Induction Versus Maintenance Immunosuppression After Intestinal Transplant: Determining Which Treatment Most Impacts Long-Term Patient And Graft Survival

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Abstract

Objectives: **Immunosuppressive strategies for intestinal transplant have changed over time. However, specific intestinal transplant-oriented protocols and reports on long-term maintenance regimens are scarce. Our objective was to evaluate the impact of 2 different initial immunosuppressive protocols based on thymoglobulin (group A) and basiliximab (anti-interleukin 2 antibody) (group B) and of changes to maintenance immunosuppression over long-term follow-up in intestinal transplant recipients.**
Materials and Methods: **We performed a retrospective analysis of a prospectively established protocol for intestinal transplant immunosuppression, conducted between May 2006 and December 2020. We analyzed 51 intestinal transplant recipients, with 6 patients excluded because of early death or graft loss. Acute cellular rejection frequency and grade, number of acute cellular rejection episodes, time to the first acute cellular rejection episode, response to treatment, number of patients who progressed to chronic allograft rejection, kidney function, infections, incidence of posttransplant lymphoproliferative disorder and graft-versus-host disease, and patient and graft survival were analyzed.**
Results: **In the study groups, there were 87 acute cellular rejection episodes in 45 patients (33 in group A and 54 in group B). We found degree of acute cellular rejection to be mild in 45 patients, moderate in 18, and severe in 24 (not significant between groups). Our comparison of induction therapy (thymoglobulin [group A] vs interleukin 2 antibody [group B]) did not show any statistical difference during clinical follow-up. Long-term review showed that all patients were on tacrolimus. Five-year patient and graft survival rates were 62% and 45% for group A and 54% and 46% for group B, respectively (not significant).**
Conclusions: **Long-term patient and graft outcomes reflected the use of an individualized follow-up with adjustments and changes in immunosuppressive medications according to the patient's clinical course and complications rather than based on the induction immunosuppressive protocol used.**

Key words: *Immunological risk, Immunosuppressive protocol, Intestinal transplant*

Introduction

Despite the improvements in surgical techniques and clinical management, the intestine is still one of the most challenging organs to be transplanted. The main reason is the immunological characteristics of the intestine, which are unique and not yet fully understood.[1,2]

Back in 1989, the use of tacrolimus and steroids became the gold standard for maintenance immunosuppression in intestinal transplant (ITx), allowing long-term survival and a reduction in the number of rejection episodes.[3-5] Because of a greater immunoreactivity of the intestine compared with other organs, required levels of tacrolimus were higher in order to reduce acute cellular rejection (ACR) rates.[6,7] Renal failure, higher infection rates, and post-transplant lymphoproliferative disorders (PTLD) were some of the negative consequences of this

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Acknowledgements: *The authors have not received any funding or grants in support of the presented research or for the preparation of this work and have no declarations of potential conflicts of interest.*

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Experimental and Clinical Transplantation (2022) 12: 1105-1113

DOI: 10.6002/ect.2022.0359

approach; therefore, the use of induction as primer immunosuppressive therapy in an effort for lower maintenance in the long-term was implemented.[4] Since then, most of the large-volume centers and the Intestinal Transplant Registry[4,6,8] have analyzed early and long-term results on ITx based on the use of an induction therapy.[9-11] These analyses opened several questions: can we justify a 10-year survival based on a given induction therapy, and are we minimizing the importance of the changes made as part of the individual clinically required adjustments in the long-term maintenance immunosuppression during a patient's clinical course?

Thus far, these questions have remained unanswered, and no immunosuppressive protocol or specific drug has been developed solely for ITx recipients.[12-18] Thus, the aim of this study was to evaluate the effects of the initial immunosuppressive protocol and the effects of the clinically indicated changes instrumented in the immunosuppressive therapy during the long-term follow up in a cohort of patients seen at a single center from 2006 to 2020.

Materials and Methods

A retrospective analysis of a prospectively established protocol and database was conducted between May 2006 and December 2020. The study was approved by our Institutional Review Board (approval number 1477-1119).

Immunological risk, definitions, and group assignments

At the time of transplant, the induction therapy for each patient was selected according to the following criteria: ABO compatible mismatch, high panel reactive antibody titer (>30%) requiring the use of a desensitization protocol, retransplant,[19] multiorgan graft (combined or multivisceral), or B-cell-positive crossmatch at the time of the transplant (group A). The other criteria were ABO compatible match or low panel reactive antibody titer (<30%) and single-organ transplant (isolated ITx) (group B).

