

Induction Therapy

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Transplantation is a suitable option for patients with end-stage organ failure. Many immunosuppressive agents are available, and this may pose difficulty in choosing an appropriate combination for maintenance therapy, treating episodes of acute rejection of varying severities, and tailoring therapies for specific patients.

Induction therapy strategies are accomplished either by relatively high doses of conventional immunosuppressants or by using poly- or monoclonal antibodies. These antibodies are an integral part of transplant medicine today. The rationale for antibody therapy aims at augmenting immunosuppression, ensuring that delayed introduction of calcineurin inhibitors is safe, encouraging steroid withdrawal, and facilitating treatment of patients sensitized to human leukocyte antigens in addition to its crucial role in immunologic conditioning either by tolerance induction or alternatively minimizing the immunosuppressive drugs.

Different trends in induction therapy initially consisted of anti-thymocyte globulin, then anti-CD3 Orthoclone, and finally anti-CD20, 25, and 52 agents. Induction therapy is associated with beneficial short- and long-term outcomes when increased risk of adverse effects related to immune system suppression are an issue, especially from cytomegalovirus and lymphomas.

Key words: *Immunosuppression, Induction therapy, Transplantation*

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Background

With the emergence of antibodies either as prophylaxis for rejection (induction therapy) or as treatment for acute rejection, transplantation has moved from an era of nonselective antiproliferative treatment to an era of selective T-cell depression [1]. During the last 9 years, a 3-fold increase in induction therapy has occurred. Currently, more than 50% of graft recipients receive induction therapy [2].

Rationale

Strategies for induction therapy include utilizing either relatively high dosages of conventional immunosuppressive agents or using monoclonal or polyclonal antibodies. Induction therapy seeks to reduce the risk of acute rejection and decrease maintenance immunosuppressive regimens in addition to its ultimate goal of benefiting high-risk populations, particularly pediatrics, African-Americans, and recipients having human leukocyte antigen mismatches or those sensitized to these antigens [3].

First and foremost, induction therapy augments immunosuppression. Second, it facilitates delayed introduction of calcineurin inhibitors safely. And third, it is useful in induction of "immunologic conditioning" either by inducing tolerance or alternatively minimizing the need for immunosuppressive drugs [3].

Variations on the Theme

The antibodies currently used in transplantation practice are either anti-thymocyte globulins, anti-CD3 (Orthoclone), or anti-CD25. However, newer agents including anti-CD52, anti-CD20, and CTLA4Ig are in use in special situations. Moreover, antibodies on the horizon (eg, efalizumab, 33B3.1, anti-Tac, Lo Tac1, and BT563) are encouraging [4]. The mechanisms of action of antibodies can be categorized into 3 levels: depletion of lymphocytes including anti-thymocyte globulin, anti-CD20, and anti-CD52;

altered signal and lymphocyte trafficking (ie, anti-CD3, LFA1, and CD154 B7); and mechanisms that affect inhibition of growth factor binding (ie, anti-CD25) [5]. Following is a brief review of each antibody.

Anti-Thymocyte Globulin

Before the introduction of cyclosporine, controlled studies evaluated conventional therapy (ie, steroid, azathioprine) with and without a 14- to 21-day course of anti-thymocyte globulin (ATG). The trials reported a delayed onset of acute rejection and a subsequent reduced need for high steroid dosages in the early postoperative period [5]. Later, sequential ATG studies highlighted the advantages of preventing acute rejection and delayed introduction of cyclosporine [6].

A retrospective study [7] evaluating the different long-term toxicities of ATG induction concluded that thymoglobulin seems to be associated with a significantly greater incidence of cytomegalovirus (CMV) disease (37% vs 23%), malignancy (12.3% vs 3.9%), and death (13.8% vs 3.9%) in comparison with ATG Fresenius. On the other hand, Hardinger and colleagues [8] demonstrated that thymoglobulin is associated with higher rates of event-free survival, graft survival, and freedom from rejection without increased incidences of posttransplant lymphoproliferative disease (PTLD) or CMV disease at 5 years compared with ATGAM. However, Uslu and colleagues [9] have assessed the risks and benefits of 2-day induction with thymoglobulin and have demonstrated acceptable acute rejection rates among renal transplant recipients. This is despite adverse reactions, particularly those from atypical bacterial and fungal infections.

