Induction Therapy in Heart Transplantation

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Abstract

Heart transplantation has been a real option for patients with end-stage heart failure, related to the discovery of effective immunosuppressive regimens.

Despite these improvements, heart transplant recipients still face important challenges in the postoperative period to manage allograft rejection and infection. Although allograft rejection is one of the main causes of early and mid-term mortality after the transplant surgery, infections and malignancies can also cause this.

The use of induction therapy to reduce rejection in the immediate posttransplant period has a potential risk to increase infections, malignancies, and other side effects. Even so, currently 50% of heart transplant recipients receive induction therapy. A careful selection of the immunosuppressive agent and individualized therapy according to the patient appear to be needed to guarantee a favorable risk/benefit ratio.

The immunosuppression treatments include: muromonab-CD3 (OKT3), antithymocyte globulin, antilymphocyte globulin, and more recently interleukin-2 receptor antagonist (basiliximab and daclizumab).

Regardless of the advances in induction therapy, it is necessary to develop new classes of immunosuppression drugs to increase efficacy and reduce toxicity and side effects. **(Trends in Transplant. 2011;5:205-16)**

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Key words

Heart transplantation. Allograft rejection. Immunosuppression. Induction therapy.

Introduction

Heart transplantation has become the choice of patients with severe end-stage heart disease and the success of this surgical procedure has been closely related to the discovery of effective immunosuppressive regimens[1]. A major challenge in heart transplantation was to provide effective immunosuppression to prevent graft rejection, while minimizing the many adverse effects of immunosuppressive therapies. In the early 1980s, the introduction of cyclosporine A (CsA) in the immunosuppressive regimens was followed by a significant improvement in survival of heart transplant recipients[2]. In the last International

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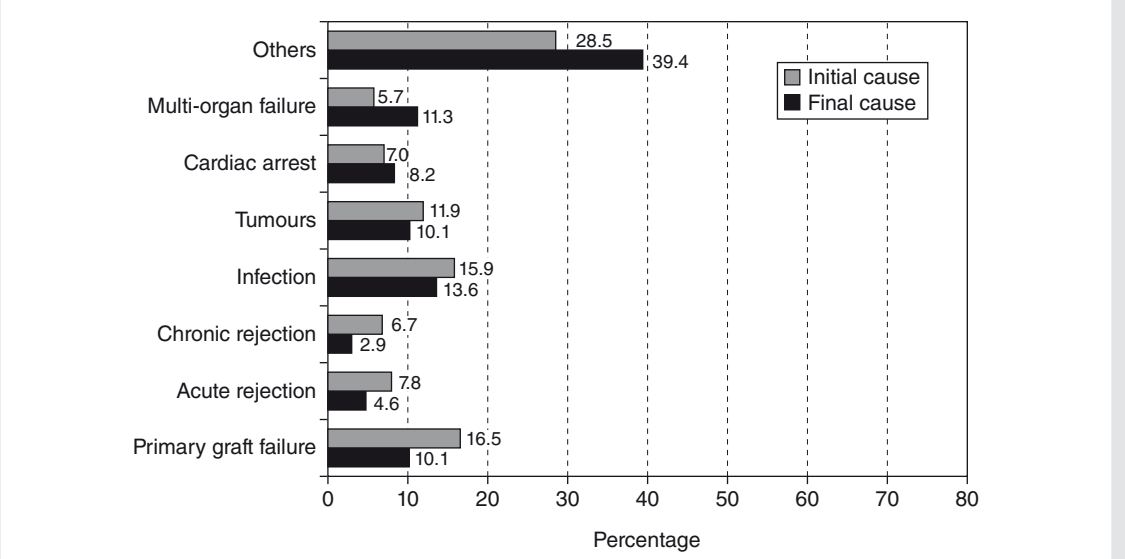

Figure 1. *Causes of mortality. Initial cause that triggered death and final cause of exitus. Spanish Heart Transplant Registry (1984-2010)[4].*

Society for Heart and Lung Transplantation (ISHLT) registry, the published survival was: 85% at one year, 70% at five years, and 50% at 10 years[3].

