.
6. Chang SH, Russ GR, Chadban SJ, et al. Trends in adult post-kidney transplant immunosuppressive use in Australia, 1991-2005. Nephrology. 2008;13:171-6.
7. Vathsala A; Asian Transplant Registry. Immunosuppression use in renal transplantation from Asian transplant centers: a preliminary report from the Asian Transplant Registry. Transplant Proc. 2004;36:1868-70.
8. Szczech LA, Berlin JA, Feldman HI. The effect of antilymphocyte induction therapy on renal allograft survival. A meta-analysis of individual patient-level data. Anti-Lymphocyte Antibody Induction Therapy Study Group. Ann Intern Med. 1998;128:817-26.
9. Szczech LA, Berlin JA, Aradhye S, et al. Effect of anti-lymphocyte induction therapy on renal allograft survival: a meta-analysis. J Am Soc Nephrol. 1997;8:1771-7.

10. Bunnapradist S, Takemoto SK. Multivariate analysis of antibody induction therapy and their associated outcomes in deceased donor transplants. Transplant Proc. 2005;37: 889-91.
11. Opelz G, Naujokat C, Daniel V, et al. Disassociation between risk of graft loss and risk of non-Hodgkin lymphoma with induction agents in renal transplant recipients. Transplantation. 2006;81:1227-33.
12. Webster AC, Ruster LP, McGee R, et al. Interleukin 2 receptor antagonists for kidney transplant recipients. Cochrane Database Syst Rev. 2010;CD003897.
13. Morton RL, Howard K, Webster AC, et al. The cost-effectiveness of induction immunosuppression in kidney transplantation. Nephrol Dial Transplant. 2009;24:2258-69.
14. Meier-Kriesche H-U, Andorfer JA, Kaplan B. Association of antibody induction with short- and long-term cause-specific mortality in renal transplant recipients. J Am Soc Nephrol. 2002;13:769-72.
15. Bustami RT, Ojo AO, Wolfe RA, et al. Immunosuppression and the risk of post-transplant malignancy among cadaveric first kidney transplant recipients. Am J Transplant. 2004;4:87-93.
16. Gralla J, Wiseman AC. The impact of IL2ra induction therapy in kidney transplantation using tacrolimus-and mycophenolate-based immunosuppression. Transplantation. 2010;90:639-44.
17. Ahsan N, Holman MJ, Jarowenko MV, et al. Limited dose monoclonal IL-2R antibody induction protocol after primary kidney transplantation. Am J Transplant. 2002;2:568-73.
18. Yussim A, Bielsky V, Bar-Nathan N, et al. Two dose daclizumab in conjunction with tacrolimus-based protocol in kidney transplantation – prospective, randomized study. Transplantation. 2004;2 [abstract P757].
19. Gabardi S, Martin ST, Roberts KL, Grafals M. Induction immunosuppressive therapies in renal transplantation. Am J Health-Syst Pharm. 2011;68:211-18.
20. Kandus A, Arnol M, Omahen K, et al. Basiliximab versus daclizumab combined with triple immunosuppression in deceased donor renal transplantation: a prospective, randomized study. Transplantation. 2010;89:1022-7.
21. Charpentier B, Rostaing L, Berthoux F, et al. A three-arm study comparing immediate tacrolimus therapy with antithymocyte globulin induction therapy followed by tacrolimus or cyclosporine A in adult renal transplant recipients. Transplantation. 2003;75:844-51.
22. Tian JH, Wang X, Yang KH, et al. Induction with and without antithynocyte globulin combined with cyclosporine/tacrolimus-based immunosuppression in renal transplantation: a meta-analysis of randomized controlled trials. Transplant Proc. 2009;41:3671-6.
23. Dharnidharka VR, Cherikh WS, Abbott KC. An OPTN analysis of national registry data on treatment of BK virus allograft nephropathy in the United States. Transplantation. 2009;87: 1019-26.
24. Ciancio G, Burke GW. Alemtuzumab (Campath-1H) in kidney transplantation. Am J Transplant. 2008;8:15-20.
25. Vathsala A, Ona ET, Tan SY, et al. Randomized trial of Alemtuzumab for prevention of graft rejection and preservation of renal function after kidney transplantation. Transplantation. 2005;80:765-74.
26. Ciancio G, Burke GW, Gaynor JJ, et al. A randomized trial of thymoglobulin vs. alemtuzumab (with lower dose maintenance immunosuppression) vs. daclizumab in renal transplantation at 24 months of follow-up. Clin Transplant. 2008;22:200-10.
27. Hanaway MJ, Woodle SE, Mulgaonkar S, et al. Alemtuzumab induction in renal transplantation. New Engl J Med. 2011;364:1909-19.
28. Morris PJ, Russell NK. Alemtuzumab (Campath-1H): a systematic review in organ transplantation. Transplantation. 2006;81:1361-7.
29. Ekberg H, Grinyo J, Nashan B, et al. Cyclosporine sparing with mycophenolate mofetil, daclizumab, and corticosteroids in renal allograft recipients: the CAESAR study. Am J Transplant. 2007;7:560-70.
30. Gaber AO, Monaco AP, Russell JA, et al. Rabbit antithymocyte globulin (Thymoglobulin). Drugs. 2010;70: 691-732.
31. Mourad G, Garrigue V, Squifflet JP, et al. Induction versus noninduction in renal transplant recipients with tacrolimus-based immunosuppression. Transplantation. 2001;72: 1050-5.
32. Andres A, Budde K, Clavien P-A, et al. A randomized trial comparing renal function in older kidney transplant patients following delayed versus immediate tacrolimus administration. Transplantation. 2009;88:1101-8.
33. Andres A, Marcén R, Valdés F, et al. A randomized trial of basiliximab with three different patterns of cyclosporin A initiation in renal transplant from expanded criteria donors and at high risk of delayed graft function. Clin Transplant. 2009;23:23-32.
34. Mourad G, Karras A, Kamar N, et al. Renal function with delayed or immediate cyclosporine microemulsion in combination with enteric-coated mycophenolate sodium and steroids: results of follow up to 30 months post-transplant. Clin Transplant. 2007;21:295-300.
35. Knight SR, Morris PJ. Steroid avoidance or withdrawal after renal transplantation increases the risk of acute rejection but decreases cardiovascular risk. A meta-analysis. Transplantation. 2010;89:1-14.
36. Vincenti F, Andrés A, Becker T, et al. Interleukin-2 receptor antagonist induction in modern immunosuppression regimens for renal transplant recipients. Transplant Int. 2006;19:446-57.
37. Rostaing L, Cantarovich D, Mourad G, et al. for the CARMEN study group. Corticosteroid-free immunosuppression with tacrolimus, mycophenolate mofetil, and daclizumab induction in renal transplantation. Transplantation. 2005;79: 807-14.
38. ter Meulen CG, van Riemsdijk I, Hené RJ, et al. Steroid-withdrawal at 3 days after renal transplantation with anti-IL-2 receptor aet al. Steroid-withdrawal at 3 days after renal transplantation with an. 2004;4:803-10.
39. Vincenti F, Monaco A, Grinyo J, et al. Multicenter randomized prospective trial of steroid withdrawal in renal transplant recipients receiving basiliximab, cyclosporine microemulsion and mycophenolate mofetil. Am J Transplant. 2003;3: 306-11.
40. Kumar MS, Xiao S-G, Fyfe B, et al. Steroid avoidance in renal transplantation using basiliximab induction, cyclosporine-based immunosuppression and protocol biopsies. Clin Transplant. 2005;19:61-9
41. Vincenti F, Schena FP, Paraskevas S, et al. A randomized, multicenter study of steroid avoidance, early steroid withdrawal or standard steroid therapy in kidney transplant recipients. Am J Transplant. 2008:307-16.
42. Vitko S, Klinger M, Salmela K, et al. Two corticosteroid-free regimens-tacrolimus monotherapy after basiliximab administration and tacrolimus/mycophenolate mofetil in comparison with a standard triple regimen in renal transplantation: results of the Atlas study. Transplantation. 2005;80: 1734-41.
43. Lebranchu Y, Aubert P, Bayle F, et al. Could steroids be withdrawn in renal transplant patients sequentially treated with ATG, cyclosporine, and cellcept? One-year results of a double-blind, randomized, multicenter study comparing normal dose versus low-dose and withdrawal of steroids. Transplant Proc. 2000;32:396-7.
44. Heilman RL, Reddy KS, Mazur MJ, et al. Acute rejection risk in kidney transplant recipients on steroid-avoidance immunosuppression receiving induction with either antithymocyte globulin or basiliximab. Transplant Proc. 2006;38:1307-13.
45. Woodle ES, First MR, Pirsch J, et al. A prospective, randomized, double-blind, placebo-controlled multicenter trial comparing early (7 day) corticosteroid cessation versus long-term, low-dose corticosteroid therapy. Ann Surg. 2008;248: 564-77.
46. Willoughby LM, Schnitzler MA, Brennan DC, et al. Early outcomes of Thymoglobulin and Basiliximab induction in kidney transplantation: application of statistical approaches to reduce bias in observational comparisons. Transplantation. 2009;87:1520-9.
47. Liborio AB, Mendoza TR, Esmeraldo RM, et al. Induction antibody therapy in renal transplantation using early steroids withdrawal: long-term results. XLVIII ERA-EDTA Congress, Prague 2011. [abstract F543].

