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.

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Key words


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.
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\textsuperscript{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\textsuperscript{4}. However, there is an emerging tendency to minimize CNI, either from the time of transplantation adding biological induction therapy\textsuperscript{5}, or after a few weeks using concomitant therapy with proliferation signal inhibitors or high doses of antiproliferatives\textsuperscript{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\textsuperscript{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\textsuperscript{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.

Imunosuppression 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”\textsuperscript{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\textsuperscript{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 post-transplantation, 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. 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. 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.

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

Amado Andrés, et al.: *Induction Therapy in Renal Transplantation*

**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 minimized¹,².

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 treatment³. However, some authors have made mild induction treatments for these patients preceding a planned withdrawal of CNI⁴,⁵,⁶.

**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\textsuperscript{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\textsuperscript{9}. Others, like Lim, et al.\textsuperscript{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)\textsuperscript{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.\textsuperscript{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\textsuperscript{13,14}. In addition, thymoglobin has also been used as low-dose single bolus (1.5 mg/kg) in living donor programs with the same good results\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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. 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.

**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. It is also used in transplants with a previous positive crossmatch in order to become negative.

**Specific immunoabsorption**

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 immunoabsorption sessions will depend on the previous antibody 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. Usually, the patient receives one or two doses of rituximab 375 mg/m². European protocols based on specific immunoabsorption 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**


**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. 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. 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. A registry study defined high-immunologic risk recipients as those with peak PRA > 20%, prior kidney transplantation, or black race. 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. New immunologic tools are being developed to analyze which patients are or are not responders. 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.

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. 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. The incidence of first-year acute rejection was lower in African American patients receiving rATG than placebo (18 vs. 47%; p < 0.05). 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%). 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.

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). 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. The results of these three studies are very similar (Fig. 1).
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\(^1^3\). Similarly, kidney transplant recipients with a PRA > 50% under rATG suffered acute rejection less frequently than IL2-RAb-treated patients (12 vs. 50%; \( p = 0.02 \))\(^1^4\). 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”\(^1^5\).

Alemtuzumab is the third most used induction agent in the USA\(^1^6\). Until 2011, few small randomized controlled trials examined the use of alemtuzumab as an induction agent in kidney transplantation\(^1^5\). 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\(^1^7\). 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)\(^1\). 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\(^1\). 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\(^2\). In a further report of the same trial with a follow-up of three years, the benefits of using IL2-RAB progressively disappeared\(^2\). 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\(^2\).

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\(^2\). 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; \(p = 0.001\))\(^2\). 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\(^2\). 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\(^2,2,3\). 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\(^3\).

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\(^2\). 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\(^2\). 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
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 patients with low-level donor-specific HLA-antibodies. Am J Transplant. 2010;10:1254-62.


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. Induction use steadily increased in the USA from 46% in 1995 to 83% in 2006. To a lesser degree, induction use increased in Spain from 27.8% in 1990 to 40.0% in 2002. 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. 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. 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.

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. 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. 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). 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. 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. 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. Nine recipients would need therapy with IL2-RAb to prevent one recipient having acute rejection and 42 to prevent one graft loss. The use of IL2-RAb has also been found to be cost-effective compared to placebo. Among others, all these studies support the KDIGO recommendation that all kidney transplant recipients must be treated with a biological
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.

![Forest plot](attachment:forest_plot.png)
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 drugs3-7. The choice of regimen depends on the preferences of clinicians and institutions, with great differences even in the same country4,19. In general, rATG is used in circumstances of heightened immunologic risk, whereas IL2-RAb is primarily used in the setting of lower immunologic risk16 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 USA3, 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 drugs20, 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 posttransplantation12. 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\textsuperscript{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\textsuperscript{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)\textsuperscript{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\textsuperscript{2}.

After rATG and IL2-RAb, alemtuzumab is the third most used induction drug in the USA\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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%: $p = 0.02$)\textsuperscript{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\textsuperscript{28}. Long-term prospective randomized studies with alemtuzumab will be necessary to determine their role as induction therapy\textsuperscript{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 effect30. 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 administration31. 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 introduction32-34. 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 loss35. 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 posttransplantation36. 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 rejection35.

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 groups37-40, while only in two trials, the group with early steroid withdrawal suffered more acute rejection rates, but without reaching statistical significance31,42. 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 rejection36.

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 globulins43.

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 patients45.

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 significant46. 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


**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 as 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\(^9\)\(^-\)\(^1\)\(^8\), or more than 65 years\(^1\)\(^9\)\(^-\)\(^2\)\(^6\). Moreover, nowadays very old donor kidneys, above 70 years, are being transplanted\(^2\)\(^7\)\(^-\)\(^3\)\(^0\). 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\(^3\)\(^1\)\(^,\)\(^3\)\(^2\).