The safety and efficacy of intraoperative bolus ATG Fresenius have been evaluated [10] and show 100% and 97.5% patient and graft survival rates respectively at 6 months. Similarly, Goggins and colleagues [11] have reported that intraoperative thymoglobulin administration in adult cadaveric renal transplant recipients is associated with a significant decrease in delayed graft function in the first month after transplant and a decreased post-transplant hospital stay.

After a course of therapy, ATG antibodies can be detected in many patients. Anaphylactic reactions and serum sickness have been diagnosed infrequently. The adverse reactions vary according to the preparations used [5]. Chills and febrile reaction

appear with the first infusion and decrease markedly with subsequent infusions. Thrombocytopenia is frequent and is dose related; less frequently seen are erythema and local phlebitis.

Anti CD3, Orthoclone, OKT3

The dramatic success of OKT3 in treating already established rejection has prompted prophylactic trials designed to prevent rejection. OKT3 was the first monoclonal antibody used to prevent allograft rejection. It is a murine antibody directed against a molecular subunit linked to the T-cell antigen receptor [12]. The immunosuppressive effect of OKT3 depends upon both T-cell depletion and antigenic modulation of the CD3 complex [13].

A retrospective comparison of outcomes was performed between OKT3 and basiliximab [14]. At 6 months, patient and graft survival rates were similar. The rejection-free recipients represented 42% in the basiliximab group and 25% in the OKT3 group (*P*, NS). Mean calculated creatinine clearance was better among patients in the basiliximab group (79.4 ± 11.9 vs 54.5 ± 15.9 mL/min), with higher rates of major opportunistic infection (50% vs 9%). Similarly, Kode and colleagues [15] have reported shorter hospital stays and lower numbers of readmissions, CMV infections, and episodes of biopsy-proven acute rejections. OKT3 administration is simpler and less expensive but has more adverse effects, especially after the first infusion.

Although several studies have demonstrated the efficacy of OKT3, its widespread clinical use has been hampered by several serious adverse effects including a cytokine-release syndrome with fever, chills, hypertension, and pulmonary edema; development of antibodies; thrombocytopenia; neutropenia; higher incidence of infectious complications; and malignancies [12]. A collaborative transplant study reported an increased risk of lymphomas during the first year after transplantation among patients who had received induction therapy by ATG or OKT3 [16].

Moreover, Cherikh and colleagues calculated the incidence of posttransplant lymphoproliferative disorders, which reached 0.85% in recipients with monoclonal antibody induction, 0.81% in recipients with polyclonal antibody induction, 0.5% in recipients with anti-interleukin 2 receptor antibodies, and 0.51% in recipients without induction [17].

Several humanized mutagenized anti-CD3 moAbs hu OKT3D γ_1 , aglycosol CD3, and Hu M291

have been used in limited trials in renal transplantation, but clearly there is a need for formal clinical development.

Anti-Interleukin 2 Receptor Antibodies

Anti-interleukin 2 receptor (IL2R) blockade provides more-specific immunosuppression because IL2R is expressed only by activated lymphocytes. Monoclonal antibodies directed against IL2R are considered a component of initial immunosuppressive therapy. Two antibody preparations, basiliximab (chimeric human/mouse) and daclizumab (humanized) are evaluated [18].

a) Basiliximab is given in a 2-dose regimen of 20 mg on the day of transplantation and day 4 postoperatively. Its efficacy has been evaluated in a double-blind multicenter trial [19] confirming a lower incidence of acute rejection with excellent tolerability as demonstrated by a complete absence of cytokine release syndrome as well as a comparable rate of infections without increased risk of malignancy in comparison with placebo. Basiliximab is cost-effective in comparison with thymoglobulin as evidenced by a significant reduction in initial hospital stay, duration, and number of infectious episodes [20].

In renal transplant recipients, when basiliximab was combined with standard dual or triple immunotherapy, the incidences of death, graft loss, and acute rejection were significantly reduced at 3 years [21]. Also, it widens the therapeutic window for area under the curve (AUC) monitored cyclosporine therapy early after kidney transplantation. Balbontin and colleagues [22] found the incidence of acute rejection to be 39% in patients in a control group versus only 8% in patients in a basiliximab group with cyclosporine AUC 0-4 < 4400 microgram Xh/L; these acute rejection rates became 15% versus 9% respectively with AUC 0-4 > 4400 microgram Xh/L.