Induction Therapy in Elderly Donor Kidney Transplantation

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Introduction

Transplantation of a functioning kidney is the best treatment for patients with end-stage renal disease (ESRD) as it increases their survival rate and quality of life[1-3]. However, there are insufficient organs for transplantation and many patients needing transplants do not receive them and die while they are in the waiting list[4]. Consequently, the criteria for donor acceptance have been modified in the last years to allow the use of organs from donors that only a few years ago would have been considered unsuitable. Older donors, donors with some cardiovascular risk factors, and those with long cold ischemia time were considered to be suitable donors and designated as marginal donors. The United Network for Organ Sharing (UNOS) instituted a formalized definition of a marginal kidney with the advent of the expanded criteria donors (ECD). These deceased donor kidneys had a 70% or greater risk of graft loss compared to an ideal donation and were characterized by donors aged ≥ 60 years, or donors aged 50-59 years with at least two of the following conditions: cerebrovascular accident as cause of death, serum creatinine > 1.5 mg/dl, or a history of hypertension[5]. However, the definition of an old donor is variable among the authors: more than 50 to 55 years[2,6-8], more than 60[9-18], or more than 65 years[19-26]. Moreover, nowadays very old donor kidneys, above 70 years, are being transplanted[27-30]. On the other hand, the characteristics of patients included in the waiting lists have also changed. While those younger than 50 years have declined since 1990, the number of new registrants aged 50 to 69 years has doubled and the number of registrants 70 years and older has increased more than fivefold during the past decade[31,32].

