Induction Immunosuppression Improves Long-Term Graft and Patient Outcome in Organ Transplantation: An Analysis of United Network for Organ Sharing Registry Data

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Background. Induction agents have been shown to reduce the rate of acute rejection. They have not been clearly shown to improve graft and patient survival.

Methods. United Network for Organ Sharing registry data were analyzed to show the status of induction therapy in the United States and to determine the effect of induction therapy on long-term graft and patient survival.

Results. Since establishment of the United Network for Organ Sharing renal transplant registry, there have been three distinct eras of induction regimen: (1) the low-induction, old antibody era, 1987 to 1993, when antilymphocyte globulin and muromonab-CD3 were the major agents; (2) a high-induction, transitional era, 1994 to 2002, when basiliximab (1998), daclizumab (1998), and rabbit antithymocyte globulin (rATG; 1999) replaced antilymphocyte globulin and muromonab-CD3, with maintenance agents also used; (3) the high-induction, modern antibody era, 2003 to present, with most patients receiving rATG, basiliximab, daclizumab, or alemtuzumab (2003). Induction recipients had higher graft and patient survival rates than nonrecipients in all categories of organ transplant. The improvement was statistically significant in kidney, liver, and lung transplants, although liver and lung recipients had a lower percentage of patients receiving induction than did kidney patients. Kidney transplant recipients on alemtuzumab with steroids had the lowest risk of graft failure, followed by those on alemtuzumab alone, rATG with steroids, rATG alone, and then basiliximab with steroids. Improvement was not statistically significant with daclizumab (alone or with steroids), basiliximab alone, or steroids alone.

Conclusion. Induction immunosuppression improved graft and patient outcome for most organ transplants. Depleting agents (alemtuzumab and rATG)—especially in combination with steroids—seem to be more efficient in preventing renal graft failure than nondepleting agents (basiliximab and daclizumab).

Keywords: Alemtuzumab, Campath-1H, Rabbit antithymocyte globulin, Thymoglobulin, Basiliximab, Simulect, Daclizumab, Zenapax, Kidney transplantation, Pancreas transplantation, Liver transplantation, Heart transplantation, Lung transplantation.

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Immunosuppressive regimens for organ transplantation can be generally characterized as induction, maintenance, or rescue therapies. Most immunosuppressive medications can fall into any or all of these categories depending on dose, route, and schedule (*1*, *2*). Induction immunosuppression is a powerful and prophylactic therapy used perioperatively to prevent episodes of acute rejection. The prevalent strategies for induction are to administer a high dose of what are otherwise maintenance drugs or to use specialized induction agents, mainly lymphocyte-specific antibodies.

Although induction agents have long been shown to reduce the rate of acute rejection (*1*, *3*), they have not hitherto been clearly shown to improve long-term graft and patient outcomes. To investigate that question, we used Kaplan-Meier methods to compare graft and patient survival rates of patients who received induction therapy with those of patients who did not receive induction therapy in five different categories of organ transplant. We also compared the efficacy in preventing renal graft failure of the most commonly used agents, including depleting agents (alemtuzumab and rabbit antithymocyte globulin [rATG]) and nondepleting agents (basiliximab and daclizumab).

RESULTS

Use of Induction Medication by Year and Era

Since the establishment of the United Network for Organ Sharing (UNOS) kidney and pancreas transplants database in

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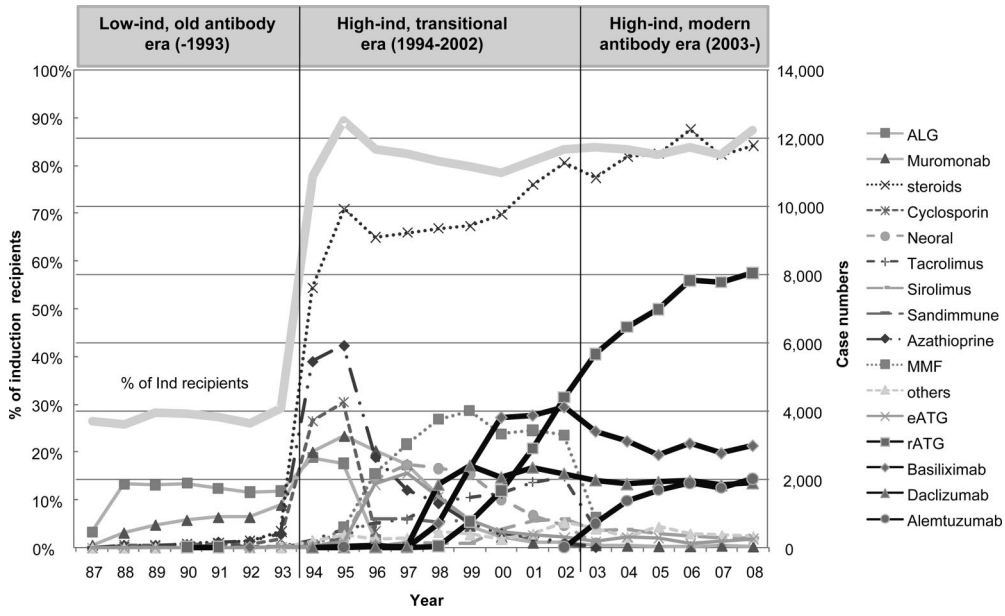