Finally, use of basiliximab entails very low risk, allows safe reduction of steroid dosage, and reduces short- and mid-term rejection rates. However, improvements in the long-term survival of renal allograft recipients treated with modern immunosuppressive protocols remain to be demonstrated [23].

b) Daclizumab: Two double-blind multicenter studies have evaluated the efficacy of daclizumab (5-dose regimen of 1 mg/kg body weight) demonstrating a reduced incidence of biopsy-proven acute

rejection rates from 43.3% to 27.7% at 1 year post-transplantation. In both studies, patients received cyclosporine and steroids, while azathioprine was added in the US trial [24].

Both daclizumab and basiliximab were evaluated in high-risk patients (including high panel reactive antibody > 50%, retransplantation, marginal donors, spouse donors, and > 4 HLA mismatches) compared with patients in a low-risk group [25]. The authors concluded that anti-IL2 R in immunologically high-risk patients results in the same rate and severity of acute rejection, and graft and patient survival, when compared with patients at normal immunologic risk.

Ter Meulen and coworkers [26] have shown that the calculated fractional excretion of soluble IL2R alpha is an excellent predictor of the blockade of IL2R alpha with a specificity of 100% and a sensitivity of 75% if the calculated fractional of IL2R alpha is lower than 0.5%. Moreover, they noticed lower mean arterial blood pressures, serum lipid levels, and hyperglycemia in patients in the daclizumab group compared with controls. Two doses of daclizumab (1 mg/kg at transplantation and after 14 days) in conjunction with low-dose cyclosporine, mycophenolate mofetil, and steroids resulted in a low incidence of acute rejection after renal transplantation with 1-year patient and graft survival rates of 98% and 95% respectively as well as excellent graft function [27].

Sundberg and colleagues [28] utilized daclizumab as bridge therapy, providing safe and effective immunosuppressive coverage while converting renal transplant recipients from calcineurin inhibitors to sirolimus-based maintenance immunosuppressive therapy. Moreover, induction with daclizumab for African-American and Hispanic renal transplant recipients treated with tacrolimus and mycophenolate mofetil for their first graft appeared to be safe and effective in helping to minimize biopsy-proven acute rejection episodes and optimize renal allograft survival [29].

To the best of our knowledge, there have been no controlled studies comparing basiliximab and daclizumab, nor have different dose regimens been directly studied in renal transplantation.

Rituximab

Rituximab is a murine/human chimeric monoclonal antibody directed against human CD20. Vieira and colleagues [30] have hypothesized that

rituximab may reduce panel-reactive antibodies via B-cell depletion. Sawada and coworkers [31] have adopted a protocol enabling kidney transplantation to be performed in an ABO-incompatible couple with an anti-donor blood type antibody titre above 1:16. This protocol consisted of weekly infusions of rituximab (375 mg/m²) for 3-4 weeks, splenectomy 1 or 2 weeks before transplantation, and 4-5 sessions of double filtration plasma exchange after splenectomy. This protocol resulted in successful transplantation without serious adverse effects in all patients with well-functioning grafts after a mean follow-up of 390 days. On the other hand, Tyden and coworkers [32] concluded that after a single infusion of both rituximab and intravenous immunoglobulin and antigen-specific immunoadsorption, blood-group-incompatible renal transplantation can be performed with standard immunosuppression without splenectomy.

Rituximab is of great value in overcoming positive cross-matching in living-donor renal transplantation. Gloor and coworkers [33] have suggested that selected cross-match-positive patients may be transplanted successfully with living-donor kidney allografts using a protocol of plasmapheresis, intravenous immunoglobulin, rituximab, and splenectomy. Longer follow-up is required, but the absence of anti-donor antibodies and good early outcomes are encouraging.

Campath-1H

Campath-1H is a humanized CD52-specific monoclonal antibody that produces profound T-cell depletion in humans and reduces the need for maintenance immunosuppression after renal transplantation.

Seven nonsensitized recipients of living donor kidney were treated by Campath-1H preoperatively and followed without maintenance immunosuppressive agents [34]. All patients developed reversible rejection episodes within the first month after transplantation. These episodes were responsive to steroids or sirolimus or both. The patients remained rejection-free on reduced immunosuppression regimens after that.