As a consequence of these changes, the scenario of renal transplantation is different from that one decade ago. Both donors and recipients are older than before. Older kidney grafts have the characteristics due to the age, and older recipients have an increased morbidity and are at high risk of infection and malignancies. This must be taken into account for establishing graft and recipient matching criteria and for selecting the adequate immunosuppressive regime (Table 1).

Evolution of old kidney and expanded criteria donor donation

The use of ECD for transplantation significantly increased the number of transplants from deceased donors in Canada between 1996 and 2003, but has not substantially increased since then[33]. Recent data from the USA show a modest increase

Table 1. Characteristics of the ageing kidney

Functional changes:
- Lower glomerular filtration rate
- Reduction of sodium excretion
- Impairment of tubular potassium secretion
- Loss of the ability to concentrate or dilute the urine
- Increased toxicities

Structural changes:
- Glomerulosclerosis
- Tubular atrophy
- Interstitial fibrosis
- Intimal fibrosis and medial thinning in blood vessels

of ECD transplants from 1999 to 2008 (20.3 to 22.7%), with a decline in standard criteria donors (SCD)[34]. These findings are different from those obtained in some European countries. In 2004, 32.5% of kidneys transplanted in the French regional area of Ile de France came from ECD[35]. Data from Eurotransplant have shown that the availability of deceased donors ≥ 65 almost doubled and had exceeded the number of recipients ≥ 65 since 2003[23]. Older donor kidneys started to be used in Spain earlier than in other countries; more than 10 years ago 27% of donors were aged ≥ 60 years[36] and there was a progressive increase in the percentage of donors over 70 years thereafter[37].

Kidney ageing

Age determines functional and structural changes in the kidney[38]. Longitudinal studies have shown that glomerular filtration rate (GFR) declines at an average of 0.72 to 1 ml/min per year, resulting in an inulin clearance of 65 ml/min at the age of 90 years. However, between one- and two-thirds of the elderly have a perfectly normal GFR[39,40]. These discrepancies raise the question whether the decline in GFR is a consequence of the normal ageing process or the result of comorbidity. But not only GFR is affected by ageing, there are also tubular functional changes such as a reduction in urinary sodium excretion, an impairment of potassium secretion predisposing to hyperkalemia, and a loss of the ability to concentrate and to dilute the urine. Moreover, the reduction in excretory capacity of the kidney may alter the pharmacokinetics of many drugs[38].

In addition, there are structural changes including glomerulosclerosis, tubular atrophy, interstitial fibrosis, and changes in the blood vessels such as intimal fibrosis and medial thickening[38,41]. Glomerular sclerosis increases with age; about 10% of glomeruli can be sclerosed in normal subjects younger than 40 years. However, the histological changes observed in the ageing human kidney are not specific and can be produced by other disorders.

Renal senescence could contribute to the diminished ability of the old donor kidneys to withstand peri- and posttransplant stress, resulting in a higher incidence of delayed graft function (DGF), chronic allograft nephropathy, and poorer graft survival[41].

Old donor transplant versus dialysis

Although one way of improving the organ supply is to increase the use of ECD, some concern exists about their use and more than one-third of the kidneys from donors ≥ 60 years are discarded in the USA[42]. Some studies have shown the risks of DGF and of primary non-functioning kidneys are increased in grafts from ECD when compared with SCD[25,35]. Moreover, kidneys from ECD presented poorer graft function than those from SCD in the first months and thereafter[10,17,22,23,35] as donor age was a risk factor for lower GFR[43]. It is important to point out that poor graft function in the first posttransplant months has a negative impact on long-term graft survival[44-46].

When the impact of older donor age on graft survival was analyzed, the results were controversial. Some reports have shown poorer results compared with SCD[2,7,10,15,16,25,47]. But in some single-center[8,11,12,22] and multicentre[9,26] retrospective studies, donor age was not a negative risk factor for even three to five year graft survival when older donor kidneys were allocated without regard to the age of the donor or recipient[8,12,17,35]. Some authors recommended evaluating clinical risk factors such as a history of hypertension and cerebrovascular cause of death in elderly donors as they

and not old age were a risk of poor graft survival[7,9]. Donor age was also associated with a negative impact on patient survival[10,16,47].

Despite the previous considerations, transplantation of ECD kidneys yielded an improved patient survival over maintenance dialysis[1,2,14,48,49]. In addition, transplantation of ECD kidneys also reduces the time on dialysis, which is a risk factor for patient survival[23]. The optimal use of ECD is not definitively established. Waiser, et al.[6] reported 10 years ago that old donors did not do well in young recipients and old donors should be matched with old recipients and similar results have been observed in other studies[23,49,50]. In another study, graft survival was similar in "old-for-old" as in HLA-matching and waiting time allocation[20,22]. Others consider that it is not necessary to match the life expectancy of the recipient with the kidney, and recipient selection should be done on the basis of their estimated need from nephron mass[11,12]. As older kidneys have shorter graft survivals and lower GFR, it is reasonable to use these organs for older recipients, in whom long-term graft survival is not as important as in younger recipients. As the most important cause of graft loss in older recipients is death with a functioning graft[6], old-for-old transplantation is a physiologically logical approach to treatment of end-stage renal failure, but this allocation process could penalize the availability of younger donor kidneys in older recipients. In 1999, Eurotransplant established the Eurotransplant Senior Program allocation scheme to match the functional capacity of organs from donors ≥ 65 years to the functional requirements of recipients ≥ 65 years. The aims of the program were: to achieve a more efficient use of kidneys from elderly donors and to offer transplantation to elderly recipients[51]. Nowadays, old-for-old kidney allocation is a practice used by many transplant centers[19,20,23,27-30,52]. In the Scientific Registry of Transplant Recipients (SRTR) database, older patients (> 65 years) and patients with the primary diagnosis of diabetes have significantly reduced survival expectancies on dialysis. An ECD transplant if performed at two years after ESRD onset gives a projected survival similar to that of four-year dialysis patients who accept an SCD transplant[21]. These findings could have contributed to recommending ECD for older patients, patients with diabetes as the primary cause of renal failure, and patients with difficult vascular access in the USA.