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\(^3\)\(^3\). Recent data from the USA show a modest increase

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**Table 1. Characteristics of the ageing kidney**

<table>
<thead>
<tr>
<th>Functional changes</th>
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</thead>
<tbody>
<tr>
<td>– Lower glomerular filtration rate</td>
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<tr>
<td>– Reduction of sodium excretion</td>
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<tr>
<td>– Impairment of tubular potassium secretion</td>
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<tr>
<td>– Loss of the ability to concentrate or dilute the urine</td>
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<td>– Increased toxicities</td>
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<table>
<thead>
<tr>
<th>Structural changes</th>
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<tr>
<td>– Glomerulosclerosis</td>
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<tr>
<td>– Tubular atrophy</td>
</tr>
<tr>
<td>– Interstitial fibrosis</td>
</tr>
<tr>
<td>– Intimal fibrosis and medial thinning in blood vessels</td>
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</tbody>
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of ECD transplants from 1999 to 2008 (20.3 to 22.7%), with a decline in standard criteria donors (SCD)\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{36} and there was a progressive increase in the percentage of donors over 70 years thereafter\textsuperscript{37}. 

**Kidney ageing**

Age determines functional and structural changes in the kidney\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{25,35}. Moreover, kidneys from ECD presented poorer graft function than those from SCD in the first months and thereafter\textsuperscript{10,17,22,23,35} as donor age was a risk factor for lower GFR\textsuperscript{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\textsuperscript{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\textsuperscript{2,7,10,15,16,25,47}. But in some single-center\textsuperscript{8,11,12,22} and multicentre\textsuperscript{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\textsuperscript{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\textsuperscript{7,9}. Donor age was also associated with a negative impact on patient survival\textsuperscript{10,16,47}.

Despite the previous considerations, transplantation of ECD kidneys yielded an improved patient survival over maintenance dialysis\textsuperscript{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\textsuperscript{23}. The optimal use of ECD is not definitively established. Waiser, et al.\textsuperscript{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\textsuperscript{23,49,50}. In another study, graft survival was similar in “old-for-old” as in HLA-matching and waiting time allocation\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{51}. Nowadays, old-for-old kidney allocation is a practice used by many transplant centers\textsuperscript{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\textsuperscript{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\textsuperscript{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.\textsuperscript{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\textsuperscript{55}. Anglichenau, et al.\textsuperscript{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
have questioned the utility of histopathological information.

### Induction therapy in elderly donor kidney transplantation

Older donor kidneys are at high risk of DGF, nephrotoxicity, and chronic allograft failure. Furthermore, acute rejection episodes increase with increasing age, and it has been reported that they are more common in old-for-old recipients than in other transplant groups. 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. On the other hand, older recipients have a lower risk of rejection and are especially susceptible to infection and malignancies. 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. 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

<table>
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<tr>
<th>Author</th>
<th>Cases (n)</th>
<th>Donor age</th>
<th>Induction</th>
<th>Immunosuppression</th>
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<td>ECD</td>
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<td>CsA (35%), TAC (52%), MMF (77%) and steroids</td>
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<td>&gt; 60 years</td>
<td>ATGF + basiliximab</td>
<td>MMF + steroids</td>
</tr>
<tr>
<td>Bodingbauer, et al. 2006</td>
<td>91</td>
<td>&gt; 65 years</td>
<td>Thymoglobulin or basiliximab</td>
<td>MMF + steroids</td>
</tr>
<tr>
<td>Anglicheau, et al. 2008</td>
<td>313</td>
<td>&gt; 50 years</td>
<td>Thymoglobulin or basiliximab</td>
<td>CsA + MMF + steroids</td>
</tr>
<tr>
<td>Guba, et al. 2008</td>
<td>56</td>
<td>&gt; 50 years</td>
<td>ATGF + basiliximab</td>
<td>MMF + steroids</td>
</tr>
<tr>
<td>Foss, et al. 2009</td>
<td>54</td>
<td>&gt; 75 years</td>
<td>Basiliximab</td>
<td>Standard triple or quadruple therapy</td>
</tr>
<tr>
<td>Collini, et al. 2009</td>
<td>38</td>
<td>&gt; 75 years</td>
<td>Basiliximab</td>
<td>TAC or CsA + MMF or SRL</td>
</tr>
<tr>
<td>Favi, et al. 2010</td>
<td>20</td>
<td>&gt; 60 years</td>
<td>Basiliximab + thymoglobulin</td>
<td>CsA or TAC + steroids</td>
</tr>
</tbody>
</table>

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.
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. 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. There are several studies in which patients were treated with MMF-based and CNi-free immunosuppression regimens and induction therapy. 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. 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. 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. 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.

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

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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

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**Induction Therapy: Recommendations in Renal Transplantation (Table 3)**

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The 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.

**Acknowledgments**

The authors thank Mary Harper for her assistance in preparing the English version of this article.

With the collaboration of **Novartis**

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