To reduce initial and long-term calcineurin inhibitor use with total elimination of steroids, Campath-1H was tried first in cadaveric and then in non-HLA identical living-donor renal transplantations [35]. Early assessment has shown that the combination of Campath-1H, low-dose tacrolimus,

and mycophenolate mofetil seems to be safe and effective for kidney transplant recipients, but longer term follow-up is recommended.

A pilot study of Campath-1H and sirolimus monotherapy conducted in 29 patients followed up for 29 months resulted in an acute rejection rate of 28%. The sirolimus levels were not significantly different in patients with and without rejection [36]. Furthermore, Cai and coworkers utilized this protocol and reported that 42% of patients developed HLA antibodies. Serum levels of these antibodies were correlated with the serum creatinine levels [37].

Campath-1H has been used in renal allograft patients maintained on half the standard dose of cyclosporine monotherapy. An acceptable outcome of equal efficacy has been reported after 2 years' follow-up among 29 patients when compared with conventional triple therapy [38].

Campath-1H is well tolerated in renal transplant patients and leads to a significant reduction in the incidence of rejection. Moreover, recipients with delayed graft function experience marked improvement in graft survival [39].

Other Monoclonal Antibodies

a) Efalizumab: Efalizumab is a non-lymphocyte-depleting, humanized IgG antibody against the CD11a chain of the leucocyte function-associated antigen. It blocks binding of the leucocyte function-associated antigen, ICAM, thereby blocking T-cell adhesion, trafficking, and activation [40]. Combination with either cyclosporine, mycophenolate mofetil and steroids, or low-dose cyclosporine, sirolimus, and steroids has resulted in a 10.4% incidence of acute rejection at 6 months. However, efalizumab is associated with development of posttransplant lymphoproliferative disease, especially at higher doses (> 2 mg/kg/week) [41].

b) 33 B 3.1: 33 B 3.1 targets the α chain of the IL2 receptor. A randomized trial was conducted that proved its equivalence to ATG among kidney transplant recipients. Forty percent of patients developed anti-33B 3.1 IgG and IgM antibodies by days 12 and 17. Increased infectious complications were observed among recipients treated with 33B 3.1 [42].

c) Anti-Tac: Anti-Tac targets the α chain of IL2R. A randomized trial comparing the efficacy and safety with cyclosporine triple therapy reported a significant reduction in early acute rejection with no difference in graft survival or infectious complica-

tions. Seventy percent of patients developed anti-mouse antibodies by day 30 [43].

d) LO-Tac1: A randomized study has revealed similar efficacy with ALG and reduced infectious episodes. IgG or IgM antibodies developed before 14 days [44].

e) BT 563: BT 563 was utilized in a randomized double-blind placebo-controlled study that reported a significant reduction in early acute rejection. Sixty percent of patients developed antibodies at 30 days [44].

f) Anti CD40 - CD154: The first attempt at blockade of CD40 - CD154 with anti CD154 MoAb was disappointing. Excellent results with anti CD45 receptor blockade MoAb have been published in experimental transplantation [45].

CTLA4 Ig

CTLA4 Ig is a fusion protein that binds B7-1 and B7-2 with greater affinity than does CD28 and therefore, acts as a potent competitive inhibitor of CD28-mediated T-cell activation. It augments allograft survival when combined with cyclosporine, sirolimus, and donor-specific bone marrow, alone or in conjunction with antilymphocyte serum.

A corollary of the tolerogenic effect of CD28-B7 blockade is that CTLA4-Ig can prevent and possibly interrupt the development of chronic rejection. It is ineffective in suppressing a primed T-cell-dependent immune response. Differential efficacy in renal and cadaveric rodent allograft models has been shown. Also, CTLA4 Ig inhibits Th1, cytokines, and spares Th2 in vivo. But questions remain. Is it appropriate for low-risk patients and primary renal allograft recipients? Is it worth using in high-risk, retransplanted, or highly sensitized individuals, or those having poor HLA matching? A second-generation of CTLA4Ig is LEA29Y, a fusion receptor protein, representing a new class of agents that blocks the second signal required for T-cell activation. It has a greater avidity to CD80 and CD86 than does CD28, leading to abrogation of T-cell responses [40].

Special Situations

Living Donors

Controversies concerning the impact of induction therapy among living donor renal transplantation have not ended. Crompton and colleagues reported a lack of economic benefit using basiliximab

induction in adult living-related renal transplant recipients. No significant differences were found regarding the incidence of acute rejection; renal function at 1, 3, 6, or 12 months; or frequency of infectious complications among recipients of living-donor renal transplantation with and without induction [46].