To improve the selection of ECD, some clinical scoring systems, based on information available at the time of graft nephrectomy, were proposed[9,53,54]. But as the predicted performance when applied to older donors could be restrictive, histologic evaluation before grafting has been recommended to optimize their use. Remuzzi, et al.[13] evaluated the components of the kidney tissue (vessels, glomeruli, tubules, and connective tissue) and gave a score ranging from 0 to 3: a score of 0 if no changes and a score of up to 3 if marked changes were present. The sum of these scores was defined as the Pirani score, which could range from 0 to 3. Kidneys with a global scoring from 0 to 3 were considered for use as single transplants; those with a score from 4 to 6 for use as dual transplants; those with a score of 7 or greater were discharged. The chronic allograft damage index (CADI) score was based on the individual component scores for interstitial inflammation, interstitial fibrosis, glomerular sclerosis, glomerular mesangial matrix increase, vascular intimal proliferation, and tubular atrophy, with each individual parameter being scored from 0 to 3[55]. Anglichenau, et al.[56] tested the different clinical and histopathological scoring systems and came to the conclusion that a composite score that included donor serum creatinine (≥ 150 µmol/l), donor hypertension, and glomerular sclerosis (≥ 10%) was the best predictor of estimated GFR at one year and of death-censored graft survival when compared with clinical scoring systems. Others

Table 2. Immunosuppression in expanded criteria donors from selected reports

Author	Cases (n)	Donor age	Induction	Immunosuppression
Waiser, et al. 2000[6]	176	> 55 years	None	AZA + steroids or CsA + steroids
De Fijter, et al. 2001[8]	144	> 50 years	None	CsA + steroids
Fritsche, et al. 2003[20]	69	ECD	Thymoglobulin (19%). IL2-RAb (52%)	CsA (35%), TAC (52%), MMF (77%) and steroids
Stratta, et al. 2006[12]	37	ECD	Thymoglobulin or alemtuzumab	Low-dose, delayed TAC + MMF
Emparan, et al. 2004[79]	15	> 60 years	Basiliximab	Delayed CsA + MMF + steroids
Segoloni, et al. 2005[52]	88	> 50 years	Basiliximab	MMF + steroids. Delayed TAC, MMF withdrawal
Arbogast, et al. 2005[80]	30	> 60 years	ATGF + basiliximab	MMF + steroids
Bodingbauer, et al. 2006[22]	91	> 65 years	Thymoglobulin or basiliximab	MMF + steroids
Anglicheau, et al. 2008[56]	313	> 50 years	Thymoglobulin or basiliximab	CsA + MMF + steroids
Guba, et al. 2008[24]	56	> 50 years	ATGF + basiliximab	MMF + steroids
Foss, et al. 2009[28]	54	> 75 years	Basiliximab	Standard triple or quadruple therapy
Collini, et al. 2009[29]	38	> 75 years	Basiliximab	TAC or CsA + MMF or SRL
Favi, et al. 2010[82]	20	> 60 years	Basiliximab + thymoglobulin	CsA or TAC + steroids

AZA: azathioprine; CsA: cyclosporin A; ECD: extended criteria donor; IL2-RAb: interleukin-2 receptor antibody; TAC: tacrolimus; MMF: mycophenolate mofetil; ATGF: antithymocyte globulin-Fresenius; SRL: sirolimus.

have questioned the utility of histopathological information[28].

Induction therapy in elderly donor kidney transplantation

Older donor kidneys are at high risk of DGF, nephrotoxicity, and chronic allograft failure[10,15,23,24,75]. Furthermore, acute rejection episodes increase with increasing age[6,15,27] and it has been reported that they are more common in old-for-old recipients than in other transplant groups[8,20,23,24]. This could be due to the older donor kidneys being more immunogenic than SCD and consequently needing more potent immunosuppression to prevent rejection. But these findings have not been confirmed by other authors[10,22]. On the other hand, older recipients have a lower risk of rejection[15] and are especially susceptible to infection and malignancies[76]. Induction therapy and maintenance immunosuppression have to be balanced according to the characteristics of both donors and recipients.