Immunosuppression by group

The primary immunosuppressive protocol assigned for group A was thymoglobulin (4.5-10.5 mg/kg), tacrolimus, sirolimus, and steroids.[7] Five patients in group A were highly sensitized and received intravenous immunoglobulin pre-ITx, achieving a successful desensitization. For group B, the induction was interleukin 2 (IL-2) antibody (given intravenously at 10 mg in patients <30 kg or at 20 mg in patients >30 kg and administered on post-ITx days 0 and 4), tacrolimus, mycophenolate mofetil (MMF), and steroids.

Within the first month after ITx and during the rejection episodes, the target tacrolimus level was 12 to 15 ng/mL (during years 2006-2008). Starting in 2009, the protocol was modified, with reduction of target tacrolimus levels to 10 to 12 ng/mL (during years 2009-2020) and tacrolimus levels gradually decreased to the 4- to 6-ng/mL range after the third month post-ITx and in the long term follow-up. Sirolimus target levels were initially 10 to 12 ng/mL and then reduced to 6 to 10 ng/mL at month 3 post-ITx (during years 2006-2008). From 2009 to 2020, the sirolimus target levels were reduced to 8 to 10 ng/mL for the first 3 months and to 4 to 6 ng/mL thereafter. All recipients had a prospective crossmatch done before the engraftment; ITx was not carried out in patients with positive T-cell crossmatch.[20]

Follow-up

Surveillance endoscopies and protocol biopsies were performed twice per week during the first 6 weeks post-ITx, weekly for the next 6 weeks, monthly up to the end of the first year, then 3 times per year up to year 3, and then every 6 months up to year 5 and yearly thereafter.

Immunosuppression and acute cellular rejection

All rejection episodes were identified through protocols or clinically indicated biopsies according to the accepted pathology criteria.[21,22] In case of a confirmed rejection episode, patients were treated based on the rejection severity. Patients with mild episodes received 2 intravenous boluses of methylprednisolone (20 mg/kg for pediatric patients or 1 g for adult patients), given as a single daily dose. Patients with moderate rejection were treated with similar steroid boluses followed by standard steroid tapering. Patients with severe rejection were treated with thymoglobulin as a daily 1 mg/kg dose over 7 days together with a steroid bolus on the first day and tapering, given simultaneously with sirolimus (it was either initiated or the doses were increased if the patient was already receiving it).

Variables analyzed

We analyzed the following variables: biopsy-proven ACR frequency and severity of episodes, number of ACR episodes, time from ITx to the first ACR episode, response to treatment, number of patients who progressed to chronic allograft rejection, tacrolimus target levels, creatinine levels as marker of kidney function, number of infection episodes, incidence of PTLD and graft-versus-host disease (GVHD), and patient and graft survival at 30 days and 6 months as well as at 1, 3, 5 and 10 years posttransplant. We used variables to compare risk between groups.

Statistical analyses

Variables are presented as mean ± SD. We used chi-square test and Z score to compare proportions and Kaplan-Meier with log-rank to analyze and compare survival rates. $P < .05$ was considered significant. We used SPSS version 25.0 for statistical analysis. Timelines were plotted using the "ggplot[2] package" in the R environment.

Results

Between May 2006 and December 2020, 51 ITx procedures were performed at our center. Six patients were excluded due to death or graft loss during the first week post-ITx. There were 21 patients in group A and 24 patients in group B. Patient characteristics are shown in Table 1.

Transplant description

Of 45 patients, 32 received isolated ITx, 4 patients received combined liver-intestine transplant, 1 patients received combined liver-intestine-kidney transplant, 3 patients had multivisceral transplant, 1 patient had multivisceral with kidney, and 1 patient had modified multivisceral. Three patients were retransplanted, with 1 the recipient of the multivisceral with the kidney graft and 1 the recipient of a combined liver-intestine-kidney graft.