Wiland and coworkers compared the results of kidney transplantation from living-unrelated donors (LURT) without induction versus cadaveric donors (CRT) with induction. Higher acute rejection rates were observed after 6 and 12 months among LURT recipients in comparison with CRT recipients. Moreover, a 3-fold greater risk of rejection was noted among the LURT recipients. This highlights the importance of induction for LURT recipients [47].

Many researchers have addressed the usefulness of induction therapy among living donor kidney transplantation recipients. An Indian study suggested that basiliximab significantly reduced the incidence of acute rejection episodes [48]. Bunnapradist and Takemoto proved that anti-IL-2R antibody therapy was associated with lower graft failure at 1 year and reduced both hazards ratios and risk of rejection by 13% and 13% respectively in living donor allografts [49]. Two other studies concluded better results in terms of patient survival (100%, 97.6%) and graft survival (100%, 93.2%) for patients receiving living donor kidneys after induction therapy [50,51].

Acceptable graft survival rates in ABO-incompatible living donor kidney transplantation can be achieved with plasmapheresis, splenectomy, and thymoglobulin induction [52]. In addition, in laparoscopic donor nephrectomy with longer warm ischemia times, basiliximab induction with sirolimus and prednisolone regimen allowed delayed use of cyclosporine with excellent 1-year graft survival rates [53].

Pediatrics

Induction therapy is of pivotal importance among children to minimize the risks of both steroids and calcineurin inhibitors to achieve better growth and fewer adverse effects. A dose of anti-CD25 was modulated for children to be 10 mg basiliximab for those weighing less than 35 kg to be given at transplantation and day 4 postoperative, causing saturation of IL2R for 3 weeks only, while the daclizumab protocol was 1 mg/kg every 2 weeks for 5 doses,

leading to 12 weeks' saturation of IL2R [54].

Acott and colleagues [55] have confirmed the safety of basiliximab in pediatric renal transplantation for children at low risk for HHV-6 or EBV infection in the first 1 to 2 months after transplantation. Induction with basiliximab for pediatric transplant recipients maintained on steroids, cyclosporine, and azathioprine resulted in a reduction of acute rejection at 6 months and CMV disease in CMV-positive recipients, with better graft survival and function in long-term follow-up for 76% of cases [56].

A study using daclizumab induction demonstrated a 0.8% incidence of clinical acute rejection with significant improvement in graft function, hypertension, and growth among pediatric transplants [57]. Induction in pediatrics is well tolerated without significant adverse effects and a higher glomerular filtration rate at 1 year; nevertheless, longer term follow-up is recommended [58].

Clinical Practice Considerations

A dramatic shift in the type of induction therapy was achieved in the last decade. Antibodies have been incorporated into daily transplant medicine. The type of transplant strongly influences the use of antibody induction. While the optimal regimen has not been defined, the availability of numerous agents allows individualization of the regimens. Before advising induction therapy, the following concerns must be raised:

Induction Versus Noninduction

Comparing induction versus noninduction in a prospective randomized study in simultaneous kidney-pancreas transplants revealed similar patient outcomes and significantly better kidney allograft survival rates at 3 years [59].

Anti-CD25 antibody induction therapy is associated with a 17% reduced risk of graft loss and a 21% reduced mortality rate when compared with no induction therapy [17].

The increasing number of highly sensitized patients awaiting renal transplantation has prompted the use of induction therapy [60].

Induction therapy facilitates delayed introduction of tacrolimus and results in a reduction in the incidence of delayed graft function in machine-perfused non-heart-beating donor kidney transplantation [61].

Acute Rejection and Outcome

Each acute rejection episode has a negative impact on long-term allograft survival and presents a major risk factor for late graft failure [48]. Rejections that occurred within the first 6 months had a more pronounced effect on subsequent graft half lives (11.6 years without and 7.6 year with rejection, $P = 0.01$) and increased the proportion of kidneys that failed because of chronic rejection from 31% to 43% between 1 and 3 years [62]. Moreover, in living donor transplantations, the incidence of chronic rejection was 0.8% among rejection-free recipients, and 20% and 43% in those who experienced acute rejection before and after 60 days of transplantation respectively. The corresponding figures for cadaveric donor transplantation were 0%, 36%, and 63% [3]. The advent of new induction regimens offers more opportunities to prolong graft life [63].