To our knowledge, there are no randomized prospective studies in which the effect of induction on patients and graft survival in ECD recipients has been examined. Therefore, there is not a definitive induction regime that can be administered to older donor or ECD recipients. Some authors do not use induction therapy, while others use induction therapy with thymoglobulin or basiliximab with or without delayed administration of calcineurin inhibitors (CNI) (Table 2). Hardigen, et al.[77] compared antithymocyte globulin and basiliximab in 278 renal transplant recipients at risk for DGF or acute rejection. About 25% of them received grafts from ECD. Some benefits such as less acute rejection and death were observed using antithymocyte globulin in recipients with SCD kidneys. The authors

emphasize the lack of effect of thymoglobulin in ECD recipients. In another study performed in 117 recipients, 50% receiving grafts from donors older than 60 years, basiliximab was administered in three different patterns of cyclosporin A (CsA) initiation. Late-onset CsA did not achieve improvement in the DGF rate and showed a higher incidence of biopsy-proven acute rejection[78]. However, good results have been reported in old-for-old transplants with basiliximab induction, delayed introduction of CsA, mycophenolate mofetil (MMF), and steroids in a small number of patients[79]. There are several studies in which patients were treated with MMF-based and CNI-free immunosuppression regimens and induction therapy[24,80]. In two of them, induction with thymoglobulin (4-10 days) gave long-term outcomes comparable with those of young recipients who have received an allograft from young cadaveric donors[80,81]. In another study, induction therapy with antithymocyte globulin-Fresenius (ATGF single dose) and basiliximab was only partially successful, the rate of acute rejection was very high (53.6%), complicated cytomegalovirus (CMV) infection occurred in 35% of patients, and primary immunosuppression had to be changed in 56% of patients during the first year[24]. In one observational study without a control group, induction therapy with basiliximab plus MMF and steroids with a later switch to tacrolimus and steroid withdrawal/minimization showed a low acute rejection rate, stable graft function, and favorable patient and graft outcomes in old-for-old allocation[52]. The efficacy and security of induction therapy with basiliximab plus thymoglobulin with low-dose CNI were evaluated in a prospective study. There were no differences at six months in graft and patient survival between old donor transplant recipients (> 60 years) and those receiving organs from donors < 60 years[82].

In accordance with the data from the literature and the lack of prospective, randomized trials, it seems reasonable to administer induction therapy with thymoglobulin to reduce the risk of DGF and rejection and to lower CNI doses when old donor grafts are transplanted to young recipients. In the case of old-for-old transplants, we have to take into account the recommendations for reducing the risk of DGF, of CNI nephrotoxicity, and of infections and malignancies by minimization or avoidance of CNI. In this setting ATGF or IL2-RAb may be the induction agents of choice as they have a better safety profile.

References

1. Wolfe RA, Ashby VB, Milford EL, 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.
2. Ojo AO, Hanson JA, Meier-Kriesche H-U, et al. Survival in recipients of marginal cadaveric donor kidneys compared with other recipients and wait-listed transplant candidates. J Am Soc Nephrol. 2001;12:589-97.
3. McDonald S, Russ G. Survival of recipients of cadaveric kidney transplants with those receiving dialysis treatment in Australia and New Zealand, 1991-2001. Nephrol Dial Transplant. 2002;17:2212-19.
4. Schold J, Srinivas TR, Sehgal AR, Meier-Kriesche H-U. Half of kidney transplant candidates who are older than 60 years now placed on the waiting list will die before receiving a deceased-donor transplant. Clin J Am Soc Nephrol. 2009;4:1239-45.
5. Port FK, Bragg-Gresham JL, Metzger MA, et al. Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors. Transplantation. 2002;74:1281-6.
6. Waiser J, Schreiber M, Budde K, et al. Age-matching in renal transplantation. Nephrol Dial Transplant. 2000;15:696-700.
7. Carter JT, Lee CM, Weinstein RJ, Lu AD, Dafoe DC, Alfrey EJ. Evaluation of the older cadaveric kidney donor: the impact of donor hypertension and creatinine clearance on graft performance and survival. Transplantation. 2000;70: 765-71.
8. De Fijter JW, Mallat MJK, Doxiadis N, et al. Increased immunogenicity and cause of graft loss of old donor kidneys. J Am Soc Nephrol. 2001;12:1538-46.
9. Pessione F, Cohen S, Durand D, et al. Multivariate analysis of donor risk factors for graft survival in kidney transplantation. Transplantation. 2003;75:361-7.
10. Oppenheimer F, Aljama P, Asensio C, Bustamante J, Crespo JF, Guirado L. The impact of donor age on the results of renal transplantation. Nephrol Dial Transplant. 2004;19(Suppl 3):iii11-15.
11. Stratta RJ, Rohr MS, Sundberg AK, et al. Increased kidney transplantation utilizing expanded criteria deceased organ donors with results comparable to standard criteria donor transplant. Ann Surg. 2004;239:688-97.
12. Stratta RJ, Sudberg AK, Rohr R, et al Optimal use of older donors and recipients in kidney transplantation. Surgery. 2006;139:324-33.
13. Remuzzi G, Cravedi P, Perna A, et al. Long-term outcome of renal transplantation from older donors. N Engl J Med. 2006;354:343-52.
14. Martin Navarro J, Ortega M, Gutierrez MJ, et al. Survival of patients older than 60 years with kidneys transplanted from Spanish expanded criteria donors versus patients continued on hemodialysis. Transplant Proc. 2009;41:2376-8.
15. Heldal K, Hartmann A, Leivestad T, et al. Clinical outcomes in elderly kidney transplant recipients are related to acute rejection episodes rather than pretransplant comorbidity. Transplantation. 2009;87:1045-51.

