NDT Plus (2010) 3 [Suppl 2]: ii9–ii14
doi: 10.1093/ndtplus/sfq066

NDT PLUS
Nephrology Dialysis Transplantation

Heterogeneity of induction therapy in Spain: changing patterns according to year, centre, indications and results

Emilio Rodrigo[1], Gema Fernández-Fresnedo[1], Carmen Robledo[1], Rosa Palomar[1], Carmen Cantarell[2], Auxiliadora Mazuecos[3], Antonio Osuna[4], Alicia Mendiluce[5], Antonio Alarcón[6] and Manuel Arias[1]

[1]Nephrology Department, Hospital Universitario Marqués de Valdecilla, Santander, Spain, [2]Nephrology Department, Hospital Vall d´Hebrón, Barcelona, Spain, [3]Nephrology Department, Hospital Puerta del Mar, Cádiz, Spain, [4]Nephrology Department, Hospital Virgen de las Nieves, Granada, Spain, [5]Nephrology Department, Hospital Clínico Universitario, Valladolid, Spain and [6]Nephrology Department, Hospital Son Dureta, Palma de Mallorca, Spain

Correspondence and offprint requests to: Emilio Rodrigo; E-mail: nefrce@humv.es

Abstract

Background. The use of induction drugs has increased markedly over the last 15 years in the USA, but there are few data about their use in other countries. Moreover, there are not enough data about when they are indicated and their long-term effects. The aim of our study was to know the rates of use and the drugs used as induction therapy, in which patients they were prescribed and the long-term graft survival effect in Spain.

Methods. We conducted a retrospective cohort study with adult patients (4861) receiving a kidney allograft in Spain over four different years (1990, 1994, 1998 and 2002) with a functioning graft at the end of the first post-transplant year. Induction therapy was defined as when the patient received polyclonal antibodies, OKT3 monoclonal antibodies or anti-CD25 monoclonal antibodies.

Results. From 1990 to 2002, the use of induction therapy in Spain changed, with a progressive reduction in the use of OKT3 and an increasing use of anti-CD25 antibodies. There were great differences in the rate of induction use from one centre to another, although with a common trend to greater use at each centre. Induction therapy was mainly prescribed in patients with a higher rejection risk (higher panel reactive antibody (PRA) titres and mismatches and re-transplants) and in older and diabetic recipients. Lastly, patients who were treated with induction therapy had significant higher allograft survival than those who did not (P value = 0.035).

Conclusions. The use of induction therapy in Spain has changed, with an increasing use of monoclonal antibodies in recent years. Induction therapy has a protective role in long-term graft survival.

Keywords: basiliximab; daclizumab; induction therapy; kidney transplantation; Thymoglobulin

Introduction

The term ‘induction therapy’ commonly refers to the administration of antibodies against specific or multiple antigenic targets of immune cells in the immediate peri-operative period [1]. These antibodies have largely been used to provide immunosuppression at the time of antigen presentation, during the initial period after solid organ transplantation, with the purpose of reorienting the immune system by depleting potentially alloreactive immune cells [2]. Induction strategies have gained increased interest in recent decades. Several meta-analyses have demonstrated that induction therapy improves renal graft outcome compared with conventional therapy. Antilymphocyte antibodies have a beneficial effect on 2-year allograft survival, and non-depleting antibodies, such as the anti-CD25 antibodies basiliximab and daclizumab, reduce acute rejection rate [3–6]. Moreover, induction drugs play a key role in the promising corticosteroid or calcineurin-inhibitor minimization strategies [7,8].