In Spain, the Heart Transplantation Registry showed a one-year survival of 78%, five-year survival of 67%, 10-year survival of 54%, 15-year survival of 41%, and for the past five years the probability of survival at one and five years was 85 and 73%, respectively[4].

Despite these improvements, heart transplant recipients still face a big challenge in the prevention of acute cellular rejection (ACR) after transplantation[1,2]. The improvements in organ preservation, anti-rejection regimens, and posttransplant management provide higher survival rates following cardiac transplantation. Also, these advances help in the progress with intensive care, prophylaxis, and treatment against infection and more effective immunosuppressive therapies for ACR. In the Spanish Heart Transplantation Registry the most frequent cause of death was primary graft failure (16.5%), followed by infection (15.9%), the combination of chronic rejection and cardiac arrest (13.7%), tumors (11.9%), and acute rejection (7.8%) (Fig. 1). By dividing the causes of mortality into various periods, there are differences in the main causes of death: during first month (primary graft failure), first month to first year (infection), and after the first year (tumors, combination of sudden death with chronic rejection and infections)[4].

Since the number of heart transplants that can be performed is limited by the scarcity donors, one must carefully select the recipient to use the hearts in those patients who are most likely to benefit and with greater guarantees of success. Moreover, there is a big difference between the supply and demand for transplantable organs, a gap that is made more severe by expanding indications and less conservative listing criteria for cardiac transplantation[5,6]. Careful selection should dismiss the possible candidates with systemic diseases or other factors that may condition their life expectancy in order to use the donor heart in the suitable recipient that theoretically will get more benefit. There are specific

Table 1. Cardiac biopsy grading system in heart transplantation

International Society for Heart and Lung Transplantation standardized cardiac biopsy grading: acute cellular rejection[8]	
Grade	**Definition**
0 R	No rejection
1 R (mild)	Lymphocytic infiltrate, with up to one focus of myocyte necrosis
2 R (moderate)	Two or more foci of infiltrate with associated myocyte damage
3 R (severe)	Diffuse inflammatory process + multifocal myocyte necrosis ± edema ± hemorrhage ± vasculitis

Findings in acute antibody-mediated rejection of the heart

- Clinical evidence of acute graft dysfunction
- Histologic evidence of acute capillary injury (a and b are required)
  - Capillary endothelial changes: swelling or denudation with congestion
  - Macrophages in capillaries
  - Neutrophils in capillaries (more severe cases)
  - Interstitial edema and/or hemorrhage (more severe cases)
- Immunopathologic evidence for antibody-mediated injury (in the absence of OKT3 induction) a or b or c are required
  - Ig (G, M, and/or A) C3d and/or C4d or C1q (equivalent staining diffusely in capillaries, 2-3)+, demonstrated by immunofluorescence
  - CD68 positivity for macrophages in capillaries (identified using CD31 or CD34), and/or C4d staining of capillaries with 2-3+ intensity by paraffin immunohistochemistry
  - Fibrin in vessels (optional; if present, process is reported as more severe)
- Serologic evidence of anti-HLA class I and/or class II antibodies or other anti-donor antibody (e.g. non-HLA antibody, ABO) at time of biopsy (supports clinical and/or morphologic findings)

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indications depending on the context of each disease. This is very important due to the big difference between supply and demand for organs. In the USA, between 25 and 30% of patients on heart transplantation waiting lists die while waiting for their organ. At first, the criteria to select a donor were very restrictive, but due to the small number of donors, these criteria have been expanded[7].

The most important challenges in the postoperative period are the management of rejection and infection. Acute cellular rejection is one of the main causes of early and mid-term mortality after heart transplantation, and it occurs most often during the first months after surgery. In 2004, under the direction of the ISHLT, a multidisciplinary review of the cardiac biopsy grading system was undertaken to address the challenges and inconsistencies in its use. Table 1 summarizes the revised consensus classification for ACR[8]. The incidence and severity appear to be reduced in accordance with best immunosuppression regimens. However, severe rejection episodes remain a serious threat for the life of the transplant recipient's heart because of antibody-mediated rejection (AMR). In human heart transplantation, AMR is an immunopathologic process in which injury to the graft is in part the result of activation of complement and it is poorly responsive to conventional therapy. The combination of clinical, histological, and immunopathologic findings as well as demonstration of circulating donor-specific antibodies, in the absence of cellular rejection, are recommended to diagnose acute AMR[9].

