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Induction Therapy in Hepatic Transplantation

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Abstract

Induction therapy in liver transplantation has not become part of the routine immunosuppressive protocol in the majority of Spanish centers. The benefit of universal induction therapy with either an interleukin-2-receptor antagonist or a polyclonal thymocyte-depleting antibody has not been demonstrated in liver transplantation. Depleting antibodies have been associated with a higher incidence of early posttransplant infections. However, antibody induction can be considered for high-immunological risk patients or in order to minimize the exposure to calcineurin inhibitors in the early posttransplant period, e.g. in patients at risk of renal failure.

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Key words

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

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Induction Therapy in Liver Transplantation

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Introduction

The regimens of immunosuppression in liver transplantation are intended, as in the context of other organs, to avoid rejection with minimal side effects. Immunosuppression in the immediate posttransplant period is based on a calcineurin inhibitor (CNI), cyclosporine, or tacrolimus, with or without steroids and/or mycophenolate.

The use of induction therapy, defined as an antilymphocyte agent or an antagonist of the interleukin-2 receptor (IL2-RAb) during or immediately after transplantation, aims to reduce the possibility of rejection or to reduce the need for other immunosuppressive drugs and thus its side effects[1].

In the context of liver transplantation, the use of induction therapy is not clearly established, and indications often depend on the protocols of each center. There are neither consensus documents nor a general indication. Their use in Spanish centers is around 30%.

Evidences

Several studies in the literature have evaluated possible indication, and risks and benefits of its use. In liver transplantation, in general, studies have been published with different types of induction[2-13] (Table 1). Initial studies performed with OKT3 still showed very high rejection rates[2,3]. Subsequently, two studies based on the use of thymoglobulin did not show differences[4,5], and in one case the use of thymoglobulin was associated with more leucopenia[5]. Only two studies are methodologically optimal to be prospective and randomized[8,13]. Only the study by Neuhaus, et al.[8] showed a decrease in rejection, which was not confirmed in hepatitis C virus (HCV)-positive patients. So, globally, the literature has not shown improvement in the rate of rejection with the use of induction. On the other hand, it has to be emphasized that any study that has observed the use of induction in the context of liver transplantation will be associated with an increased risk of infection or *de novo* tumor.

Recommendation: In the general context of liver transplantation, there is no evidence to recommend routine use of induction therapy.

There is no evidence in the literature about induction therapy according to the etiology of the transplant. There is also no evidence in the context of fulminant hepatitis. However, given the frequently associated renal failure in this situation, a pattern of immunosuppression based on induction and delayed initiation of CNI could be suggested[14-16].

Recently, a retrospective study by the American Transplant Registry has demonstrated a global improved survival in patients transplanted for hepatocarcinoma who received induction with anti-CD25 antibodies[17].

Special situations (Table 2)

Reduction patterns with calcineurin inhibitors[18-20]

Patients receiving a liver transplant often present with renal failure in the pretransplant

Table 1. Published studies using induction in liver transplantation (general population)

Antibody type	Reference	Study type	Group treatment	(n)	Rejection (%)	Comments
OKT3	Cosimi[2]	PR/R	CsA + Ste + Aza	41	78	Decrease stay
			CsA + Ste + OKT3	38	68	
	Farges[3]	PR/R	CsA + Ste + Aza	50	75	Better renal function
			CsA + Ste + OKT3	44	67	Less infection
ATG	Tchervenkov[4]	R	ATG + CNI + MMF	231	29	Less dialysis
			CNI + AZA	67	30	
	Boillot[5]	PR/R	ATG + Tac + MMF + Ste	44	11	More leukopenia
			Tac + MMF + Ste	49	14	
Daclizumab	Otero[6]	PR/R	Dac + Tac + MMF			Monitoring 24 weeks.
			Tac + MMF			Infection/side effect similar
Basiliximab	Calmus[7]	PR	Bas + CsA + Ste + Aza	101	23	No significant events
	Neuhaus[8]	PR/R	Bas + CsA +Ste	188	35	Reduction rejection HCV
			Plac + CsA + Ste	193	43	Infection/side effect similar
	Marino[9]	PR	Bas + Tac + Ste	50	12	Infection/side effect similar
	Gruttaduria[10]	R	Bas + Tac + Ste	152	13	No CMV. 2 tumor de novo.
	Ramirez[11,12]	R	Bas + TAC + Ste	42	6.5	Monitoring 18 month 0 CMV, 0 lymphoproliferative
	Schmeding[13]	PR/R	Bas + CsA + Ste	51	56	Infection/side effect similar
			Plac + CsA + Ste	48	51	