The frequency of use of the different induction drugs has varied markedly over the last 15 years. While in the early 1990s the majority of US kidney transplant recipients did not receive induction therapy, in 2004 nearly 72% of recipients received some kind of antilymphocyte drug. Currently, Thymoglobulin is the most frequently used (37%) induction agent in the USA, and anti-CD25 antibodies are used only rarely [9]. Apart from the USA, little has been published providing an overview of trends in induction use. Data from the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry showed a decline in OKT3 and polyclonal antibody use and an increase in the prescription of anti-CD25 antibodies to 57.1% in 2001 [10]. Non-serial studies provide data about induction use in some Asian centres (18.4%) [11], international registries (37.7%) [12] and one South American centre (36%) [13]. One of the aims of our study was to describe the trends in induction use

from 1990 to 2002 in Spain and the differences in use among centres.

The high rate of variation between countries and centres in induction use revealed not only differences between transplant populations but also differences in indication. Some centres reserve induction therapy for patients at high immunological risk. Other centres use lymphocyte-depleting agents for high-risk patients and non-depleting agents for low-risk patients [1]. The lack of common indications for induction therapy would suggest that it is not well known which patients should receive it and what induction drug must be prescribed. The benefits of using induction must be weighed against the potential risk of infection and malignancy. Commonly, induction is used in patients with a higher rejection risk (African-American, highly sensitized patients, patients undergoing re-transplantation), a higher delayed graft function risk (longer cold ischaemia time, expanded criteria donors, donors after cardiac death) or in patients under minimization immunosuppressive strategies [1,3,14]. The second purpose of our study was to know in which patients in Spain induction was prescribed and the differences in use between polyclonal antibodies and anti-CD25 antibodies.

Over the last few years, focus on kidney transplantation has shifted towards long-term graft survival due to the improvements in short-term graft survival [15]. The effect of induction antibodies over long-term graft survival is controversial. By means of a meta-analysis of individual patient-level data, Szczech *et al*. showed a benefit of induction at 2 years in all patients and even at 5 years in recipients with panel reactive antibodies (PRA) ≥20% [3]. A single-centre study comparing polyclonal antibody induction against no induction demonstrated that induction improved graft survival only during the first post-transplant year and did not exert its effect further [16]. Antibody induction is also associated with an elevated risk for cardiovascular death, infection-related death and malignancy-related death [17]. Data about the long-term effect of induction on patient and graft survival are scarce. We analysed this issue in our Spanish kidney recipient population.

Materials and methods

We conducted a retrospective cohort study with patients receiving a kidney allograft in Spain over four different years (1990, 1994, 1998 and 2002). Only adult patients (≥18 years), receiving a single kidney and remaining alive with a functioning graft at the end of the first post-transplant year were included in the study [18].

The following data were recorded for each patient at the time of transplantation and during hospitalization until discharge by chart review: age and gender of the donor and the recipient, source of the organ (living or deceased donor), cause of donor death, primary kidney disease, recipient body mass index, peak and current PRA, number of transplants, time on renal replacement therapy, mismatches, presence of hepatitis C antibodies in the recipient, and cold ischaemia time. Graft and patient survival, delayed graft function, acute rejection, first-year creatinine and first-year hypertension were also collected from the clinical charts. Delayed graft function was defined as the need for dialysis within the first week after transplantation. The diagnosis of acute rejection was defined according to the criteria of each centre based on clinical and histological data. Arterial hypertension was defined as blood pressure more than 140/90 mmHg or need for antihypertensive therapy [18].

Initial immunosuppressive therapy was recorded. Induction therapy was defined when the patient received polyclonal antibodies (ALG, ATG, ATGAM, Thymoglobulin), OKT3 monoclonal antibodies or anti-CD25 monoclonal antibodies (basiliximab, daclizumab). Other induction drugs were used under clinical trials and were excluded from the analysis. During the study period, 4928 kidney transplant patients fulfilled the inclusion criteria. In 67 patients, there were inadequate data with respect to induction therapy (data absence or duplicate), or they received different induction drugs for clinical trials.

Medical record review was performed by a transplant physician at each centre taking part in the study according to Spanish law with reference to clinical data confidentiality (Spanish Official Bulletin, BOE No. 298, 1999, pp. 43088–43099). The study was conducted according to the principles described in the Declaration of Helsinki.

