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

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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 transplant 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-
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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; IC95%=[13.767–14.416] vs 13.595; IC95%=[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

| Characteristic                  | 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

| Characteristic                  | 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.
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, while the recipient age and diabetes are more related with the risk for 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].

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/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.

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