Immunosuppressed patients are at increased risk for infectious complications post-transplantation. It is necessary to maintain the lowest degree of immunosuppression possible to avoid an increased risk of infection.

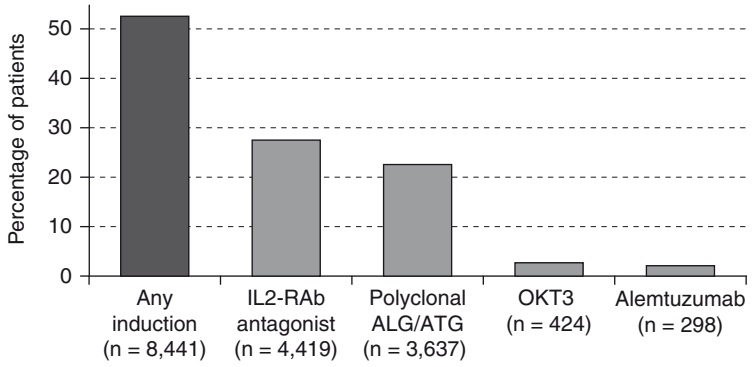


Figure 2. *International Society for Heart and Lung Transplantation Registry. Adult heart recipients: Induction Immunosuppression (Transplants: January 2002 to June 2010)[3].*

Infections are responsible for an important part of the morbidity among transplant patients. The most important infections appear during the first three months and the most common are nosocomial and at the surgical site[2]. Cytomegalovirus (CMV) infection is common in heart transplant patients, with an incidence that varies, depending on the series, between 60 and 100%. It can be asymptomatic or cause severe clinical problems such as pneumonitis, liver disease, chorioretinitis, gastrointestinal ulcers, fever, and leukopenia. Its possible relation to ACR and graft vascular disease has also been postulated. Cytomegalovirus prophylaxis is still a controversial issue, but recently guidelines on the management of CMV in solid organ transplantation have been published[10].

Immunosuppressive induction therapy

The use of induction therapy was introduced to reduce graft rejection in the immediate posttransplant period when the alloimmune response is most intense. Induction therapy mainly consists of early posttransplant use of polyclonal or monoclonal antibodies. Whether prophylactic monoclonal or polyclonal antibody therapy facilitates development of tolerance to the allograft remains unclear. Despite extensive experience with induction therapy in heart transplantation, early preventive anti-cytolytic treatment remains controversial[1,11]. Currently, 50% of heart transplant recipients receive induction therapy (Fig. 2). The assessment of its effectiveness is in terms of incidence of ACR, infections, tumors, and overall survival. The use of induction therapy seems to reduce the incidence of ACR, reducing deaths from this cause and being more pronounced in high-risk populations. It has been suggested that induction therapy has a negative effect on overall survival in populations with low risk of rejection, possibly due to increased deaths due to infections[11]. A cautious selection of the immunosuppressive agent and individualized therapy according to the patient appear to be needed to guarantee a favorable risk/benefit ratio.

Induction therapy currently has three well-defined drug groups. In general, their action focuses on cytolytic T lymphocytes, and produces a significant decrease in these cells after administration. Despite the variety of available drugs, none have demonstrated a

Table 2. Immunosuppressive therapy currently used for induction therapy in heart transplantation

	Antithymocyte globulin rabbit (Thymoglobulin)*	Muromonab-CD3 (Orthoclone OKT3)	Basiliximab (Simulect)†
Type	Polyclonal antithymocyte globulin	Murine monoclonal antibody	Chimeric monoclonal antibody
Target	Circulating T lymphocytes	T-cell receptor (CD3)	CD25 (IL2-RAb)
Dose	1.5 mg/kg/IV per day	5 mg per day in a single (bolus)	20 mg per day
Dosing schedule	3-7 days	7-12 days	Two doses (day 0 and 4)
Side effects	CRS, leukopenia, thrombocytopenia, PTLD	CRS, PTLD	Allergic reactions