Statistical analysis was performed using SPSS 8.0 (SPSS, Inc., Chicago, IL, USA). Comparison between variables was made by using Student's *t*-test for numerical values and chi-square test for categorical data. Stepwise multiple regression analysis was used to select independent risk factors for receiving induction therapy among parameters selected by univariate analysis. Graft and patient survivals were analysed using Kaplan–Meier estimate (log rank test). Independent risk factors for graft loss were studied by means of Cox's regression analysis. A P value of less than 5% was reported as statistically significant. Results were considered statistically significant for $P < 0.05$.

Results

Year of transplantation

Induction therapy showed marked changes throughout the study period (Figure 1). There were significant differences in the percentages of transplant patients that received induction therapy (25.7% in 1990, 40.7% in 1994, 27.1% in 1998 and 37.2% in 2002, $P < 0.0001$) but without a clear trend. Similarly, there were significant differences in the percentages of transplant patients under polyclonal antibodies (19.9% in 1990, 31.1% in 1994, 17.0% in 1998 and 9.2% in 2002, $P < 0.0001$). During the study period, there was a significant reduction in the number of patients receiving OKT3 (4.9% in 1990, 9.3% in 1994, 5.0% in 1998 and 1.0% in 2002, $P < 0.0001$). By contrast, a significant increase in the percentages of patients treated with anti-CD25 antibodies was found (1.3% in 1990, 0.9% in 1994, 5.6% in 1998 and 27.2% in 2002, $P < 0.0001$).

Transplant centre

Throughout the study period, there was great variability in the use of induction therapy among the different Spanish transplant centres. Induction use ranged from 1.6% to 98.1% (mean 36.4%) for any patient in each centre. Polyclonal antibody use ranged from 0% to 78% (mean 21.1%) and anti-CD25 antibodies from 0% to 73% (mean 9.5%). Nearly half (48.5%) of the centres used induction therapy in less than 25% of patients, while 24.2% of the centres used induction from 25% to 50% of patients and 27.3% of the centres in more than half their transplant recipients. From 1990 to 2002, the percentages of centres using induction therapy in less than 25% of their patients fell from 62.9% to 39.3%, while the centres using induction therapy with between 25% and 50% of their recipients increased from 3.6% to 32.1%. Nearly a third of the centres treated more than 50% of their patients with induction drugs (33.3% in 1990 and 28.6% in 2002).

Most of the centres that treated more than 50% of their transplant patients with induction therapy in 1990 were using polyclonal antibodies (86%). In 2002, these same cen-

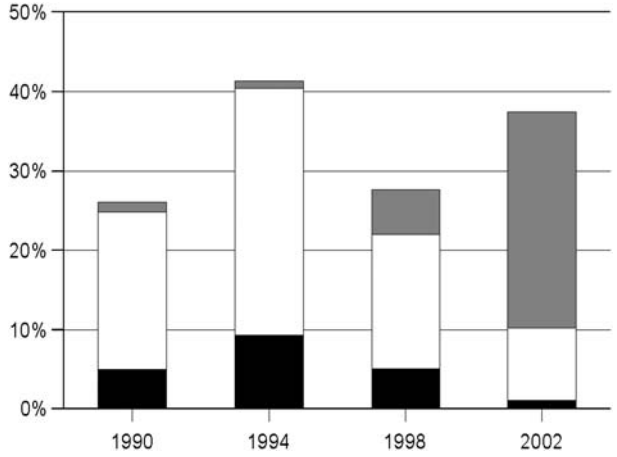

Fig. 1. Trends in the percentage of patients receiving antibodies as induction immunosuppression, 1990–2002 cohorts. Polyclonal antibodies in white, OKT3 in black and anti-CD25 antibodies in grey.

tres used induction treatment in 56% of patients, but only 18% of them received polyclonal antibodies, while 38% received anti-CD25 antibodies ($P < 0.01$). On the other hand, centres that used induction therapy in less than 25% of their patients (3%) in 1990 increased the use of induction to more than a quarter of the patients (27%) and used anti-CD25 antibodies (18%) more frequently than polyclonal antibodies (9%).