Selection of Induction Therapy

Thymoglobulin has been used frequently in sensitized and retransplant recipients and in those with delayed graft function. Vella and Nylan [3] reported that antilymphocytic globulin induction conferred an improvement in clinical outcome in blacks though not whites. Pan T-cell antibodies did not improve graft survival in any cohort [64].

While Jirasiritham and coworkers [25] highlighted that anti-CD25 antibodies became the dominant induction therapy for immunologic high-risk patients resulting in the same graft- and patient-survival acute rejection rates as well as severity of rejection, as recipients with normal immunologic risk. This induction therapy was associated with the smallest risk of posttransplant lymphoproliferative disorders and the best rates of graft and patient survival [17]. Heifets and coworkers [65] proved that recipients older than 60 years benefit from induction with basiliximab followed by steroid-free maintenance immunosuppression as evidenced by reduced rates of both acute rejection and delayed graft function.

On the other hand, Chapman and coworkers [66] demonstrated that daclizumab was used more often in pediatric recipients and those receiving mycophenolate mofetil, as well as in nonimmunologic risk patients (eg, those with diabetes, obesity, or kidneys from suboptimal donors).

Tailoring Combination Therapy

A regimen of daclizumab with low-dose tacrolimus,

mycophenolate mofetil, and steroids is effective in lowering delayed graft function, especially in transplantations from non-heart-beating donors [67], enabling early discontinuation of steroids and providing better 1-year graft survival rates when compared with normal-dose tacrolimus regimens without induction [68].

A strategy of combining sirolimus and basiliximab for low immunologic risk recipients and thymoglobulin for high-risk patients led to prompt recovery of renal function [69]. Basiliximab plus cyclosporine-based double or triple therapy was associated with lower morbidity and mortality rates [70]. Meanwhile, a combination of ATG and tacrolimus had a significantly lower rejection rate when compared with ATG and cyclosporine or tacrolimus triple therapy [71]. Lastly, a cost-effectiveness analysis of outcomes in older patients showed a clear benefit in using a calcineurin-sparing protocol with basiliximab induction [72].

Conclusions

While much data have accumulated with regard to some of the older induction agents, research on the newer agents is, as yet, in its infancy. Despite the relatively short-term follow-ups of these studies and minimal supportive data for effective maintenance immunosuppression, steroid-free lymphocyte depletion may offer an exciting new treatment paradigm. Future research, however, may introduce new classes of biological induction agents that may displace some of the currently utilized drugs.