*There are other polyclonal antibodies from rabbit (Fresenius-ATG) and horse-derived preparations (ATGAM).
†Daclizumab, another IL2-RAb, is no longer commercially available.
CRS: cytokine release syndrome; PTLD: posttransplant lymphoproliferative disorder; IL2-RAb: interleukin-2 receptor antibody.

clear superiority in the suppression of rejection, only getting delayed onset of the first ACR. Therefore, the main differences between treatments are focused on their adverse effects and posology. The induction therapies currently available are: polyclonal antilymphocyte antibodies (antithymocyte globulin [ATG] and antilymphocyte globulin [ALG]), murine monoclonal CD3 antibody (OKT3) and interleukin-2 receptor antagonist (Table 2). There are new induction therapies such as alemtuzumab (humanized anti-CD52 monoclonal antibody). This drug rapidly depletes CD52-expressing lymphocytes in central and peripheral lymphoid tissues. However, there are no published trial data on the use of alemtuzumab in heart transplant recipients, only a retrospective study[12].

Polyclonal antilymphocyte antibodies

This drug class is characterized by a variable amount of specific antibodies against T-cells (CD2, CD3, CD4, CD8 and CD25), B-cells (CD19, CD20 and CD21), the heavy chains of HLA-donor/recipient class I, and against β2 microglobulin[13].

The polyclonal antibodies are obtained by immunization of heterologous species, currently the rabbit (Thymoglobulin®) and horse (ATG). This antigen is injected as pure preparations of human thymocytes, and after a period of immunization, serum is collected to isolate the immunoglobulin G (IgG). This serum undergoes various purification procedures, and after this process, a concentrated serum is obtained with some variability in the number and specificity of the IgG[13].

The main problem with these drugs is their variable potency of immunosuppression, requiring a lymphocyte count to assess their effectiveness. Thus, it is considered that the dose is appropriate when it reaches a CD3 decrease to below 10% of its pretreatment value.

Other less important problems are:

- Allergic reactions caused by the animal origin: mostly the symptoms are urticaria, chills, fever, and rash, all more common in the first dose.
- Serum sickness: this is much less common but with serious consequences. The risk appears greater with ATG.
- Increased infections: there is a clear increase in the rate of CMV, so we recommend using prophylaxis, although its duration is not well defined.

CD3 monoclonal antibodies

Muromonab-CD3 (OKT3) is a murine IgG2a directed against the epsilon chain of the molecule of T lymphocytes CD3. Binding to this receptor causes a transient activation of T lymphocytes, cytokine release, and blocking of proliferation and differentiation of the lymphocyte. Along with this, the binding of OKT3 to CD3 facilitates opsonization and removal of these cells by macrophages of the liver and spleen.

The production is made from OKT3 hybridoma (mixture of myeloma cell lines with healthy B-cells) so that they can secrete antibodies against any antigen present. Thus, unlike how polyclonal antibodies are obtained, there is a single antibody and unlimited number so that the immunosuppressive capacity is constant and predictable, not requiring monitoring[14].

Despite its recognized antirejection potency, its use has declined significantly in recent years. The reasons for this are the frequent and important adverse effects and the emergence of new drugs that are better tolerated[15].

Adverse effects of OKT3 best known are:

– Cytokine release syndrome: this is the most common, occurring at the time of the first or second dose. It is due to the initial activation of T-cells that occurs upon binding of OKT3 to CD3. It includes fever, chills, headache, dyspnea, and even (though rarely) pulmonary edema. Its frequency decreases with subsequent doses.

– Generation of antibodies produced with the devolved administration, due to the creation of antibodies against xenogeneic epitopes. This implies a loss of efficacy in subsequent administrations.

– A carcinogenic effect has been associated in a dose-dependent way with an increased incidence of lymphomas in the long term.

– Increased infections: polyclonal antibody, and especially CMV, is also indicated for prophylaxis.