Induction indication

The only donor characteristic related in univariate analysis with a higher rate of induction prescription was donor age (Table 1). We found no differences in the use of induction according to donor sex, death cause or donor status (deceased vs live-donor). No donor characteristic was related with induction use after multivariate analysis.

Recipient characteristics related with a higher rate of induction therapy were recipient age, the title of PRA, the length of renal replacement therapy, the number of mismatches, the number of transplants and recipient diabetes (Table 1). After multivariate analysis, 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 more than 15% of PRA (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 diabetic (RR 1.54, 95% CI 1.13–2.09, $P = 0.0055$).

In 2002, a higher number of patients under induction therapy received anti-CD25 antibodies (323) than polyclonal antibodies (104). Patients treated with polyclonal antibodies were younger, had a higher rate of current and peak PRA and were more frequently re-transplants (Table 2).

Induction results

Considering a follow-up period of 15 years (since 1990) and censoring patients with functioning graft but with a shorter follow-up, the average time of graft survival in patients who were treated with induction therapy has been significantly higher than those who were not (14.092 years; $IC_{95\%}$= [13.767–14.416] vs 13.595; $IC_{95\%}$=[13.338–13.852]; P value = 0.035) (Figure 2). Likewise, 14% of patients who received induction and 15.6% of patients who did not receive induction lost their grafts. After adjusting for delayed graft function, acute rejection, first year creatinine, pre-transplant PRA, first year hypertension and receptor age, the use of induction therapy remained significant as a protective factor for graft survival (HR 0.686, 95% CI 0.587–0.801, $P < 0.001$). By contrast, induction therapy was neither a risk nor a protective factor for patient survival (log rank test $P = 0.072$).

Table 1. Donor and recipient characteristics of transplant patients receiving induction therapy vs those not receiving

	Induction therapy (n = 1633)	Non-induction therapy (n = 3228)	P
Donor age (years)	43.0 ± 17.3	41.6 ± 16.7	0.010
Donor age (>60)	19.3%	16.7%	0.027
Donor sex (male)	61.7%	62.9%	0.394
Death cause (CVA)	50.6%	50.0%	0.676
Donor status (deceased)	99.0%	98.6%	0.222
Recipient age (years)	46.7 ± 14.4	45.7 ± 13.8	0.017
Recipient age (>60)	20.1%	15.7%	<0.001
Current PRA	6.8 ± 18.2	3.0 ± 10.6	<0.001
Peak PRA	15.7 ± 27.5	9.1 ± 19.4	<0.001
PRA > 15%	13.5%	6.8%	<0.001
RRT length	3.8 ± 4.3	3.1 ± 3.5	<0.001
Recipient diabetes	8.7%	5.8%	0.001
Transplant number (>1)	17.6%	9.7%	<0.001
Recipient HCV	15.3%	11.9%	0.001
Body mass index	24.4 ± 4.0	24.6 ± 4.0	0.209
Mismatches	3.2 ± 1.2	3.0 ± 1.2	<0.001
Cold ischaemia time (hours)	19.0 ± 6.4	19.2 ± 7.2	0.393

RRT, renal replacement therapy; CVA, cerebro-vascular accident.