Donor features

Intestinal transplant was performed with organs from deceased donors. Mean donor age was 5.6 ± 5.4 years for pediatric patients (<18 years) and 24.9 ± 7.7 years for adult patients (>18 years). Thirty-six ITx procedures were done with ABO compatible donors and 6 patients had ITx procedures with ABO compatible mismatched donors. Total ischemia time was 7:28 ± 2:09 hours. Warm ischemia time was 39.43 ± 11.83 minutes (39.50 ± 13.59 min in group A and 39.36 ± 10.31 min in group B; P = not significant [NS]). Forty-three donors were cytomegalovirus (CMV) IgG positive (19/21 in group A and 18/24 in group B).

Table 1. Characteristics of Intestinal Transplant Recipients

Characteristic	Group A (n = 21)	Group B (n = 24)	*P*
Mean age ± SD, y	17 ± 14	17 ± 18	
Median age, y	12	8	
Male patients, No. (%)	14 (67%)	19 (79%)	.54
Adult patients, No.	7	9	1.00
Pediatric patients, No.	14	15	
Diagnosis at evaluation, No. (%)			.74
Intestinal atresia	1 (5%)	2 (8%)	
Gardner syndrome	1 (5%)	0 (0%)	
Gastroschisis	0 (0%)	2 (8%)	
Hirschsprung disease	3 (14%)	5 (21%)	
Necrotizing enterocolitis	1 (5%)	1 (4%)	
CIPO	1 (5%)	2 (8%)	
Thrombosis	0 (0%)	0 (0%)	
Trauma	0 (0%)	2 (8%)	
Volvulus	6 (29%)	6 (25%)	
Other	1 (5%)	0 (0%)	
Ischemia	2 (10%)	1 (4%)	
Microvillus inclusions disease	1 (5%)	1 (4%)	
Postsurgical complications	0 (0%)	1 (4%)	
ACR-resistant enterectomy	3 (24%)	0 (0%)	
Cystic lymphangioma	1 (5%)	1 (4%)	
Indication for transplant, No. (%)			.84
Lack of vascular access	6 (29%)	12 (50%)	
Catheter-related sepsis	2 (10%)	3 (13%)	
IFPNALD	7 (33%)	7 (21%)	
Unresectable tumor	1 (5%)	0 (0%)	
No reconstructible GIT	1 (5%)	1 (4%)	
Hypersensitized	1 (5%)	0 (0%)	
Exfoliative ACR/enterectomy	2 (10%)	0 (0%)	
Familial adenomatous polyposis	1 (5%)	0 (0%)	
Microvillus inclusion disease	0 (0%)	1 (4%)	
Mean time on wait list ± SD, days	247 ± 251	183 ± 201	.34

Abbreviations: ACR, acute cellular rejection; CIPO, chronic intestinal pseudo-obstruction; GIT, gastrointestinal tract; IFPNALD, intestinal failure parenteral nutrition-associated liver disease

Group A had immunosuppression based on thymoglobulin, and group B had immunosuppression based on basiliximab (anti-interleukin 2 antibody).

Immunosuppression

Induction therapy was given as established in our protocol, with 21 patients in group A receiving thymoglobulin and 24 patients in group B receiving IL-2 antibody.