PR: prospective, R: randomized retrospective; n: number of patients included. ATG: anti-thymoglobulin; CsA: cyclosporin A; Ste: steroids; Aza: azathioprine, MMF: mycophenolate mofetil; Tac: tacrolimus; Bas: basiliximab; CNI: calcineurin inhibitor; CMV: cytomegalovirus.

or immediate posttransplant period. Kidney failure can be worsened by the use of CNI immediately after transplantation. Similarly, kidney failure may prevent the use of full doses of these drugs, with increased risk of rejection. This is one of the contexts where the use of induction therapy may have more relevance. Published studies evaluating the use of induction therapy with reduced doses of CNI have demonstrated the safety of these standards, with improvement in the evolution of renal function in all studies. Published studies are heterogeneous, with different drugs and different ways to delay or reduce the CNI dose. Recommendation: We can recommend the use of induction (anti-IL2-RAb), and postpone the onset of CNI 3-4 days and/or start half-dose CNI (according to renal function).

Reduction patterns of steroids[22-33]

Corticosteroids are associated with multiple side effects, especially diabetes mellitus and increased risk of infection. The immediate posttransplant infection rate is 50%, relating to mortality. It therefore seems of interest to avoid its use. Multiple studies have evaluated the possibility of immunosuppressive therapy without corticosteroids. Initial studies were performed with antithymocyte globulin (ATG). Later studies with anti-IL2-RAb

Table 2. Published studies using induction in liver transplantation in special situations

Antibody type	Reference	Study Type	Group treatment	(n)	Rejection (%)	Comments
Reduction patterns calcineurin inhibitors						
ATG	Soliman[18]	R	ATG + CNI day 3 + Ste	262	14.5	Better renal function
			CNI + Ste	129	31.8	Infection/side effects similar
DAC	Yoshida[19]	PR/R	Dac + Tac + Ste	76	23	Better renal function
			Tac/2 + MMF + Ste	72	27	
	Neuberger[20]	PR/R	Dac + Tac/2 + MMF	172	19	Better renal function
			Tac/2 + MMF + Ste	170	29	
			Tac + Ste	183	27	
Basiliximab	Lin*[21]	PR	Bas + Tac (red)	11		Better renal function
			Tac	27		
Reduction patterns of steroids						
ATG	Eason[23]	PR/R	ATG + Tac + MMF	60	20	Less DM, Less CMV
			Tac + MMF + Ste	59	32	
DAC	Boillot[24]	PR/R	Dac + Tac	351	26	Less infection, DM
			Tac + Ste	347	25	
	Washburn[25]	PR/R	Dac + Tac + MMF	15	6.7	No differences
			Tac + MMF + Ste	15	6.7	
	Kato[26]		Dac + Tac + MMF	19	13	Less DM
			Tac + MMF + Ste	20	20	
Basiliximab	Filipponi[27]	PR/R	Bas + CsA + Aza	66	30	No differences
			Bas + CsA + Aza + Ste	74	37	
	Lupo[28]	PR/R	Bas + CsA	26	15	No differences
			Ste + CsA	21	28	
	Lladó[29]	PR/R	Bas + CsA + Ste	96	13	Less infection, HTA, DM
			Bas + CsA	102	18	
	Pelletier[30]	PR/R	Bas + Tac + MMF	50	14	No differences
			Bas+ Tac and MMF + Ste	50	25	
	Liu*[31]	R	Bas + Tac + MMF	31	6	Less DM
			Tac + MMF + Ste	49	27	Less CMV
	Marubashi*[32]		Bas/Dac + Tac/CsA	9	22	Less DM
			CNI + Ste (historical)	13	23	Less HTA
	Ringe*[33]	R	Bas/Dac + Tac	21	19	Safe in adults

(Continue)

Table 2. Published studies using induction in liver transplantation in special situations *(Continued)*