References

- Hong JC, Kahan BD. The history of immunosuppression. In: Sayegh MH, Remuzzi G, eds. *Current and Future Immunosuppressive Therapies Following Transplantation*. Netherlands, Kluwer Academic Publisher; 2001, pp 3-17
- Bunnapradist S, Daswani A, Takemoto SK. Patterns of administration of antibody induction therapy and their associated outcomes. *Clin Transpl* 2002;: 351-358
- Vella J, Neylan J. Why do we need induction therapy? In: Sayegh MH, Remuzzi G, eds. *Current and Future Immunosuppressive Therapies Following Transplantation*. Netherlands, Kluwer Academic Publisher; 2001, pp 187-204
- Xu H, Tadaki DK, Elster EA, Burkly LC, Berning JD, Cruzata F, et al. Humanized anti-CD154 antibody therapy for the treatment of allograft rejection in nonhuman primates. *Transplantation* 2002; 74: 940-943
- Abrahamian GA, Cosimi AB. Antilymphocyte globulin and monoclonal antibodies. In: Morris PJ, ed. *Kidney Transplantation Principles and Practice*, 5th ed. Philadelphia, WB Saunders; 2003, pp 289-309
- Mourad G, Rostaing L, Legendre C, Garrigue V, Thervet E, Durand D. Sequential protocols using basiliximab versus antithymocyte globulin in renal transplant patients receiving mycophenolate mofetil and steroids. *Transplantation* 2004; 78: 584-590
- Ducloux D, Kazory A, Challier B, Coutet J, Bresson-Vautrin C, Motte G, et al. Long-term toxicity of antithymocyte globulin induction may vary with choice of agent: a single-center retrospective study. *Transplantation* 2004; 77: 1029-1033
- Hardinger KL, Schnitzler MA, Miller B, Lowell JA, Shenoy S, Kock MJ, et al. Five-year follow up of thymoglobulin versus ATGAM induction in adult renal transplantation. *Transplantation* 2004; 78: 136-141
- Uslu A, Nart A, Coker I, Kose S, Aykas A, Kahya MC, et al. Two-day induction with thymoglobulin in kidney transplantation: risks and benefits. *Transplant Proc* 2004; 36: 76-79
- Abou-Jaoude MM, Almawi WY. Intraoperative anti-thymocyte globulin-Fresenius (ATG-F) administration as induction immunosuppressive therapy in kidney transplantation. *Mol Immunol* 2003; 39: 1089-1094
- Goggins WC, Pascual MA, Powelson JA, Magee C, Tolkoff-Rubin N, Farrell ML, et al. A prospective, randomized, clinical trial of intraoperative versus postoperative thymoglobulin in adult cadaveric renal transplant recipients. *Transplantation* 2003; 76: 798-802
- Kuyper DR, Vanrenterghem YF. Monoclonal antibodies in renal transplantation: old and new. *Nephrol Dial Transplant* 2004; 19: 297-300
- Galante NZ, Camara NO, Kallas EG, Salomao R, Pacheco-Silva A. Modulation of peripheral blood T-lymphocytes in kidney transplant recipients treated with low dose OKT3 therapy. *Immunol Lett* 2004; 91: 75-77
- Chow FY, Polkinghorne K, Saunderson A, Kerr PG, Atkins RC, Chadban SJ. Historical controlled trial of OKT3 versus basiliximab induction therapy in simultaneous pancreas-renal transplantation. *Nephrology (Carlton)* 2003; 8: 212-216
- Kode R, Fa K, Chowdhury S, Ranganna K, Fyfe B, Stabler S, et al. Basiliximab plus low-dose cyclosporine vs. OKT3 for induction immunosuppression following renal transplantation. *Clin Transplant* 2003; 17: 369-376
- Opelz G, Dohler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. *Am J Transplant* 2004; 4(2): 222-230
- Cherikh WS, Kauffman HM, McBride MA, Maghirang J, Swinnen LJ, Hanto DW. Association of the type of induction immunosuppression with posttransplant lymphoproliferative disorder, graft survival, and patient survival after primary kidney transplantation. *Transplantation* 2003; 76(9): 1289-1293
- Shield CF 3rd, Kahana L, Pirsch J, Vergne-Marini P, First MR, Schroeder TJ, et al. Use of indomethacin to minimize the adverse reactions associated with orthoclone OKT3 treatment of kidney allograft rejection. *Transplantation* 1992; 54: 164-166
- Kahan BD, Rajagopalan PR, Hall M. Reduction of the occurrence of acute cellular rejection among renal allograft recipients treated with basiliximab, a chimeric anti-interleukin-2-receptor monoclonal antibody. United States Simulect Renal Study Group. *Transplantation* 1999; 67: 276-284
- Lilliu H, Brun-Strang C, Le Pen C, Buchler M, Al-Najjar A, Priol G, et al. Cost-minimization study comparing Simulect vs. Thymoglobulin in renal transplant induction. *Clin Transplant* 2004; 18: 247-253
- Chapman TM, Keating GM. Basiliximab: a review of its use as induction therapy in renal transplantation. *Drugs* 2003; 63: 2803-2835
- Balbontin F, Kiberd B, Singh D, Squires J, Fraser A, Belitsky P, Lawen J. Basiliximab widens the therapeutic window for AUC-monitored Neoral therapy early after kidney transplantation. *Transplant Proc* 2003; 35: 2409-2411
- Boggi U, Danesi R, Vistoli F, Del Chiaro M, Signori S, Marchetti P, et al. A benefit-risk assessment of basiliximab in renal transplantation. *Drug Saf* 2004; 27: 91-106
- Nashan B, Light S, Hardie IR, Lin A, Johnson JR. Reduction of acute renal allograft rejection by daclizumab. Daclizumab Double Therapy Study Group. *Transplantation* 1999; 67: 110-115
- Jirasiritham S, Sumethkul V, Mavichak V, Lertsithichai P,