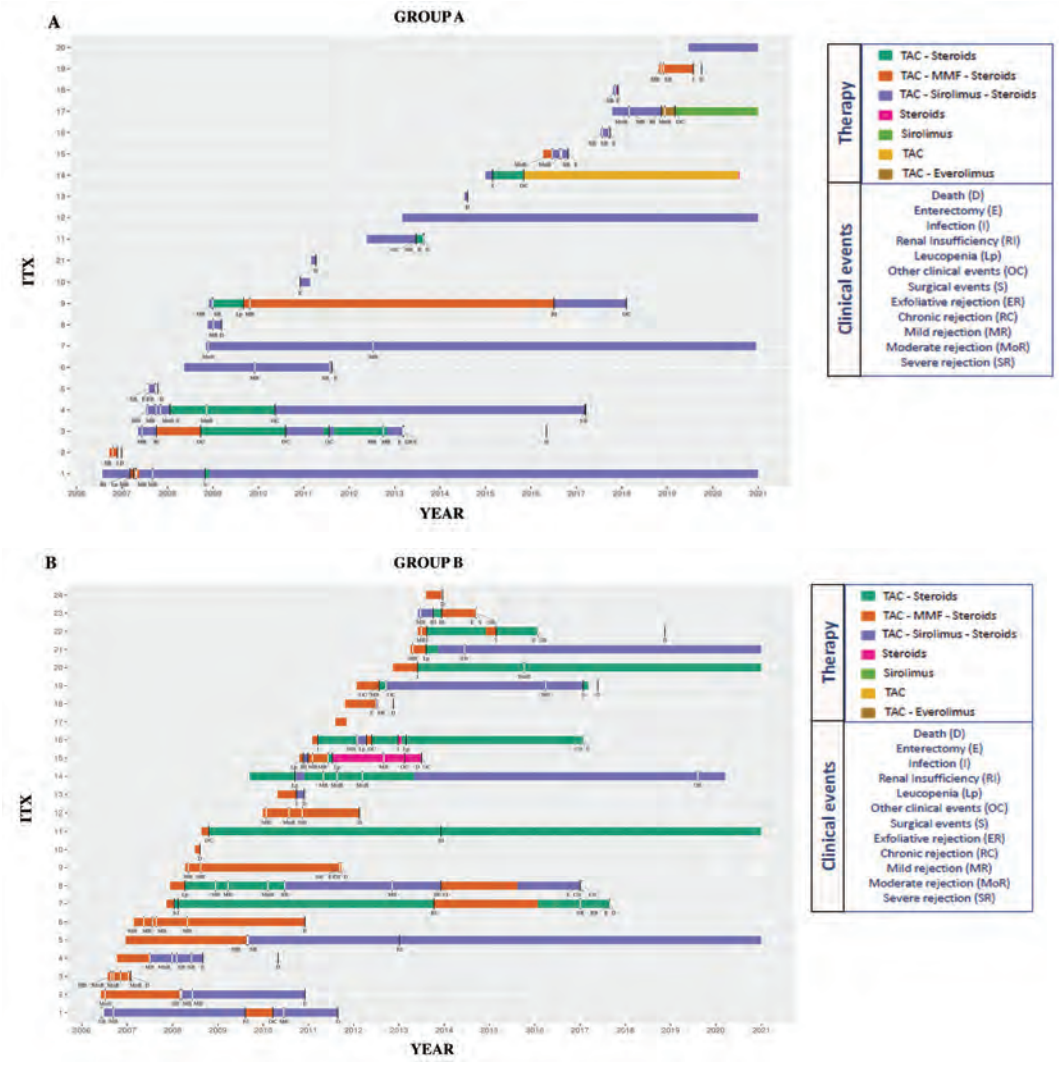
Long-term immunosuppression and adjustments due to clinical requirements are shown in Figure 1 (changes during the first 30 days were graphed as different initial therapy). In all cases, immediate post-ITx maintenance immunosuppression was started as planned by the predetermined protocol.

At day 30 post-ITx, 20/21 patients in group A continued under follow-up: 16 patients (80%) remained on sirolimus/tacrolimus/steroids, 3 patients (15%) were switched from sirolimus to MMF, and 1 patient

(5%) was switched to other therapy. At day 90 post-ITx, 11 patients (52%) remained on sirolimus/tacrolimus/steroids, 1 patient (5%) was switched to MMF, and 2 patients (10%) were left on double therapy. At the end of year 1, 11/21 group A patients continued under follow-up: 7 patients (33%) remained on sirolimus/tacrolimus/steroids, 2 patients (10%) were on MMF/tacrolimus/steroids, 1 (5%) was on double therapy, and 1 patient (5%) was switched to another drug. At the end of year 5, there were 7/21 patients in group A on follow-up: 4 (19%) were on sirolimus/tacrolimus/steroids, 1 (5%) was on MMF/tacrolimus/steroids, 1 (5%) was on double therapy, and 1 (5%) was receiving other therapy (Figure 1A).

In group B, at 30 days post-ITx, 23/24 patients were under follow-up, with 20 patients (87%) remaining on MMF/tacrolimus/steroids, 2 patients (9%) switched from MMF to sirolimus, and 1 patient (4%) left on tacrolimus/steroids. At 90 days post-ITx, 22/24 group B patients were under follow-up: 16 (66%) remained on the initial protocol, 3 (13%) were switched to sirolimus, and 3 (13%) were left on double therapy. At the end of 1 year, 17/24 group B patients were under follow-up: 6 (25%) remained on MMF/tacrolimus/steroids, 5 (21%) were on sirolimus/tacrolimus/steroids, 5 (21%) were on double therapy, and 1 (4%) was switched to other therapy. At year 5, there were 8 group B patients under follow-up: 1 (4%) remained on

Figure 1. Long-Term Immunosuppression Changes and Clinical Events During Patient Follow-Up



Abbreviations: TAC, tacrolimus

(A) Group A follow-up. **(B)** Group B follow-up. Group A had immunosup-pression based on thymoglobulin, and group B had immunosuppression based on basiliximab (anti-interleukin 2 antibody).