FIGURE 1. Three eras of induction therapy and the commonly used induction agents by year and era. Percentage of patients receiving induction therapy is shown as a *solid gray line* without marker. Antibodies are shown as *solid lines*, *gray* (commonly used in earlier time periods) or *black lines* (commonly used recently) with markers. Maintenance immunosuppressants are shown as *dotted lines* or *dashed lines*. ALG, antilymphocyte globulin; MMF, mycophenolate mofetil; eATG, equine antithymocyte globulin; rATG, rabbit antithymocyte globulin.

1987, more than 40 agents have been used as induction medication alone or in combination. However, only 15 of them have been used extensively (i.e., in 4000 or more patients). These are steroids (1987–2009, n=166,036), rATG (1990–2009, n=60,141), basiliximab (1992–2009, n=35,517), mycophenolate mofetil (1994–2003, n=24,511), daclizumab (1994–2009, n=24,525), azathioprine (1987–2003, n=19,817), muromonab-CD3 (1987–2009, n=19,508), antilymphocyte globulin (ALG) (1987–1996, n=16,473), neoral (1988–2003, n=12,342), tacrolimus (1987–2003, n=11,408), alemtuzumab (1995–2009, n=10,754), equine ATG (1987–2009, n=9415), cyclosporine (1987–1996, n=9205), sirolimus (1992–2009, n=5055), and sandimmune (1987–2003, n=4559). In Figure 1, percentage of patients receiving induction therapy is shown as a solid gray line without marker, maintenance immunosuppressants as lines of dots or dashes, and antibodies as solid lines, gray (commonly used earlier) or black (commonly used more recently) with markers.

Figure 1 also shows that since establishment of the UNOS registry in 1987, there have been three distinct time periods of induction regimens: (1) 1987 to 1993, the old, low-induction antibody era, when fewer than 30% of all kidney recipients received induction therapy, consisting mostly (>80%) of ALG or muromonab-CD3; (2) 1994 to 2002, the transitional, high-induction era, when approximately 80% of kidney transplant recipients received induction therapy, with both maintenance drugs and antibodies used as induction agents, and ALG and muromonab-CD3 starting to be replaced by daclizumab (1998), basiliximab (1998), and rATG (1999); and (3) 2003 to present, the modern high-induction antibody era, with induction therapy remaining high, more than 80% of all transplant patients receiving induction, mostly rATG, basiliximab, daclizumab, or alemtuzumab (2003), alone or in combination with steroids.

Induction Medication Recipients Had Higher Long-Term Graft and Patient Survival Rates Than Recipients Without Induction Therapy

In the high-induction, modern antibody era (2003–2009), UNOS received reports of 112,902 kidney, 3380 pancreas, 43,407 liver, 14,728 heart, and 9485 lung transplants. The percentages of patients in each category who received induction medication are 84% kidney, 77% pancreas, 61% liver, 72% heart, and 67% lung. As shown in Table 1, recipients of induction medication had a higher graft and patient survival rate at 3 months, 1 year, and 5 years than did patients without induction treatment in all transplants (e.g., "97–91" in the "3-month" box for "Kidney" means 97% graft survival for "Ind" recipients, 91% for "noninduction"). Induction therapy significantly improved graft or patient outcomes in both deceased and living-donor transplantation. The difference was more marked with deceased donors (data not shown). The differences in graft and patient survival rates between induction recipients and nonrecipients were statistically significant with kidney, liver, and lung transplants although liver and lung transplant recipients had a significantly lower percentage of recipients receiving induction therapy than did kidney patients.