Interleukin-2 receptor antagonist

This class of drugs acts against the Tac receptor chain of interleukin-2 (IL-2). When this chain is found only in activated lymphocytes, its specificity is higher than that of OKT3 and the polyclonal antibodies. Its production is performed in mice, but is achieved through genetic mechanisms for the substitution of up to 90% of human-murine sequences, thus reducing almost completely the problems of antigenicity[16]. The use of IL-2 receptor antibody (IL2-RAb) as an innovative drug adds a new concept in induction therapy[17]. These drugs are the paradigm of induction drugs, by blocking an important and selective immune system, and have a long half-life and minimal toxicity. There are currently two drugs in this group, daclizumab and basiliximab. Without their being directly compared, both have proven safe and effective in renal transplantation, with minor studies in heart transplantation[18]. With none of the anti-CD25 has an increased rate of infections or tumors been reported, and therefore CMV prophylaxis is not necessary. The IL2-RAb has no direct cytolytic effect, which adds undeniable advantages in perioperative clinical management. Basiliximab is a chimeric monoclonal antibody (human/murine) that specifically binds to the alpha chain (CD25) of IL-2. It is administered in two doses of 20 mg on days 0 and 4 after cardiac transplantation. In a controlled study of the Spanish groups, its effectiveness has been shown in terms of acute rejection. It was safer and better tolerated than OKT3 in combination with cyclosporine, mycophenolate, and prednisone. Administration of basiliximab

showed no cytokine release syndrome compared with OKT3 and the infection rate was low[19].

Recent comparative studies in induction therapy

Monoclonal (OKT3) versus polyclonal antibody therapy for rejection prophylaxis early after heart transplantation has been analyzed. Most studies found both strategies were comparable in their ability to delay the onset of the first ACR episode; however, there appeared to be differences in side effects and types of infections seen. Patients treated with OKT3 had a higher incidence of adverse reactions, including respiratory distress and aseptic meningitis. The polyclonal antibody strategy seemed to increase the risk of bacterial infections, whereas OKT3-treated patients had a higher incidence of viral infections, specifically CMV[20].

The interleukin-2 receptor blockers have been studied more recently in heart transplantation as induction therapy. In 2005, Mehra, et al.[21] conducted a multicenter, randomized, double-blind trial of basiliximab (two doses, days 1 and 5) versus placebo. Fifty-six patients were included and maintenance therapy was cyclosporine, mycophenolate mofetil (MMF), and steroids. No differences were seen in adverse events or infections. The time to first biopsy-proven rejection was higher with basiliximab (73.7 ± 59.68 days) than placebo (40.6 ± 53.3 days) at six months, but this was not statistically different.

It was also in 2005 when Hershberger, et al.[22] conducted a multicenter, double-blind, randomized study in 434 patients with daclizumab (five doses, days 1, 8, 22, 36, and 50) versus placebo. Maintenance treatment was performed with cyclosporine, MMF, and steroids. The primary endpoint was combined (moderate or severe ACR, graft dysfunction with hemodynamic compromise, need for retransplantation, death, loss to follow-up). The analysis at six months showed that the average time to reach the primary endpoint was 21 days in the placebo group versus 61 days in the daclizumab group. However, in the daclizumab group there were more deaths per year (21 vs. 12) and more deaths due to infections when administered concomitant with cytolytic therapy.

In 2006, Ortiz, et al.[23] carried out a comparative study of two doses of daclizumab (days 1 and 14) versus five doses (days 1, 15, 29, 43 and 57). The study compared 81 patients in their series with 28 of the series published by Beniaminovitz, et al.[24]. Maintenance medication was with cyclosporine, MMF (azathioprine in the Beniaminovitz series), and steroids. There were no significant differences at 1.5 years of follow-up in infections or mortality. Paradoxically, however, more rejections were found in the 28 patients with five doses (61 vs. 30%).