MMF/tacrolimus/steroids, 5 (21%) were on sirolimus/tacrolimus/steroids, and 2 (8%) were on double therapy (Figure 1B).

The main reason for changing from MMF to sirolimus was the occurrence of ACR, and the main reason for changing from sirolimus to MMF was progressive renal insufficiency. All patients were kept on tacrolimus for the entire follow-up, except for 1 patient in group A, who received only sirolimus. No differences were found in tacrolimus levels over time between group A and group B, and mean target levels were within the expected level at 30 days (15.1 ± 4.7 ng/mL), 1 year (8.6 ± 2.9 ng/mL), and 5 years posttransplant (8.0 ± 2.5 ng/mL) in all patients.

Acute cellular rejection

The total number of ACR episodes was 87 (33 patients in group A vs 54 patients in group B): 45 with mild episodes (16 in group A vs 29 in group B), 18 with moderate episodes (7 in group A vs 11 in group B), and 24 with severe episodes (10 in group A vs 14 in group B) but with no significant difference between ACR number of episodes and severity when comparing both groups (Table 2 and Figure 2A). The global mean time from ITx to the first ACR episode was 148 ± 501 days (66 ± 150 days in group A vs 219 ± 672 days in group B; *P* = NS).

During the first 30 days post-ITx, 10 patients (48%) in group A and 8 patients (33%) in group B experienced ACR, and, from day 30 to day 90, 3 patients (14%) in group A and 2 patients (8%) in group B experienced ACR. By the end of the first year, 30 of 45 patients (66%) developed new ACR episodes, with 13 (44%) in group A and 17 (56%) in group B (*P* = NS between groups and periods; Table 3). The long-term rejection-free survival rate was 38.5% in group A and 26.9% in group B (*P* = NS). Figure 2B shows the rejection-free survival at the end of the first year.

Table 2. Number of Rejection Episodes by Group

Group	No. of Rejection Episodes			
	Mild	Moderate	Severe	Total
A (n= 21)	16	7	10	33
B (n= 24)	29	11	14	54
Total	45	18	24	87

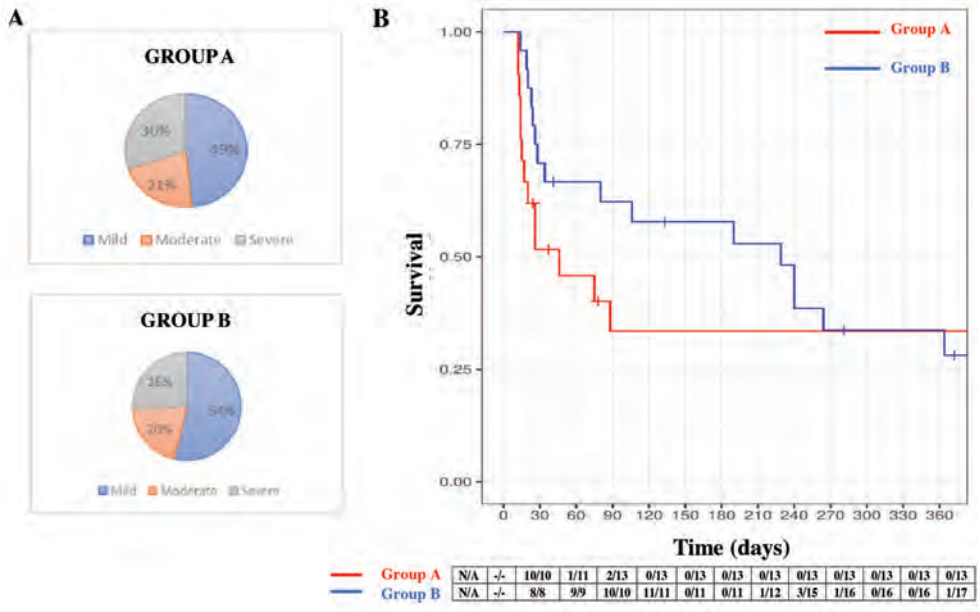
Group A had immunosuppression based on thymoglobulin, and group B had immunosuppression based on basiliximab (anti-interleukin 2 antibody).