Table 2. Characteristics of patients receiving polyclonal antibodies or anti-CD25 antibodies in 2002

	Polyclonal antibodies (n = 104)	Anti-CD25 antibodies (n = 323)	P
Donor age (years)	47.3 ± 16.1	49.6 ± 16.4	0.229
Donor age (>60)	22.5%	30.7%	0.112
Donor sex (male)	55.7%	66.5%	0.046
Death cause (CVA)	55.4%	64.5%	0.139
Donor status (deceased)	96.2%	98.4%	0.160
Recipient age (years)	47.8 ± 13.9	52.6 ± 12.9	0.001
Recipient age (>60)	23.1%	32.2%	0.066
Current PRA	18.5 ± 27.9	3.2 ± 12.9	<0.001
Peak PRA	29.7 ± 37.0	8.1 ± 21.3	<0.001
PRA > 15%	35.4%	5.3%	<0.001
RRT length	4.8 ± 5.2	3.1 ± 3.5	<0.001
Recipient diabetes	12.5%	10.2%	0.169
Transplant number (>1)	26.9%	13.3%	0.001
Recipient HCV	9.8%	6.7%	0.298
Body mass index	24.7 ± 5.0	25.4 ± 4.2	0.221
Mismatches	3.4 ± 1.3	3.6 ± 1.1	0.338
Cold ischaemia time (h)	16.3 ± 6.3	18.4 ± 5.4	0.002

RRT, renal replacement therapy; CVA, cerebro-vascular accident.

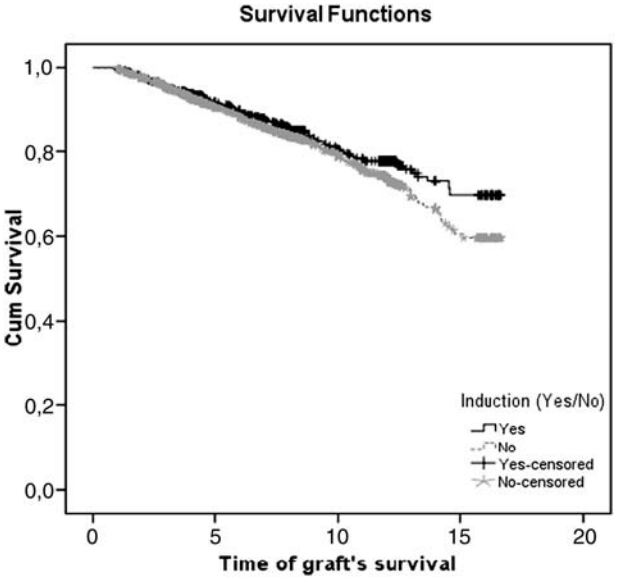

Fig. 2. Kaplan–Meier analysis for graft survival. Upper line represents those patients receiving induction therapy. Lower line represents patients not receiving such therapy.

This advantage over graft survival related with induction therapy was not the same for all groups of patients. Patients younger than 55 years who received induction therapy had a significantly higher allograft survival than the others who did not receive induction treatment (P = 0.008). Also, 15.1% of the patients who received induction therapy had graft loss vs 17.6% without induction. There were, however, no graft survival advantages in those patients older than 55 years who received induction therapy (graft loss after induction therapy 10.5% vs 10.3% without induction, P = 0.758).

Patients with current PRA lower than 20% benefited more by receiving induction therapy (graft loss after induction therapy 13.2% vs 16.0% without induction, P = 0.014). On the other hand, patients with current PRA equal to or higher than 20% showed no advantage for being treated with induction (graft loss after induction therapy 20.5% vs 27.1% without induction, P = 0.224).

Discussion

Unlike US data, we cannot find a trend toward increasing use of induction drugs in kidney transplantation between 1990 and 2002 in Spain. Moreover, such use is quite lower than the reported induction use in the USA (from 46% in 1995 to 72% in 2004) [9]. It seems that induction therapy has been used at a higher rate in Spain beyond 2002, but we cannot conclude this from our data. Clearly, the use of the monoclonal antibody OKT3 has waned in Spain progressively (1.0% in 2002), similar to that reported by US and ANZDATA registries [9,10]. Nowadays, depleting induction therapy is based on polyclonal antibodies in Spain, the USA, Australia and New Zealand [9,10]. From the Brennan *et al*. report comparing Thymoglobulin with ATGAM in 1999, Thymoglobulin has become the preferred polyclonal agent [9,19], although this finding could not be demonstrated in our study since that polyclonal induction use registry includes different agents.