In Spain, a randomized multicenter study (SIMCOR trial) led by Segovia, et al.[19] in 2006 compared basiliximab (two doses, days 1 and 5) with muromonab-CD3 (seven doses) in 99 heart transplant patients. There were large differences in tolerability in favor of basiliximab. There was no difference in the incidence of biopsy-proven rejection, number of infections, and mortality. Flaman, et al.[25] compared the safety and efficacy of basiliximab versus rabbit ATG (rATG) in heart transplant recipients. There was a significant difference in the average biopsy score (ABS) at one and at three months (0.75 ± 0.24 in the basiliximab group vs. 0.46 ± 0.12 in the rATG group ($p = 0.032$), but not at six and 12 months. Also, the number of episodes of infection was similar in both groups.

In 2007, two multicenter, randomized studies were published comparing basiliximab to rATG and maintenance therapy with cyclosporine, MMF, and steroids[26,27]. After a six-month follow-up, the result was that basiliximab offered

greater tolerability with similar efficacy against rejection as rATG. The incidence of the primary composite safety end-point was significantly lower with basiliximab and there was a higher rate of infectious deaths in the rATG group. On the other hand, the rATG induction was associated with higher rates of CMV viral load in plasma.

Despite recent studies, induction therapy continues to be empirical, but it marked the trend away from classical cytolytic therapy in favor of the use of IL2-RAb. This is based on safety, efficacy, and absence of cytokine release syndrome. They can be of help in the management of new immunosuppressants, such as sirolimus and everolimus, in a bid to get low rates of calcineurin.

Safety and tolerability of induction therapy

There are differences in the induction treatment between the drugs used to date. Thus, it is universally accepted that ATG is the most effective, while basiliximab and daclizumab are safer and better tolerated[11]. Induction therapy has been related with more infectious complications among heart transplant patients. In the SIMCOR study, there were less infections in the basiliximab group comparing with OKT3 (56.3 vs. 76.5%; $p = 0.03$). In pediatric patients, Gajarsky, et al.[28] analyzed 2,374 patients, of whom 1,258 (53%) received induction, more frequently from 1999 to 2008 compared with 1993 to 1998 (70.8 vs. 57.5%; $p < 0.001$), but this increase in induction therapy has not been associated with an increased risk of overall infection or risk of malignancy, predominantly posttransplant lymphoproliferative disease (PTLD).

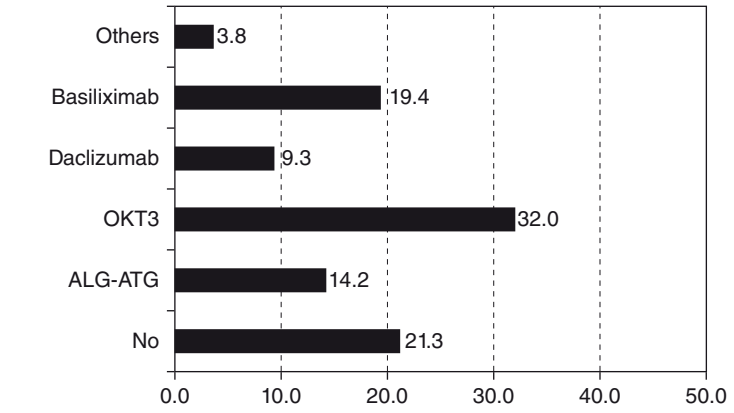
However, in the long term, an increase in the presentation of neoplasms has been seen with induction therapy. A link has been documented between cytolytic induction therapy and lymphoproliferative disorders. In a retrospective analysis of 154 consecutive heart transplant recipients, Swinnen, et al.[29] discovered a nine-fold higher incidence of PTLD in the OKT3-treated patients. In addition, a dose-related risk was also discovered, where PTLD developed more frequently in patients who received a cumulative dose of OKT3 exceeding 75 mg than in those who received a lower total dose (35.7 vs. 6.2%; $p < 0.001$). There is insufficient evidence to suspect that treatment with thymoglobulin or IL2-RAb increases the risk of malignancy.

In 2007, Crespo, et al.[30] published data from the Spanish Registry of Tumors in Heart Transplantation. The study was performed on 3,393 patients. It was found that induction therapy with OKT3 or ATG/Thymoglobulin® was associated with the development of lymphomas, but this association was not significant if the patient had been treated with acyclovir prophylactically.