Table 3. Time to First Acute Cellular Rejection Episode

Time to First Rejection, days	No. of Episodes		
	Total	Group A	Group B
<30	17	10	8
30-90	5	3	2
90-365	7	0	7
>365	3	2	1
No rejection >365	12	6	6

Group A had immunosuppression based on thymoglobulin, and group B had immunosuppression based on basiliximab (anti-interleukin 2 antibody).

Figure 2. Total Number, Severity of Acute Cellular Rejection, and Association With Immunosuppression Therapy



(A) Number and percentages of rejection episodes by degree and by group. **(B)** Years free of acute cellular rejection (survival) by risk group (*P* = not significant). Group A had immunosuppression based on thymoglobulin, and group B had immunosuppression based on basiliximab (anti-interleukin 2 antibody).

The total number of graft losses related to rejection episodes was 7/87 (8%) in group A and 8/87 (9%) in group B (P = NS). Two graft losses due to chronic rejection were identified in group A and 2 in group B (P = NS).

Infectious episodes

Figure 3 shows the distribution of the infections during the immediate posttransplant, induction, and maintenance periods. There were a total of 38 infectious episodes. During the first 30 days post-ITx, 5 episodes (13%) were diagnosed in group A (3 bacterial and 2 viral episodes) and 3 episodes (7%) were diagnosed in group B (2 bacterial and 1 viral episodes) (P = NS). From day 31 to the end of the first year, 6 episodes (16%) were recorded in group A (3 bacterial, 2 fungal, and 1 viral) and 5 episodes (13%) in group B (1 viral, 2 bacterial, and 2 fungal) (P = NS). During the maintenance period, 4 infectious episodes (11%) were observed in group A (3 bacterial and 1 parasitic) and 13 episodes (34%) were observed in group B (4 bacterial, 1 fungus, and 8 viral) (P = .03 between groups).

From a total of 15 viral infections (3 in group A and 12 in group B; P = .03), 13 occurred in pediatric patients and 2 occurred in adults patients. The etiologies were CMV (n = 4), Epstein-Barr virus (EBV; n = 8), coinfection of CMV and EBV (n = 2), or another virus (n = 2). After year 1 post-ITx, a diagnosis of EBV-related PTLD was shown in 8 children and in 1 adult.

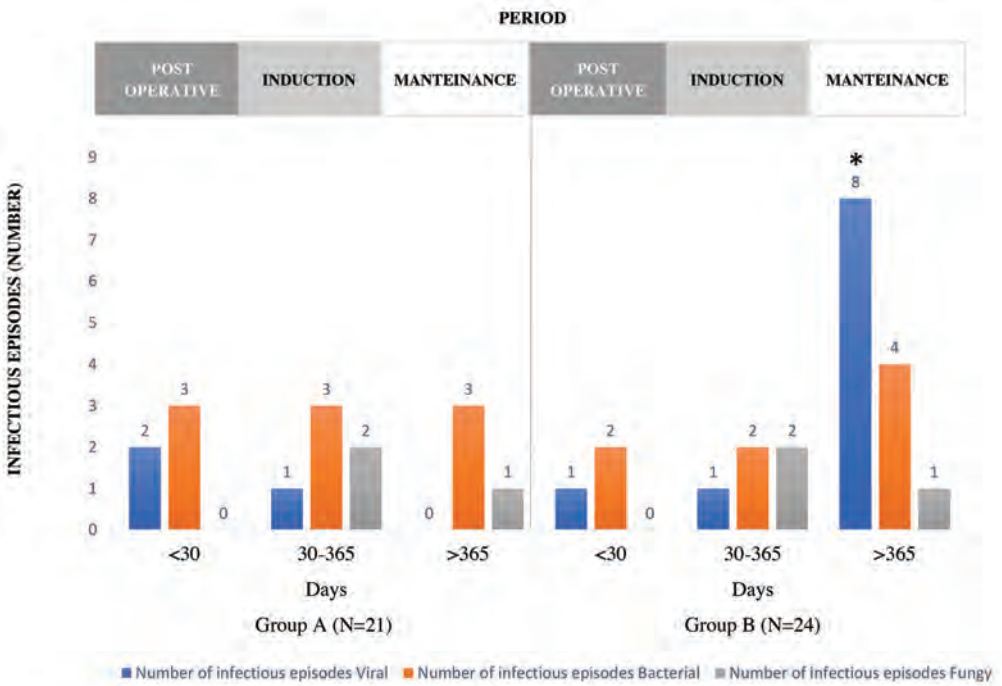
Kidney function

The mean estimated creatinine clearances for group A and group B were 147 and 130 mL/min at 30 days, 124 and 100 mL/min at 60 days, 108 and 106 mL/min at 90 days, and 107 and 90 mL/min at the end of year 1 (P = NS at each time point and by groups).