All over the world, non-depleting anti-CD25 monoclonal antibodies are being used in a higher percentage of patients. Anti-CD25 antibodies were used in 27.2% of patients in 2002 in Spain, in 57.1% in 2005 in Australia and New Zealand and in 21% in 2004 in the USA [9,10]. This increasing use can be attributed both to initial studies [20–22] and to further meta-analysis that have shown that anti-CD25 antibodies reduce acute rejection rates compared with placebo [4–6]. Together with their efficiency reducing rejection rates, the costs with anti-CD25 are lower compared to transplant without induction [23]. As a result of these data, a progressively increasing use of anti-CD25 antibodies is expected in future years.

The use of induction antibodies varies between centres, although there are few reported data about this issue [1]. The wide range of induction use (1.6–98.1%), polyclonal antibody use (0–78%) and anti-CD25 use (0–73%) in Spain can only be partly explained by differences in population characteristics in Spanish centres. Some such centres in Spain have a very high rate of diabetic recipients or re-transplants. However, lack of consensus about specific indications seems the main cause of this heterogeneity. The global Spanish trend to use induction drugs in a higher rate of patients at each centre, at more similar rates among the different centres and mainly anti-CD25 antibodies, would indicate that induction indications will be more homogeneous in the future.

No previous report has analysed which kidney recipients have received induction therapy in such a high number of patients. Prospective induction trials have defined 'high-risk patients' in several ways. For example, Noël *et al*. defined this kind of patient as having one or more of the following risk factors: a current PRA ≥ 30%, a peak PRA ≥ 50%, scheduled for a second transplantation when the first graft was lost to rejection within 2 years or receiving a third or fourth kidney graft [24]. By contrast, Brennan *et al*. designed their trial to include patients at risk for both acute rejection and delayed graft function, taking into account cold ischaemia time, donor age, non-heart-beating donor, high-dose inotropic support of donor, repeated transplantation, current PRA > 20%, black race and mismatches [25]. In our retrospective study, induction therapy was used in older recipients, with a higher PRA rate, receiving a second or more transplantation, with more mismatches and diabetic. Among studied variables, no donor characteristic was related with induction indication. Some of these recipient variables were related with a higher immunological risk for acute rejection, such as PRA, re-transplantation and mismatches, while the recipient age and diabetes are more related with the risk for delayed graft function and the intention to use steroid or calcineurin-inhibitor minimization strategies. Surprisingly, the use of induction therapy in the USA was no different among groups with varying PRA [9]. By contrast, most of the US patients on steroid-avoidance regimens received induction drugs [9].

As several meta-analyses have shown that induction therapy improves kidney transplant outcomes in a cost-effective way compared with no induction, a possible future

scenario is that induction therapy will be used in all kidney transplants [3–6,23]. In this case, the doubt will be what induction we must use (polyclonal antibodies, mainly Thymoglobulin, or anti-CD25 antibodies). Nowadays, the optimal prophylactic induction immunosuppressive therapy remains controversial. Several trials including low-immunological-risk patients have found similar rates of acute graft rejection and graft and patient survival, with higher rates of cytomegalovirus infection with polyclonal antibodies compared with anti-CD25 antibodies [26]. In high-risk patients, the rate of acute rejection was greater in those patients treated with anti-CD25 antibodies, but graft and patient survival was the same at the first and fifth years [24,25,27]. Our study cannot allow us to compare outcomes of patients receiving polyclonal antibodies vs anti-CD25 antibodies, but we analysed which kidney graft recipients were prescribed either of them. Thus, Spanish centres used polyclonal antibodies instead of anti-CD25 in patients with a higher acute rejection risk (high PRA and re-transplants) but with a lower infection risk due to their younger age.