16. Lim WH, Chang S, Chadban S, et al. Donor-recipient age matching improves years of graft function in deceased-donor kidney transplantation. Nephrol Dial Transplant. 2010;25:3082-9.
17. Solá R, Guirado L, López-Navidad A, Bonfill X, et al. Is it appropriate to implant kidneys from elderly donors in young recipients. Transplantation. 2010;90;286-91.
18. Lai Q, Nudo F, Levi Sandri GB, et al. Survival after kidney transplantation does not differ with 50-59- or over 60-year-old expanded-criteria donors. Transplant Proc. 2011;43:1030-2.
19. Beckurts UTE, 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.
20. Fritsche L, Hörstrup J, Budde K, et al. Old-for-old kidney allocation allows successful expansion of the donor and recipient pool. Am J Transplant. 2003;3:1434-9.
21. Schold JD, Meier-Kriesche H-U. Which renal transplant candidates should accept marginal kidneys in exchange for a shorter waiting time on dialysis? ClinJ Am Soc Nephrol. 2006;1:532-8.
22. Bodingbauer M, Pakrah B, Steininger, R et al. The advantage of allocating kidneys from old cadaveric donors to old recipients: a single center experience. Clin Transplant. 2006;20:471-5.
23. Frei U, Noeldeke J, Machold-Fabrizii V, et al. Prospectively age-matching in elderly kidney transplant recipients- a 5-year analysis of the Eurotransplant Senior Program. Am J Transplant. 2008;8:50-7.
24. Guba M, Rentsch M, Wimmer CD, et al. Calcineurin-inhibitor avoidance in elderly renal allograft recipients using ATG and basiliximab combined with mycophenolate mofetil. Transplant Int. 2008;21:637-45.
25. Moers C, Kornmann NSS, Leuvenink HGD, Ploeg RJ. The influence of deceased donor age and old-for-old allocation on kidney transplant outcome. Transplantation. 2009;88:542-52.
26. Karatzas T, Bokos J, Katsargyris A, et al. Advanced donor age alone is not a risk factor for graft survival in kidney transplantation. Transplant Proc. 2011;43:1537-43.
27. Chavalitdhamrong D, Gill J, Takemoto S, et al. Patient and graft outcomes from deceased kidney donors age 70 years and older: an analysis of the Organ Procurement Transplant Network/United Network of Organ Sharing database. Transplantation. 2008;85:1573-9.
28. Foss A, Heldal K, Scott H, et al. Kidneys from deceased donors more than 75 years perform acceptably after transplantation. Transplantation. 2009;87:1437-41.
29. Collini A, Kalmar P, Dhamo A, Ruggieri G, Carmellini M. Renal transplant from very old donors: how far can we go? Transplantation. 2009;87:1830-6.
30. Galeano C, Marcén R, Jimenez S, et al. Utilization of elderly kidney donors (>70 years) does not affect graft survival in the medium term. Transplant Proc. 2010;42:3935-7.
31. Rao PS, Merion RM, Ashby VB, Port FK, Wolfe RA, Kayler LK. Renal transplantation in elderly patients older than 70 years of age: results from the Scientific Registry of Transplant Recipients. Transplantation. 2007;83:1069-74.
32. Huang E, Poommipanit N, Samaio MS, et al. Intermediate-term outcomes associated with kidney transplantation in recipients 80 years and older: an analysis of the OPTN/ UNOS database. Transplantation. 2010;90:974-9.
33. Gill JS, Klarenbach S, Cole E, Shemie SD. Deceased organ donation in Canada: an opportunity to heal a fractured system. Am J Transplant. 2008;8:1580-7.
34. Klein AS, Messersmith EE, Ratner LE, Kochik R, Baliga PK, Ojo AO. Organ donation and utilization in the United States 1999-2008. Am J Transplant. 2010;10:973-86.
35. Dahmane D, Audard V, Hiesse C, et al. Retrospective follow-up of transplantation of kidney from `marginal´ donors. Kidney Int. 2006;69:546-52.
36. Miranda B, Gonzalez Alvarez I, Cuende N, et al. Update on organ donation and retrieval in Spain. Nephrol Dial Transplant. 1999;14:842.
37. Coll E, Miranda B, Dominguez-Gil B, et al. [Organ donors in Spain: evolution of donation rates per regions and determinant factors]. Med Clin. 2008;131:52-9.
38. Zhou XJ, Rakheja D, Yu X, Saxena R, Vaziri ND, Silva FG. The aging kidney. Kidney Int. 2008;74:710-20.
39. Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. J Am Geriatr Soc. 1985;33:278-85.
40. Feinfeld DA, Guzik H, Carvounis CP, et al. Sequential changes in renal function tests in the old: results from the Bronx Longitudinal Aging Study. J Am Geriatr Soc. 1995;43:412-14.
41. Melk A. Senescence of renal cells: molecular basis and clinical implications. Nephrol Dial Transplant. 2003;18: 2474-8.
42. Cecka JM, Cohen B, Rosendale J, Smith M. Could more effective use of kidneys recovered from older deceased donors result in more kidney transplants for older patients? Transplantation. 2006;81:966-70.
43. Siddidi N, McBride MA, Hariharan S. Similar risk profiles for post-transplant renal dysfunction and long-term graft failure: UNOS/OPTN database analysis. Kidney Int. 2004;65:1906-13.
44. Hariharan S, McBride MA, Cherik WS, Tolleris CB, Bresnahan BA, Johnson CP. Post-transplant renal function in the first year predicts long-term kidney transplant survival. Kidney Int. 2002;62:311-18.
45. Salvadori M, Rosati A, Bock A, et al. Estimated one-year glomerular filtration rate is the best predictor of long-term graft function following renal transplant. Transplantation. 2006;81:202-6.
46. Schnitzler MA, Johnston K, Axelrod D, Gheorghian A, Lentine KL. Associations of renal function at 1-year after kidney transplantation with subsequent return to dialysis, mortality, and healthcare costs. Transplantation. 2011;91:1347-56.
47. Keith DS, Demattos A, Golconda M, Prather J, Norman D. Effect of donor recipient age match on survival after first deceased donor renal transplantation. J Am Soc Nephrol. 2004;15:1086-91.
48. Whiting JF, Woodward RS, Zavala EY, et al. Economic cost of expanded criteria donors in cadaveric renal transplantation: analysis of Medicare payments. Transplantation. 2000;70:755-60.
49. Merion RM, AshbyVA, Wolfe RA, et al. Deceased-donor characteristics and the survival benefit of kidney transplantation. JAMA. 2005;294:2726-33.
50. Meier-Kriesche H-U, Schold JD, Gaston RS, Wadstrom J, Kaplan B. Kidneys from deceased donors: maximizing the value of a scarce resource. Am J Transplant. 2005;5:1725-30.
51. Cohen B, Smits JM, Haase B, Persijn G, Vanrenterghem Y, Frei U. Expanding the donor pool to increase renal transplantation. Nephrol Dial Transplant. 2005;20:34-41.
52. Segoloni GP, Messina M, Squiccimarro G, et al. Preferential allocation of marginal kidney allograft to elderly recipients combined with modified immunosuppression gives good results. Transplantation. 2005;80:953-8.
53. Nyberg SL, Matas AJ, Rogers M, et al. Donor scoring system for cadaveric renal transplantation. Am J Transplant. 2001;1: 162-70.
54. Nyberg SL, Matas AJ, Kremers WK, et al. Improved scoring system to assess adult donors for cadaver renal transplantation. Am J Transplant. 2003;3:715-21.
55. Isoniemi H, Taskinen E, Hayry P. Histological chronic allograft damage index accurately predicts chronic renal allograft rejection. Transplantation. 1994;58:1195-8.
56. Anglicheau D, Loupy A, Lafaucheur C, et al. A simple clinico-histopathological composite scoring system is highly predictive of graft outcomes in marginal donors. Am J Transplant. 2008;8:2325-34.
57. Charpentier B, Rostaing L, Berthoux F, et al. A three-arm study comparing immediate tacrolimus therapy with antithymocyte globulin induction therapy followed by tacrolimus or cyclosporine A in adult renal transplant recipients. Transplantation. 2003;75:844-51.
58. Glotz D, Charpentier B, Abramovicz D, et al. Thymoglobulin induction and sirolimus versus tacrolimus in kidney transplant recipients receiving mycophenolate mofetil and steroids. Transplantation. 2010;89:1511-17.
59. Ducloux D, Kazory A, Challier B, et al. Long-term toxicity of antithymocyte globulin induction may vary with choice of agent: a single-center retrospective study. Transplantation. 2004;77:1029-33.
60. Kaden J, May G, Volp A, Wesslau C. Improved long-term survival after intra-operative single high-dose ATG-Fresenius induction in renal transplantation: a single centre experience. Ann Transplant. 2009;14:7-17.