Depleting Induction Agents Were Associated With Lower Risk of Graft Failure in Renal Transplantation Than Were Nondepleting Agents

To compare the efficacy in preventing renal graft failure of the induction agents commonly used recently (1998–2009), other influencing factors had to be weighed for

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TABLE 1. Induction therapy and graft and patient survival (2003–2009)

Variables	Organs				
	Kidney	Pancreas	Liver	Heart	Lung
No. cases	112,902	3,380	43,407	14,728	9,485
Induction recipient (%)	84	77	61	72	67
Graft survival (%) (induction vs. noninduction)					
3 mo	97–91	89–84	92–89	93–92	93–90
1 yr	93–87	79–73	85–81	88–86	83–80
5 yr	74–69	52–51	68–64	72–72	49–47
P	0.0000	0.0798	0.0000	0.1877	0.0020
Patient survival (%) (induction vs. noninduction)					
3 mo	99–95	98–97	95–92	94–92	93–91
1 yr	97–93	94–91	89–86	89–87	84–81
5 yr	86–83	80–79	73–70	74–73	52–51
P	0.0000	0.1023	0.0000	0.1665	0.0041

TABLE 2. Characteristics of patients on different induction protocols

Variables	No		Steroids		Alemtuzumab		rATG		Basiliximab		Daclizumab		
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	*P*
No. maintenance drugs	**2.48**	0.01	2.84	0.01	**2.07**	0.01	2.67	0.00	2.85	0.00	2.89	0.00	0.0000
Patient age (yr)	46.30	0.12	46.40	0.16	**49.02**	0.15	**48.25**	0.08	47.78	0.13	44.39	0.18	0.0000
Donor age (yr)	38.19	0.11	38.08	0.15	**39.62**	0.16	**39.02**	0.08	38.60	0.11	37.33	0.15	0.0000
HLA mismatches	3.36	0.01	3.23	0.02	**3.53**	0.02	**3.66**	0.01	3.34	0.01	3.40	0.02	0.0000
PRA at Tx	8.96	0.19	6.56	0.24	**14.39**	0.34	**13.73**	0.15	5.48	0.14	5.88	0.18	0.0000
Ischemic time (hr)	13.34	0.09	12.02	0.12	**15.05**	0.14	**13.74**	0.06	13.06	0.09	12.15	0.10	0.0000
Male patient (%)	61.86		61.50		59.54		58.46		**62.97**		**62.32**		0.0000
Black patient (%)	**26.55**		21.66		24.84		**27.06**		18.35		23.27		0.0000
Dialysis at Tx (%)	78.22		81.26		78.67		**82.85**		**82.42**		82.22		0.0000
Regraft (%)	11.83		7.88		**13.15**		**15.68**		7.92		7.72		0.0000
Diabetes (%)	20.38		21.27		**25.14**		21.64		**22.55**		19.33		0.0000
Donor (nonhead trauma) (%)	56.23		55.99		**63.50**		**58.60**		56.44		49.14		0.0000
Deceased donor (%)	**61.28**		55.94		57.16		**65.80**		58.16		58.83		0.0000

The two highest-risk patient groups in each variable category are indicated in bold.
HLA, human leukocyte antigen; PRA, panel reactive antibody; Tx, transplantation; SE, standard error.