Antibody type	Reference	Study Type	Group treatment	(n)	Rejection (%)	Comments
			Studies on live donor			
Basiliximab						
	Gruttaduria[34]	PR	Bs + Tac + Ste	60	5	0 CMV, 0 tumor de novo
	Vigano[35]		Bas + Tac + Ste			Compared to dead donor
			Studies on hepatocellular carcinoma			
Anti-CD2						
	Toso[17]	R	Anti-CD25	299		Better survival (patients with HCC)
			No anti-CD25	2,192		
			Studies on fulminant hepatitis			
No available specific studies						

PR: prospective; R: randomized retrospective; n: number of patients included; HCC: hepatocellular carcinoma; ATG: antithymocyte globulin; CsA: cyclosporin A; Ste: steroids; Aza: azathioprine, MMF: mycophenolate mofetil; Dac: daclizumab; Tac: tacrolimus; Bas: basiliximab; CNI: calcineurin inhibitor; CMV: cytomegalovirus; DM: diabetes mellitus; HTA: hypertension.
*Studies focused on living donor; and initial tacrolimus delayed if renal failure.

have demonstrated the safety of the guidelines without steroids, combining induction. Thus the pattern with anti-IL2-RAb associated with a CNI (full or reduced doses in renal failure, adding mycophenolate in this case), have been shown to be safe (same rejection rate), and have a tendency to decrease the incidence of diabetes mellitus, *de novo* hypertension and lower incidence of infection. Recommendation: When using immunosuppression without corticosteroids, is useful and safe add anti-IL2-RAb to induction therapy.

Studies in living donor recipients[34-35]

Two prospective nonrandomized studies have demonstrated the safety of induction therapy in living donor recipients. Two other studies also have evaluated the guidelines without steroids, in this context, and with reduced doses of CNI, being safe and improving metabolic profile. Recommendation: It may be recommended to use steroid-free therapy and/or reduced-dose CNI, associated with induction therapy with anti-IL2-RAb in the context of living donor recipient.

Personal experience

Our experience at the University of Bellvitge Hospital is the systematic use of induction therapy. At the beginning of our experience we used induction with ATG in 512 patients. The incidence of rejection in the group of patients who received ATG was 30%. Later, with the availability of anti-IL2-RAb, specifically basiliximab, we started its routine use in all patients (except for specific cases: retransplantation, etc.). So we used basiliximab in 450 patients, with a global incidence of rejection of 20% and an incidence of infection of 48%. In the current situation of liver transplantation, a large percentage of patients are transplanted according to prioritization by the Model for End-stage Liver Disease (MELD), and therefore can be considered severe patients, often with renal insufficiency. Moreover, the increasing age of the donor is more frequently associated with

graft dysfunction. In this context, it seems even more relevant to reduce CNI and/or guidelines without steroids to reduce the possibility of kidney failure and infection. Therefore, in our experience, the use of induction therapy allows the use of these guidelines and facilitates initial management of immunosuppression.

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Use of Polyclonal or Monoclonal Antibodies as Induction Immunosuppression in HCV-Positive Liver Transplant Patients

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Introduction

The mechanism of action of polyclonal antibodies is a rapid depletion of lymphocytes due to cell lysis mediated by complement, captured by the reticuloendothelial system and T-cells opsonized. These were routinely used as induction in the past with corticosteroids and azathioprine before the discovery of cyclosporine. Its current use is limited in liver transplant units. The main side effect, affecting nearly 80% of patients is a "reaction to the first dose", with febrile episodes that can be reduced with antipyretic, anti-histamine medication, and steroids intravenously. This effect is probably due to the release of pyrogen by the massive destruction of lymphocytes. Other side effects include thrombocytopenia, anemia, infection by cytomegalovirus (CMV), posttransplant lymphoproliferative disorders (PTLD), itching, skin rash, serum sickness, and anaphylaxis.

The monoclonal anti-IL-2 receptor antibody (IL2-RAb), basiliximab, a chimeric protein (Simulect®) and daclizumab, a humanized protein (Zenapax®), are specific for the alpha chain of IL-2 receptor, CD25, which is only expressed by activated T-cells. They remain in the blood circulation for weeks and have been used with cyclosporine or tacrolimus to prevent rejection in the early stages of liver transplantation. They have few side effects compared with antilymphocyte globulin and are associated with a lower risk of opportunistic infections or PTLD.