61. Sageshima J, Ciancio G, Chen L, Burke GW. Anti-interleukin-2 receptor antibodies-basiliximab and daclizumab-for the prevention of acute rejection in renal transplantation. Biologics. 2009;3:319-36.
62. Sollinger H, Kaplan B, Pescovitz MD. et al. Basiliximab versus antithymocyte globulin for prevention of acute renal allograft rejection. Transplantation. 2001;72:1915-19.
63. Lebranchu Y, Bridoux F, Buchler M. et al. Immunoprophylaxis with basiliximab compared with antithymocyte globulin in renal transplant patients receiving MMF-containing triple therapy. Am J Transplant. 2002;2:48-56.
64. Mourad G, Rostaing L, Legendre C, Garrigue V, Thervet E, Durand D. Sequential protocols using basiliximab versus antithymocyte globulins in renal-transplant patients receiving mycophenolate mofetil and steroids. Transplantation. 2004;278:584-90.
65. Kyllönen LE, Eklund BH, Pesonem EJ, Salmela KT. Single bolus antithymocyte globulin versus basiliximab induction in kidney transplantation with cyclosporine triple immunosuppression: efficacy and safety. Transplantation. 2007;84:75-82.
66. Brennan DC, Daller JA, Lake KB, Cibrik D, del Castillo D. Rabbit antithymocyte globulin versus basiliximab in renal transplantation. N Engl J Med. 2006;355:1967-77.
67. Noël C, Abramowicz D, Durand D, et al. Daclizumab versus antithymocyte globulin in high-immunological-risk renal transplant recipients. J Am Soc Nephrol. 2009;20:1385-92.
68. Willoughby LM, Schnitzler MA, Brennan DC, et al. Early outcomes of thymoglobulin and basiliximab induction in kidney transplantation: application of statistical approaches to reduce bias in observational comparisons. Transplantation. 2009;87:1520-9.
69. Margreiter R, Klempnauer J, Neuhaus P, Muehlbacher F, Boesmueller C, Calne RY. Alemtuzumab (Campath-1H) and tacrolimus monotherapy after renal transplantation: results of a prospective randomized trial. Am J Transplant. 2008;8:1480-5.
70. Farney AC, Doares W, Rogers J, et al. A randomized trial of alemtuzumab versus antithymocyte globulin induction in renal and pancreas transplantation. Transplantation. 2009;88: 810-19.
71. Ciancio G, Burke GW, Gaynor JJ. A randomized trial of thymoglobulin vs alemtuzumab (with lower dose maintenance immunosuppression) vs daclizumab in renal transplantation at 24 months of follow-up.Clin Transplant. 2008;22:200-11.
72. Kaufman DB, Leventhal JR, Axelrod D, Gallon LG, Parker MA, Stuart FP. Alemtuzumab induction and prednisone-free maintenance immunotherapy in kidney transplantation: comparison with basiliximab induction-long-term results. Am J Transplant. 2005;5:2539-48.
73. Schadde E, D´Alessandro AM, Knechtle SJ, et al. Alemtuzumab induction and triple maintenance immunotherapy in kidney transplantation from donors after cardiac death. Transplant Int. 2008;21:625-36.
74. Huang E, Cho YW, Hayashi R, Bunnapradist S. Alemtuzumab induction in deceased donor kidney transplantation. Transplantation. 2007;84:821-8.
75. Meier-Kriesche H-U, Cibrik DM, Ojo AO, et al. Interaction between donor and recipient age in determining the risk of chronic allograft failure. J Am Geriatr Soc, 2002;50:14-21.
76. Meier-Kriesche HU, Ojo AO, Hanson JA, Kaplan B. Exponential increased risk of infectious death in older renal transplant recipients. Kidney Int. 2001;59:1539-43.
77. Hardinger KL, Brennan DC, Schnitzler MA. Rabbit antithymocyte globulin is more beneficial in standard kidney than in extended donor recipients. Transplantation. 2009;87:1372-6.
78. Andrés A, Marcén R, Valdés F, et al. A randomized trial of basiliximab with three different patterns of cyclosporin A initiation in renal transplant from expanded criteria donors and at high risk of delayed graft function. Clin Transplant. 2009;23:23-32.
79. Emparan C, Wolters H, Laukötter M, Senninger N. Long-term results of calcineurin-free protocols with basiliximab induction in old-to-old programs. Transplant Proc. 2004;36:2646-8.
80. Arbogast H, Hückelheim H, Scheneeberger H, 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;19:309-15.
81. Arbogast HP, Hoffmann JN, Illner W-D, et al. Calcineurin inhibitor-free immunosuppressive strategy in elderly recipients of renal allografts from deceased donors: 1-year results from a prospective single center trial. Transplant Proc. 2009;41:2529-32.
82. Favi E, Gargiulo A, Spagnoletti G, 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;42:1114-17.