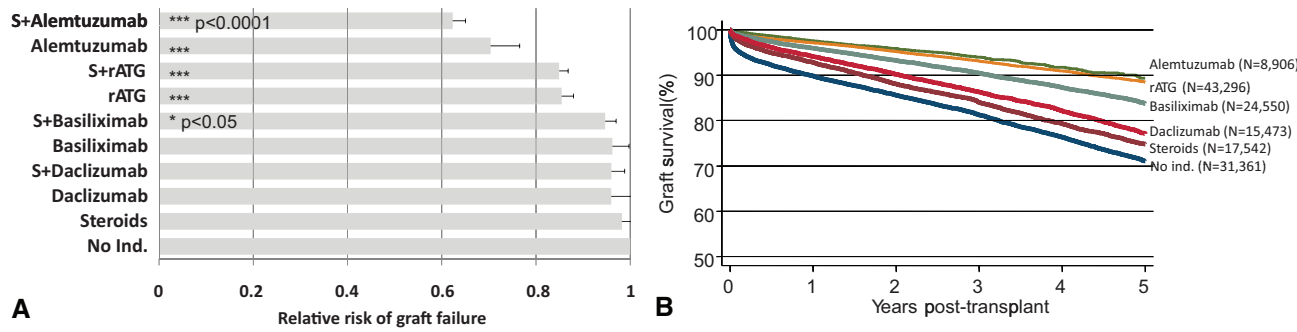


FIGURE 2. (A) Relative risks of graft failure of the most commonly used induction protocols in kidney transplantation (***$P<0.001$ and *$P<0.05$). (B) Adjusted 5-year graft survival rates of the most commonly used induction protocols in kidney transplantation. Adjustments applied to graft survival rates include numbers of maintenance immunosuppressants used, patient and donor ages, gender, race, human leukocyte antigen mismatches, panel reactive antibody level, ischemic time, dialysis status, previous transplantation, original disease, cause of donor death, and deceased or living donor. rATG, rabbit antithymocyte globulin.

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each induction agent. Table 2 lists the variables that were tested for significant association with graft loss. Clearly, clinicians gave their more high-risk patients alemtuzumab or rATG. After adjustment for all influencing variables listed in Table 2, Figure 2(A) shows that patients on alemtuzumab combined with steroids had the lowest risk of graft failure, followed by patients on alemtuzumab alone, rATG with steroids, rATG alone, then basiliximab with steroids. Improvement with daclizumab (alone or with steroids), basiliximab alone, and steroids alone was not statistically significant compared with the reference group that did not receive induction therapy. Adjusted 5-year graft survival rates of patients on alemtuzumab (89.3%, $P<0.0001$), rATG (88.5%, $P<0.0001$), and basiliximab (83.8%, $P<0.05$) were significantly higher than those of patients who did not receive induction (71.0%). Again, the improvement with daclizumab and steroids was not significant (Fig. 2B).

DISCUSSION

It is generally agreed that loss of allografts is greatest within the first 3 to 6 months posttransplant—except for the period immediately after transplantation, when it is even more pronounced. Induction immunosuppression, an intense and prophylactic therapy used perioperatively, was introduced for use in this immediate postoperative period in hopes of preventing episodes of acute rejection (*1*, *2*). Indeed, most induction medications in current clinical use do prevent acute rejection. However, it has not been clear, up to now, whether these medications also improve long-term graft survival.

The most significant finding of this study is that induction medications—independent of other predictors of graft failure—do improve graft outcome. The mechanism by which induction agents reduce risk of graft failure may involve two possibilities:

1. Induction medications prevent the episodes of acute rejection that are independent risk factors for long-term graft survival (*4–7*). The variable of treated rejection was not included in the final Cox model for this study, because too many reports of treated rejection episodes were missing from the database. At 6 months, 25% of the cases simply had no mention of rejection episodes; at 1 year, that increased to 32%. Nevertheless, it stands to reason that the ability of induction immunosuppression to prevent episodes of rejection may account for the improved graft survival documented by this study. After all, because acute or chronic graft function loss results from a progressive damage-repair-damage pathologic process, which follows the law of "quantitative change to qualitative change," any treatment effectively controlling or minimizing this pathologic process must certainly prolong graft survival (*8*).
2. Induction medications may induce allotolerance in transplant recipients. Of course, one cannot conclude that tolerance was induced in these recipients without total withdrawal of all maintenance immunosuppressants from the recipients' regimens.But an accumulation of experimental and clinical evidence does imply that tolerance may have been induced. Knechtle et al. (*9*, *10*) demonstrated in rhesus monkeys that use of T-cell-depleting anti-CD3 immunotoxin as the sole induction agent before renal transplantation led to excellent graft survival and to genuine tolerance as evidenced by the survival of subsequent skin allografts from the same donors. In another instance, Calne et al. (*11*) demonstrated that induction medication allowed patients to use lower doses of maintenance immuosuppressants or fewer of them. Our study's analysis of UNOS renal transplant data in the modern induction era (2003 to present) found that 77% of the patients who received alemtuzumab and 33% of those who received rATG also received double maintenance or monomaintenance immunosuppression at discharge, whereas 80% of basiliximab and daclizumab recipients remained on triple drug therapy. All these observations imply that induction immunosuppression may have induced tolerance in some—although not all—of the transplant recipients we studied, enabling some to be maintained on lower immunosuppression with good graft function. It may depend on the induction agent, as suggested by the triple immunosuppression required by basiliximab and daclizumab recipients. What is more, induction medications may not be equally efficient for all recipients. In a tolerance-induction mouse model that used T-cell-depleting agents, Wu et al. (*12*) demonstrated that residual nondeleted T cells may undergo substantial homeostatic expansion and show dominant resistance to tolerance.