The use of induction immunosuppression with monoclonal or polyclonal antibodies aims to reduce the incidence of acute rejection, the dose of steroids and, due to their lack of renal toxicity, could reduce renal failure or acute renal failure in the immediate posttransplant period, allowing lower doses of calcineurin inhibitors (CNI) or a delay in the time of application. Ultimately, it is intended to reduce cases of graft failure, patient death, and development of secondary complications to the use of other immunosuppressants.

Its application in patients with hepatitis C virus (HCV) infection theoretically allows there to be less acute rejection and it was less necessary to use bolus of steroids or high doses of immunosuppressants that contribute to virus replication and recurrent and severe hepatitis C.

Evidences

There is very little information in the literature about the use of these drugs in patients infected with HCV in liver transplantation.

These drugs include polyclonal antibodies (antilymphocyte globulin and antithymocyte globulin), monoclonal antibodies, and interleukin-2 receptor antibodies (IL2-RAb).

No study using polyclonal antibodies as induction has shown significant advantages among HCV-positive patients in order to reduce the frequency of recurrence or severity of this. Moreover, improvements in long-term outcomes compared with other triple therapies or therapies without steroids could not be achieved. Certainly, in none of the studies were these the main objectives[1-3].

In the case of monoclonal anti-CD25 antibodies, early studies with basiliximab, used in conjunction with mycophenolate mofetil (MMF), found an increased risk of acute rejection in HCV-positive patients[4].

In a double-blind study comparing the effect of using basiliximab with or without steroids, in addition to cyclosporine and azathioprine on the recurrence of HCV in HCV-positive transplant patients, found no difference in frequency or severity of recurrence of hepatitis C in the first year after transplantation (41 vs. 37.5%; p = 0.354). In this study, the frequency of acute rejection was more common in patients not receiving steroids, so it might be assumed that its use would entail a higher need for treatment of rejection episodes, which carries a greater risk of recurrence and severity of hepatitis (41 vs. 37.5%; p = 0.354)[5,6].

In the largest study conducted, a double-blind, randomized controlled study of basiliximab versus placebo and stratified by HCV positivity, no advantages in the frequency of recurrence of hepatitis C were detected. The incidence of acute rejection in HCV-positive patients was higher in the group receiving basiliximab (difference 2.9%), but did not reach statistical significance[7].

Another large open study to analyze the efficacy of basiliximab on the incidence of acute rejection, including 70 HCV-positive patients (basiliximab with cyclosporine and steroids azathioprine), found a higher rate of acute rejection among HCV patients receiving basiliximab (29%) versus those without (20%), but did not reach statistical significance (p = 0.441)[8].

By contrast, in a small study of 46 HCV-positive patients who received tacrolimus, basiliximab and steroids, there was a lower incidence of histological recurrence of hepatitis C, 8/26 (31%) than in the historical group who received tacrolimus, MMF, and steroids, 17/24 (71%; p = 0.005), although there was no difference in the recurrence progression. This study has some deficiencies due to the difference in time between the group and possible changes in diagnostic criteria or certainty of recurrence or rejection caused by the time difference. There is no comment on the biopsy criteria[9]. The same group subsequently published data of the study with similar results[10].

Another study of 83 HCV patients who received tacrolimus, MMF, and basiliximab found a recurrence rate of 39% (33/83) versus 56% (46/83) in the historical group used as control (p = 0.05), but found no difference in the development of recurrence[11].

Finally, in a Spanish study where the objective was to study the influence of steroids on the recurrence of hepatitis C, 198 patients were randomized to cyclosporine and steroids versus cyclosporine and basiliximab and there were 89 HCV-positive patients, though no difference was found in the frequency of recurrence of hepatitis (97%). Inflammation was detected less frequently at two years in the group without steroids (p = 0.04) and with a lower incidence of severe fibrosis, although without reaching significance in this case (22 vs. 31%)[12].

Therefore, there is no scientific evidence that induction with polyclonal or monoclonal antibodies offers an advantage in HCV-positive transplant patients.

However, in a study referred to as abstract, which collected data from 40,796 patients in the UNOS database, where 18,329 were HCV positive and 2,891 of them received induction therapy defined as the use of thymoglobulin, antilymphocyte globulin, OKT3, daclizumab or basiliximab, survival was better at five years in the group receiving induction therapy (71 vs. 69%; p = 0.008), and there was also a better graft survival (65 vs. 62%; p <0.0001). Also in the multivariate analysis, induction therapy was significantly better (OR: 0.86; p = 0.004)[19].