Induction Therapy: Recommendations in Renal Transplantation (Table 3)

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– When analyzing induction therapy in kidney transplantation, it is necessary to distinguish between lymphocytes-depleting antibodies (monoclonal or polyclonal) and anti-IL-2 receptor antibodies (IL2-RAb). The first ones produce a stronger immunosuppression, but have a worse safety profile with greater risk of inducing infections and cancer.

– In the deceased donor kidney transplant with low-immunological risk recipient and if the donor and recipient age is under 60 years, when considering an initial immunosuppressive therapy with full calcineurin inhibitor (CNI) doses and mycophenolic acid, it is recommended to use anti-IL2-RAb, if the employed CNI is cyclosporine; if the CNI is tacrolimus, the

Table 3. Summary table (this may include the recommendation and level of evidence)

	Anti-IL2-RAb	Lymphocyte-depleting antibodies
Standard deceased donor kidney recipient	Yes with CsA	No
Standard living donor kidney recipient	Yes	No
Second or successive kidney transplant or black recipients	Yes	No
High immunological risk kidney recipient (PRA > 50%)	No	Yes
Moderate immunological risk kidney recipient (PRA 20-50%)	Yes	Yes, short courses (5-7 doses)
NHBD or donor with ARF	No	Yes, sequential
CNI minimization CNI or steroid-free IS kidney recipient	Yes	Yes, short cycles or anti-CD52
ECD kidney recipient	Yes with low doses of CNI	No

IL2-RAb: interleukin-2 receptor antibody; CsA: cyclosporin A; PRA: panel reactive antibody; NHBD: non heart beating donor; ARF: acute renal failure; IS: immunosuppression; ECD: expanded criteria donor; CNI: calcineurin inhibitor.

need for anti-IL2-RAb induction is questionable.

– In high-immunological risk kidney transplant recipients, if the maximum rate of panel reactive antibodies (PRA) is over 50% it is recommended to use a 7-10 day course of lymphocyte-depleting antibodies with full CNI dose and mycophenolic acid.

  If the maximum PRA rate is between 20 and 50%, then induction therapy with anti-IL2-RAb or a short 5-7 day course of lymphocyte-depleting antibodies is recommended.

  In all transplant recipients with PRA rates, it is recommended, regardless of the magnitude of this rate, to monitor the development of anti-HLA donor-specific antibodies after transplantation.

– In second or subsequent transplant recipients and in black recipients without other immunological risk, induction with anti-IL2-RAb is recommended.

– In living donor kidney recipients without immunological risk, induction with anti-IL2-RAb is recommended.

– In the kidney recipients from donors over age 60 or from expanded criteria donors, induction with anti-IL2-RAb associated with mycophenolic acid and CNI delayed introduction or minimization is recommended

– In non heart beating donor kidney recipients or in recipients of long ischemia time kidneys or from donors with hemodynamic instability or with acute renal failure, we recommend a sequential therapy with a cycle of seven doses of lymphocyte-depleting antibodies, mycophenolic acid, and delayed introduction of a CNI.

– If we consider an immunosuppression with CNI minimization, CNI-free or steroid-free induction with anti-IL2-RAb or with a five-day course of lymphocyte-depleting antibodies (antithymocyte globulin or OKT3) or anti-CD52 is recommended.

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