Other variables

There were 9 patients with PTLD (median day of appearance at 1525 ± 703 days), including 8 pediatric patients and 1 adult patient, with 7 patients in group B (1 adult and 6 pediatric patients) and 2 pediatric patients in group A (P = 0.1). Furthermore, 8 of 9 patients (89%) developed EBV-related PTLD. We also observed 1 patient with GVHD in group A who was a recipient of a retransplant with multivisceral graft, including a kidney and spleen.

Figure 3. Total Number of Infectious Episodes



Group **A** had immunosuppression based on thymoglobulin, and group **B** had immunosuppression based on basiliximab (anti-interleukin 2 antibody). *P = .03 viral infections group A versus group B. From 15 viral infections, 13 occurred in pediatric patients and 2 occurred in adult patients.

Mortality and long-term survival

Overall, at 30 days, 6 months, and 1, 3, 5, and 10 years posttransplant, patient survival rates were 95%, 73%, 68%, 68%, 62%, and 53%, respectively, in group A and 100%, 91%, 82%, 68%, 54%, and 37%, respectively, in group B respectively (Figure 4A). Graft survival rates at 30 days, 6 months, and 1, 3, 5, and 10 years posttransplant were 95%, 67%, 62%, 51%, 45%, and 29% in group A, respectively, and 100%, 92%, 79%, 58%, 46%, and 21%, respectively, in group B (Figure 4B). There were no significant differences in patient or graft survival between groups (P = NS).

In our patient cohort, mortality occurred in 21 of 45 patients (47%). At 180 days, 7 patients had died due to infectious episodes (5 in group A and 1 in group B) and rejections (1 in group A). At 1 year, 3 patients had died from infections (2 in group B) and GVHD (1 in group A). Seven patients died between 1 and 5 years post-ITx. The causes of death were PTLD (1 in group A and 1 in group B), infectious episodes (3 in group B), suicide (1 in group B), and unknown (1 in group B). Four deaths were related to PTLD (1 in group B), rejection (1 in group 1), and infectious diseases (1 in group A and 1 in group B).

Discussion

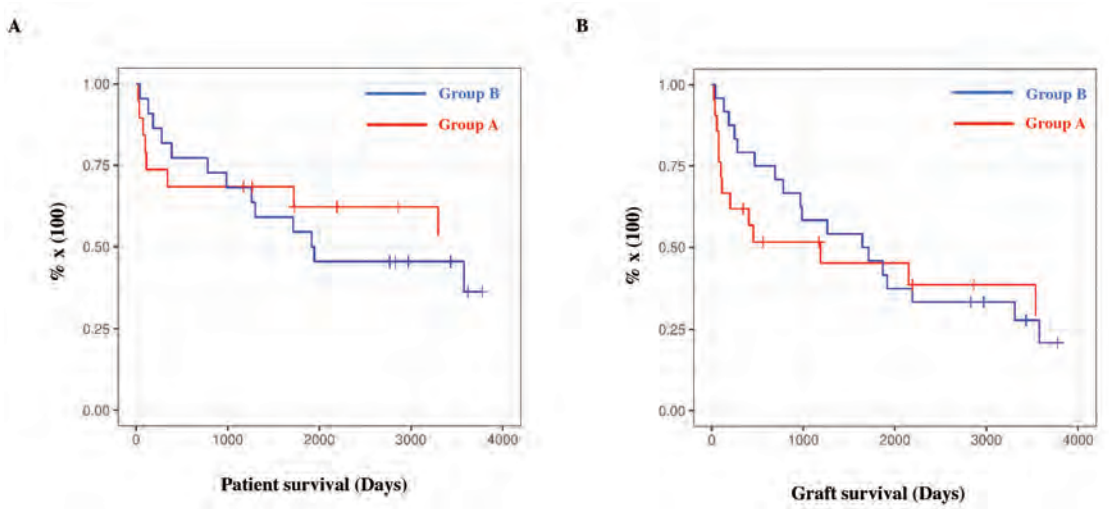
Despite improvements made in the field of ITx over the past decades, immunological management remains the major challenge and continues to be the main cause of graft loss and death.