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Induction Therapy in Pediatric Liver Transplantation

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Introduction

The primary immunosuppression in children is designed on the basis of a calcineurin inhibitor (CNI) as primary drug. It could be combined with steroids and/or interleukin-2 receptor antibodies (IL2-RAb).

The main purpose of the use of IL2-RAb is to reduce the rate of rejection or avoid the use of steroids. In children with renal disease, antibody induction is used to delay or reduce CNI use.

Evidences

Table 3 summarizes the results of the three published studies using basiliximab[1-3]. Overall, a decline in rejection rates is shown without side effects associated with the drug. Only one study was methodologically optimal (randomized).

The primary immunosuppression including anti-IL2-RAb is used in 55% of pediatric centers in Europe according to a survey conducted in 2007[4]. This survey revealed that

Table 3. Published studies using induction in liver transplantation, general child population

Type antibody	Reference	Study type	Groups treatment	Patients (n)	Rejection (%)	Comments
Basiliximab	Grãs, et al. 2008[1]	Compare with historical control	Bas + Tac	50	At 3 years: 28%	Bas + Tac: less viral infection
			Pred + Tac	34	59%	Better size
Basiliximab	Spada, et al. 2006[2]	Prospective/ randomized			At 1 year:	Bas + Tac: less infection
			Bas + Tac	36	12%	
			Pred + Tac	36	32%	
Basiliximab	Ganschow, et al. 2005[3]	Compare with historical control	Bas + CsA + Pred	54	16.6%	No PTLD in any group
			CsA + Pred	54	53.7%	

CsA: cyclosporin A; Tac: tacrolimus; Pred: steroids; Bas: basiliximab; PTLD: posttransplant lymphoproliferative disease.

most centers use anti-IL2-RAb added to conventional immunosuppression to decrease the risk of rejection, not to avoid or reduce the use of steroids.

Recommendations

The recommendations to use anti-IL2-RAb should consider the current low rate of loss of graft rejection using the guidelines that do not associate basiliximab, and the high risk of infections that are observed in the post-transplant period, suggesting the need to seek a balance by avoiding excessive immunosuppression[5]. Further studies are needed now to identify populations of children who can enhance anti-IL2-RAb immunosuppression. In the general population of children transplanted, anti-IL2-RAb application should pursue the reduction of other drugs.

Recommendations in liver transplantation

In the general context of liver transplantation, there is no evidence to recommend routine use of induction therapy. However, in view of the fact that kidney failure often is associated with this situation, one might propose a pattern of immunosuppressants based on induction and delayed initiation of CNI.

Liver transplant recipients often present kidney failure already in the pretransplant or immediate posttransplant period. The kidney failure can be worsened by the use of CNI immediately after transplantation, leading to the avoidance or minimization of CNI use in the early postoperative phase, increasing the risk of rejection. This is one of the contexts where the use of induction therapy may have more relevance. The use of induction with anti-IL2-RAb can be recommended to postpone the onset of the CNI drug for 3-4 days and/or start with half-dose of CNI (according to renal function).

Corticosteroids have been part of the immunosuppressive protocols in liver transplantation since the beginning. Corticosteroids are associated with multiple side effects, especially diabetes mellitus and increased risk of infection. That is why their use should be avoided. In the case of using an immunosuppression regimen without corticosteroids, it is useful and safe to add anti-IL2-RAb as induction therapy.

In recipients of a living donor liver transplant, steroid-free therapy and/or reduced dose of CNI associated with induction therapy with anti-IL2-RAb may be recommended.

Moreover, with the increasing age of the donor, the possibility of graft dysfunction

becomes more frequent. In this context, strategies to reduce CNI and/or regimens without steroids to reduce the possibility of kidney failure and infection seem even more relevant. Therefore, the use of induction therapy allows the use of these regimens and provides safe initial management of immunosuppression.

In the context of the use of polyclonal or monoclonal antibodies as an immunosuppression of induction in hepatitis C virus-positive liver transplant patients, there is no scientific evidence that such antibody induction offers an advantage.

In pediatric liver transplantation, it is advisable to seek a balance by avoiding excessive immunosuppression. In the general population of children transplanted, anti-IL2-RAb application should be used to permit the reduction of other drugs.

References

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