Current status of induction treatment in national and international registries

The latest release of the Spanish Registry of Heart Transplantation includes 6,291 patients, including all transplants performed since the beginning of the transplant activity in Spain (May 1984) until December 31, 2010. Most transplant patients in our country received induction therapy; only 23% were not given any of these drugs (Fig. 3). This percentage has changed over the years so that at the beginning of transplantation, 33% of patients had no induction therapy, while in recent years only 12% were not receiving any drug of this type (Fig. 4)[4].

The drug most commonly used is OKT3; 36% of patients throughout the series were induced with this treatment. The second place is occupied by the combination of

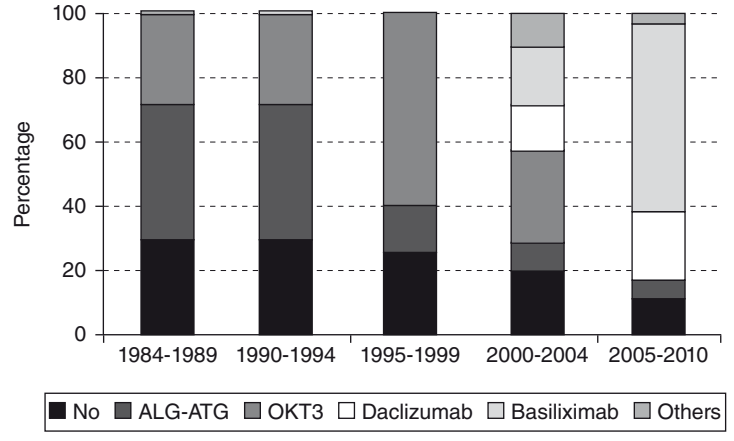


ALG: antilymphocyte globulin; ATG: antithymocyte globulin.

Figure 3. *Induction therapy in adult heart transplant recipients (n = 6,291). Spanish Heart Transplant registry (1984-2010)[4].*

basiliximab and daclizumab (24%), and thirdly ALG/ATG (13%).

This relationship has changed over time, so different inducers were administered at different times. In the period between 1984 and 1988, coinciding with the onset of transplant activity in Spain, the most commonly used induction agent was ALG/ATG, followed by OKT3. In the 12 following years, OKT3 was the most administered, exceeding 50% of transplant patients. Since 1999, there has been a rapidly progressive increase of daclizumab and basiliximab, such that in the period between 2004 and 2008, they were the drugs used in 75% of transplants, with infrequent



ALG: antilymphocyte globulin; ATG: antithymocyte globulin.

Figure 4. *Drugs used for Induction therapy in adult heart transplant recipients (n = 6,291). Distribution by periods in Spanish Heart Transplant Registry (1984-2010)[4].*

use of ALG/ATG (3%), and OKT3 being practically unused (0%).

In the Spanish Registry of Heart Transplantation, the independent predictors of mortality have been examined. Thus we see that induction therapy reduces the risk of death by 61% at 30 days posttransplantation, whereas no influence on mortality is seen in the longer term[4].

In the International Registry of Heart Transplantation, we can see that induction is administered in approximately 50% of patients. Immunosuppressive drugs most commonly used are IL2-RAb, followed by polyclonal antibodies (ALG/ATG); OKT3 treatment is minimal. The evolution over time shows a gradual increase in the administration of IL2-RAb. No difference in survival depending on the administration of inducing agents or which of them is used is seen[3].

Clinical recommendations for induction therapy in heart transplantation

Present controversies about induction therapy in heart transplantation involve the classification of candidate patients in whom the risk/benefit ratio is favorable, and the choice of the appropriate regimen for each patient. Until now, there is not enough evidence to systematically manage heart transplant patients with induction therapy. Recently, Moller, et al.[31] published a systematic review with a meta-analysis of randomized trials of induction therapy based on IL2-RAb. The comparison was with placebo and polyclonal and monoclonal antibodies. This analysis included nine randomized trials and evaluated the development of rejection, infection, malignancy, and mortality. Treatment with IL2-RAb versus placebo or polyclonal or monoclonal antibodies showed no significant differences in infections, malignancy, or mortality. Analysis of rejection was unclear, although the result was that treatment with IL2-RAb was not associated with more or less rejections than placebo and monoclonal antibodies, but with more rejection than polyclonal antibodies. The systematic review found no convincing evidence of a survival benefit or reduction of rejection. The conclusion of this analysis was that the evidence for the use of induction therapy after transplantation is scarce[31].