It has been difficult to know the effect of induction therapy on long-term graft survival [1]. In a single-centre study, 1-year graft survival was better in patients receiving polyclonal induction (93% vs 79%), but no difference was observed from the second to the 20th year in graft survival [16]. A meta-analysis of seven randomized trials comparing lymphocyte-depleting induction with no-induction therapy showed a statistically significant improvement in 2-year graft survival in patients treated with induction drugs [28]. This improvement did not remain significant in 5-year graft survival [3]. Another meta-analysis including 17 trials and 2786 patients found no differences in graft loss at the first and third years between those patients treated and those not treated with anti-CD25 antibodies [4]. In a recent retrospective USRDS analysis between 1997 and 2004, Gill *et al*. reported no differences in 1- and 5-year graft survival in low-risk renal transplant recipients receiving polyclonal antibodies vs no-induction therapy [29]. The benefits of using induction therapy must be weighed against the potential risk of overimmunosuppression, including the risks of infection and malignancy that may occur years after the induction use. Lymphocyte-depleting induction is related with a significantly increased risk for early deaths within 6 months and after 6 months post-transplantation in relation with infection, malignancy and cardiovascular problems [17].

However, patients with a kidney surviving more than 1 year who received induction therapy in Spain showed a significantly better long-term graft survival with the same patient survival than those not treated with induction drugs. Induction therapy exerts its protective role over graft survival independently of other confounding factors, such as acute rejection. This result cannot be compared with previous studies due to the fact that we analysed only kidneys functioning beyond the first year. The high number of patients in our study allows us to assert that an immunosuppressive regimen including induction drugs can improve long-term graft survival, this favourable effect being different according to which groups received treatment. In our study, recipients younger than 55 years and with low PRA benefited more from receiving induction therapy.

In conclusion, from 1990 to 2002, the use of induction therapy in Spain changed, with a progressive reduction in the use of OKT3 and an increasing use of anti-CD25 antibodies. There were great differences in the rate of induction use among the different centres, although with a common trend to its use in more patients. Induction therapy was mainly prescribed in patients with a higher rejection risk (higher PRA titres and mismatches and re-transplants) and/or needing calcineurin-inhibitor or steroid minimization regimens to prevent delayed graft function and other secondary effects (older and diabetic recipients). Lastly, induction therapy has a protective role in long-term graft survival.

Acknowledgements. We are grateful to M. Luz Samaniego and Jordi Curto for statistical advice and Jorge Muñoz for critical reading of the paper.

Conflict of interest statement. None declared.