In 2006, protocols were established with an aim for a close follow-up to evaluate the long-term results of immunosuppression. The induction therapy of each transplant candidate was defined ahead of the procedure; the protocols were designed based on the protocols used for ITx recipients, kidney transplant, and the unpublished experience at the Intestinal Transplant Program at Mount Sinai Hospital.[23-29] Under the premise that inclusion of the liver in ITx increases the receptor lymphoid cells load with a higher risk of ACR and GVHD, thymoglobulin was proposed for induction therapy[3,30,31] in multivisceral grafts. The protective effects of the liver, when transplanted along with other organs, has been proposed, mainly based on its immunoglobulin absorptive capacity, which can reduce the chances of ACR. However, a direct effect on cellular-mediated rejection has not been proven.[32-34] Results from single centers and the International ITx Registry have shown a positive effect on long-term graft survival, but not on early graft survival, supporting our hypothesis.[4,35-37]

Despite single-center reports on the use of thymoglobulin or IL-2 antibody,[6,10,38] our study represents, to our knowledge, the first and the largest prospective single-center comparison of thymoglobulin and IL-2 antibody induction in ITx recipients and to consider changes in the immunosuppressive regimen during follow-up.

In this study, we observed a higher incidence of graft and patient survival in favor of the regimen

Figure 4. Patient **(A)** and Graft **(B)** Survival



Group **A** had immunosuppression based on thymoglobulin, and group **B** had immunosuppression based on basiliximab (anti-interleukin 2 antibody).

used for group B within the first year posttransplant but also with comparable results in the long-term. The early mortality rate observed in patients receiving thymoglobulin may be related to the fact that most multiorgan recipients receive thymoglobulin, implying the inherited complications associated with this regimen as a main reason for graft and patient loss but not to rejection. Although the number of patients in our study was limited, when nonrejection-related early deaths were removed from the analysis, we observed no significant difference in the early incidence of rejection between the groups, supporting that thymoglobulin administration reduces the risk of more severe types of rejection and graft loss early posttransplant.

With regard to maintenance therapy and modifications over time, the introduction of sirolimus as a third drug resulted in a significantly lower incidence of early rejection and has improved graft survival in kidney transplant recipients.[39-41] Although equivalent results were reported in ITx, the major benefit observed was tolerability of the drug for periods longer than 1 year.[41] In our experience, 20% of the patients in group A discontinued sirolimus due to intolerance (15%), worsening renal function (5%), or other side effects (5%). These patients were switched to MMF (15%) or double therapy (5%).

If we analyze the development of infectious complications by group, group A had higher mortality associated with bacterial infections during the first year posttransplant. In the long-term, the infectious episodes then became mainly viral. The first observation might be related to the need for a more aggressive therapy in patients with higher immunological risk, and, as a consequence of the accumulative immunosuppressive effect, the second observation might be associated with a higher proportion of pediatric patients surviving the ITx procedure in the long-term once immunosuppressive doses and levels are reduced.[15]

Our study confirmed the null hypothesis that long-term results after ITx are the result of long-term individualized care, close follow-up, and personalized immunosuppressive management. When we analyzed the drugs used for maintenance, crossover between regimens could be observed and switches occurring because of clinically necessary reasons (rejection episodes, infectious complications, renal disfunction, or other clinical observations such as leukopenia, hypertension, diabetes, or diarrhea). The multiple confounders make it extremely difficult to interpret differences between groups. Therefore, the pretransplant stratification proposed is adequate to classify groups in the early after ITx period. In the long-term, clinical care can equalize immunological risks and rejection results, supporting the statement that long-term results cannot be justified as result of the elected induction therapy, as previously proposed.

Conclusions

Induction therapies chosen based on immunological risk impact early results and may have an effect on infectious outcomes[6,10]; however, the long-term outcomes are the consequence of the long-term maintenance immunosuppressive regimens, according to the clinical events that each patient has during the course after ITx.

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