Are there special subgroups where induction therapy should be administered?

Currently, there are two situations requiring the administration of these drugs: in the presence of preformed antibodies and with coexisting renal dysfunction.

The presence of circulating preformed antibodies is more common in multiparous women, patients with prior bypass surgery, recipients of blood transfusions, and those with ventricular assist devices. Patients with panel reactivity greater than 10% can develop early and severe graft rejection, despite a negative donor-crossmatch[32]. In these patients, it has been suggested that induction therapy may prevent the occurrence of antibody-mediated rejection.

Renal dysfunction, both early and late, is associated with a high probability of death. Therefore, induction therapy has been used to delay the start of the administration of calcineurin inhibitors (CNI). There are many well-designed studies in this field, although the literature suggests that in transplanted patients at high risk of renal dysfunction, induction therapy with basiliximab or ATG to delay the introduction of cyclosporine improved renal function. Also, this strategy does not imply a significant increase in graft rejection. The potential possibility of renal protection by

delaying the use of CNI in selected patients using induction therapy could also improve the long-term survival[33,34].

Higgins, et al.[35] investigated the impact of induction therapy on heart transplantation outcomes in 6,553 patients (4,161 with no induction vs. 1,736 with OKT3 or antithymocyte preparations as cytolytic induction therapy) using the Cardiac Transplant Research Database (CTRD). They concluded that those patients who experienced a combination of longer support with a ventricular assist device, who were of black ethnicity, and had extensive HLA mismatching may in all likelihood see benefit from cytolytic induction therapy. More recently, Ensor, et al.[36] concluded that patients at significant risk for fatal rejection were those presenting one or more of the following conditions: undergoing repeat transplantation, supported with ventricular assist device before transplantation, African Americans 40 years or younger, patients who have four or more donor-recipient HLA mismatches, or those with panel reactive antibody ≥ 40%.

Conclusion

In the current era of heart transplantation, cytolytic therapy remains controversial, with wide variation depending on indications of the centers. The most accepted current indication is the presence of renal insufficiency in order to delay the achievement of optimal levels of cyclosporine or tacrolimus.

Due to the current immunosuppressive drugs having side effects such as cardiac allograft vasculopathy, chronic renal failure, and malignancies, it is necessary to develop new classes of drugs to allow increased efficacy and less toxicity. In recent years, several agents have been studied in basic research to find novel methods to block T- and B-cell activation and proliferation[37].

Therefore, it is necessary to establish firm evidence with well-designed, large-scale randomized trials to assess the positive and negative aspects as well as the costs/benefits of induction therapy. Hence, it is recommended to do individualized induction therapy for each patient in heart transplantation, and each center should decide and follow their own protocol to supply the induction therapy[38].

Despite the considerable progress that has been achieved, it is necessary to improve the development of safer drugs with fewer side effects, the correct classification of patients to determine which patients would benefit more or less from this treatment, and the development of tolerance mechanisms[11].

Consensus key points

1. The decision to induce or not induce in heart transplantation is controversial, with an individualized decision for each transplant center.

2. Induction therapy is effective and delays the onset of the first episode of rejection, but increases the risk of infection.

3. Induction therapy can slow the introduction of CNI especially in patients with renal failure, in turn facilitating low-dose regimens with CNI.

4. Induction therapy is useful in patients at risk of acute cellular or antibody rejection (young, sensitized patients, or those with ventricular assist devices).

5. The use of IL2-RAb, at equivalent efficiency, is better tolerated than other induction antibody therapies and therefore provides a more widespread use in heart transplantation.

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