References

1. Padiyar A, Augustine JJ, Hricik DE. Induction antibody therapy in kidney transplantation. *Am J Kidney Dis* 2009; [Epub ahead of print]
2. Arias M, Campistol JM, Vincenti F. Evolving trends in induction therapy. *Transplant Review* 2009; 23: 94–102
3. Szczech LA, Berlin JA, Feldman HI. The effect of antilymphocyte induction therapy on renal allograft survival. *Ann Intern Med* 1998; 128: 817–826
4. Webster AC, Playford EG, Higgins G *et al*. Interleukin 2 receptor antagonists for renal transplant recipients: a meta-analysis of randomized trials. *Transplantation* 2004; 77: 166–176
5. Keown P, Balshaw R, Khorasheh S *et al*. Meta-analysis of basiliximab for immunoprophylaxis in renal transplantation. *BioDrugs* 2003; 17: 271–279
6. Adu D, Cockwell P, Ives NJ *et al*. Interleukin-2 receptor monoclonal antibodies in renal transplantation: meta-analysis of randomized trials. *BMJ* 2003; 326: 789–793
7. Matas AJ, Kandaswamy R, Humar A *et al*. Long-term immunosuppression without maintenance prednisone, after kidney transplantation. *Ann Surg* 2004; 240: 510–516
8. Guba M, Renstch M, Wimmer CD *et al*. Calcineurin-inhibitor avoidance in elderly renal allograft recipients using ATG and basiliximab combined with mycophenolate mofetil. *Transpl Int* 2008; 21: 637–645
9. Meier-Kriesche H-U, Li S, Gruessner RWG *et al*. Immunosuppression: evolution in practice and trends, 1994–2004. *Am J Transplant* 2006; 6: 1111–1131
10. Chang SH, Russ GR, Chadban SJ *et al*. Trends in adult post-kidney transplant immunosuppressive use in Australia, 1991–2005. *Nephrology* 2008; 13: 171–176
11. Vathsala A. Immunosuppression use in renal transplantation from Asian transplant centres: a preliminary report from the Asian Transplant Registry. *Transplant Proc* 2004; 36: 1868–1870
12. Opelz G, Döhler B *et al*. Influence of immunosuppressive regimens on graft survival and secondary outcomes after kidney transplantation. *Transplantation* 2009; 87: 795–802
13. Castro MCR, Araujo LMP, Nahas WC *et al*. Induction versus noninduction therapy in kidney transplantation: considering different PRA levels and different induction therapies. *Transplant Proc* 2004; 36: 874–876
14. Hardinger KL. Rabbit antithymocyte globulin induction therapy in adult renal transplantation. *Pharmacotherapy* 2006; 26: 1771–1783

15. Hariharan S. Long-term kidney transplant survival. *Am J Kidney Dis* 2001; 38: S44–S50
16. Cantarovich M, Durrbach A, Hiesse C *et al*. 20-year follow-up results of a randomized controlled trial comparing antilymphocyte globulin induction to no induction in renal transplant patients. *Transplantation* 2008; 86: 1732–1737
17. Meier-Kriesche H-U, Arndorfer 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: 769–772
18. Hernandez D, Sánchez-Fructuoso A, González-Posada JM *et al*. A novel risk score for mortality in renal transplant recipients beyond the first posttransplant year. *Transplantation* 2009; 88: 803–809
19. Brennan DC, Flavin K, Lowell JA *et al*. A randomized double-blind comparison of Thymoglobulin versus Atgam for induction immunosuppressive therapy in adult renal transplant recipients. *Transplantation* 1999; 67: 1011–1018
20. Nashan B, Moore R, Amlot P *et al*. Randomised trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients. *Lancet* 1997; 350: 1193–1198
21. Kahan BD, Rajagopalan PR, Hall M. United States Simulect Renal Study GroupReduction 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: 276–284
22. Ponticelly C, Yussim A, Cambi V *et al*. A randomized, double-blind trial of basiliximab immunoprophylaxis plus triple therapy in kidney transplant recipients. *Transplantation* 2001; 72: 1261–1267
23. Morton RL, Howard K, Webster AC *et al*. The cost-effectiveness of induction immunosuppression in kidney transplantation. *Nephrol Dial Transplant* 2009; 24: 2258–2269
24. 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: 1385–1392
25. Brennan DC, Daller JA, Lake KD *et al*. Rabbit antithymocyte globulin versus basiliximab in renal transplantation. *N Engl J Med* 2006; 355: 1967–1977
26. Mandelbrot D. Anti-IL-2 receptor antibodies versus anti-thymocyte globulin for induction therapy in kidney transplantation. *J Am Soc Nephrol* 2009; 20: 1170–1171
27. Brennan DC, Schnitzler MA. Long-term results of rabbit antithymocyte globulin and basiliximab induction. *N Engl J Med* 2008; 359: 1736–1738
28. 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: 1771–1777
29. Gill JS, Johnston O, Rose CL *et al*. Are there any benefits to using depleting antibodies in low risk kidney transplant recipients? *Am J Transplant* 2008; 8: 215

Received for publication: 18.12.09; Accepted in revised form: 29.3.10