Since 2003, rATG, basiliximab, daclizumab, and alemtuzumab have been the four major agents commonly used for transplant recipients. rATG and alemtuzumab are lymphocyte-depleting agents, whereas basiliximab and daclizumab are CD25-specific nonlymphocyte-depleting monoclonal antibodies. Even though all these agents have been shown to prevent or reduce episodes of acute rejection in transplant recipients, the role of these agents in long-term graft survival remained to be established (*13–19*). After adjustment for the variables influencing graft survival, our analysis of UNOS registry data demonstrated for the first time that patients on alemtuzumab with steroids had the lowest risk of graft failure, followed by patients on alemtuzumab alone, rATG and steroids, rATG alone, and then basiliximab and steroids. Improvement was not statistically significant with daclizumab (alone or with steroids), basiliximab alone, or steroids alone. The insignificant effect of daclizumab may explain why it faced diminishing market demand, finally resulting in its discontinuation by Roche in 2009. Our findings also suggest that lymphocyte-depleting protocols—especially in combination with steroids—seem to be more efficient in preventing graft failure than nondepleting agents, which inactivate donor-specific T lymphocytes. It is yet to be tested whether deletion of donor-specific T cells will enable lymphocyte repopulation and establishment of chimerism, educating newly developed lymphocytes to recognize the allograft as antigens of its own.

In summary, induction therapy was proved to be associated with low risk of graft failure. Depleting antibodies (alemtuzumab and rATG) were superior to nondeletional agents (basiliximab and daclizumab) in significantly reducing the risk of graft failure.

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MATERIALS AND METHODS

Patients

In the high-induction, modern antibody era (2003–2009), UNOS received reports of 112,902 kidney, 3380 pancreas, 43,407 liver, 14,728 heart, and 9485 lung transplants. The percentages of patients in each category who received induction medication are 84% kidney, 77% pancreas, 61% liver, 72% heart, and 67% lung. Graft and patient survival of induction recipients and nonrecipients in the modern antibody era were analyzed and compared. UNOS kidney registry data were used in multivariate analyses to compare the efficacy of the induction agents most commonly used between 1998 and 2009.

Induction Medications

Almost 40 medications have been used as induction agents since the establishment of the UNOS renal transplant registry in 1987. Among them, lymphocyte-specific or lymphocyte surface marker-specific polyclonal and monoclonal antibodies are the major agents used as induction medications. In addition to these, antibodies, antiinflammatory agents (steroids), and most of the commonly used maintenance immunosuppressants were also used as induction agents, especially between 1994 and 2002. Patients receiving any induction agents were included in this study and were compared with those who did not receive any induction treatment. Patients without induction therapy were treated only with maintenance immunosuppression without any enhanced therapy perioperatively. The agents most commonly used in recent years—basiliximab (1998), daclizumab (1998), rATG (1999), and alemtuzumab (2003)—were further compared in a Cox regression model to investigate their efficacy in preventing graft failure after adjustment for other factors. Because the information on immunomodulatory maneuvers such as donor-specific transfusion or irradiation was not available for most of the patients, these treatments were not included in this study.

Statistic Analyses

The difference in distribution of categorical variables between groups was investigated using the chi-square test. Unpaired *t* test or one-way analysis of variance was used for numerical variables. Death-censored graft survival rates and patient survival rates of transplant recipients, both with and without induction therapy, were estimated using Kaplan-Meier methods, with significance determined by log-rank test. To establish multivariate Cox models, the registry data were first explored using univariate analyses to screen for potential predictors of graft loss. The log-rank test was used for categorical variables, whereas univariate Cox proportional hazard regression was used for continuous variables. The final Cox model included donor and recipient age, recipient gender and race (black/non-black), recipient's original diseases (diabetes/nondiabetes), cause of donor death (head trauma/nonhead trauma), human leukocyte antigen mismatches, most recent panel reactive antibody, ischemic time, dialysis status at transplant, previous transplantation, and transplant type (deceased/living). The variable with a *P* value of less than or equal to 0.25 was included as a potential predictor of graft failure in a stepwise Cox model. Final multivariate Cox analyses, data were reported as a hazard ratio (relative risk of graft failure) with a 95% confidence interval. Two-side *P* value less than 0.05 was considered significant. All statistical analyses were performed using STATA version 10 (StataCorp LP, College Station, TX) with all available updates as of March 2010.

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