- Jirasiritham S. The role of anti-IL-2 receptor in high-risk kidney transplant patients. *Transplant Proc* 2004; 36: 2110-2112
26. ter Meulen CG, Jacobs CW, Wetzels JF, Klasen IS, Hilbrands LB, Hoitsma AJ. The fractional excretion of soluble interleukin-2 receptor-alpha is an excellent predictor of the interleukin-2 receptor-alpha status after treatment with daclizumab. *Transplantation* 2004; 77: 281-286
 27. Ekberg H, Persson NH, Kallen R, Gul-Baykurt N. Two doses of daclizumab in conjunction with low-dose cyclosporine, mycophenolate mofetil and steroids resulted in a low incidence of acute rejection after renal transplantation. *Scand J Immunol* 2003; 58: 670-677
 28. Sundberg AK, Rohr MS, Hartmann EL, Adams PL, Stratta RJ. Conversion to sirolimus-based maintenance immunosuppression using daclizumab bridge therapy in renal transplant recipients. *Clin Transplant* 2004; 18(suppl 12): 61-66
 29. Ciancio G, Burke GW, Suzart K, Mattiazzi A, Vaidya A, Roth D, et al. The use of daclizumab, tacrolimus and mycophenolate mofetil in African American and Hispanic first renal transplant recipients. *Am J Transplant* 2003; 3: 1010-1016
 30. Vieira CA, Agarwal A, Book BK, Sidner RA, Bearden CM, Gebel HM, et al. Rituximab for reduction of anti-HLA antibodies in patients awaiting renal transplantation: 1. Safety, pharmacodynamics, and pharmacokinetics. *Transplantation* 2004; 77: 542-548
 31. Sawada T, Fuchinoue S, Kawase T, Kubota K, Teraoka S. Preconditioning regimen consisting of anti-CD20 monoclonal antibody infusions, splenectomy and DFPP-enabled non-responders to undergo ABO-incompatible kidney transplantation. *Clin Transplant* 2004; 18: 254-260
 32. Tyden G, Kumlien G, Fehrman I. Successful ABO-incompatible kidney transplantations without splenectomy using antigen-specific immunoadsorption and rituximab. *Transplantation* 2003; 76: 730-731
 33. Gloor JM, DeGoey SR, Pineda AA, Moore SB, Prieto M, Nyberg SL, et al. Overcoming a positive crossmatch in living-donor kidney transplantation. *Am J Transplant* 2003; 3: 1017-1023
 34. Kirk AD, Hale DA, Mannon RB, Kleiner DE, Hoffmann SC, Kampen RL, et al. Results from a human renal allograft tolerance trial evaluating the humanized CD52-specific monoclonal antibody alemtuzumab (CAMPATH-1H). *Transplantation* 2003; 76: 120-129
 35. Ciancio G, Burke CW, Gaynor JJ, Mattiazzi A, Roohipour R, Carreno MR, et al. The use of Campath-1H as induction therapy in renal transplantation: preliminary results. *Transplantation* 2004; 78: 426-433
 36. Knechtle SJ, Pirsch JD, H Fechner J Jr, Becker BN, Friedl A, Colvin RB, et al. Campath-1H induction plus rapamycin monotherapy for renal transplantation: results of a pilot study. *Am J Transplant* 2003; 3: 722-730
 37. Cai J, Terasaki PI, Bloom DD, Torrealba JR, Friedl A, Sollinger HW, Knechtle SJ. Correlation between human leucocyte antigen antibody production and serum creatinine in patients receiving sirolimus monotherapy after Campath-1H induction. *Transplantation* 2004; 78: 919-924
 38. Calne R, Moffat SD, Friend PJ, Jamieson NV, Bradley JA, Hale G, et al. Prope tolerance with induction using Campath 1H and low-dose cyclosporin monotherapy in 31 cadaveric renal allograft recipients. *Nippon Geka Gakkai Zasshi* 2000; 101: 301-306
 39. Knechtle SJ, Fernandez LA, Pirsch JD, Becker BN, Chin LT, Becker YT, et al. Campath-1H in renal transplantation: The University of Wisconsin experience. *Surgery* 2004; 136: 754-760
 40. Vincenti F. Chronic induction. What's new in the pipeline? *Contrib Nephrol* 2005; 146: 22-29
 41. Salmela K, Wrammer R, Ekberg H, Hauser I, Bentdal O, Lins LE, et al. A randomized multicenter trial of the anti-ICAM-1 monoclonal antibody (enlimomab) for the prevention of acute rejection and delayed onset of graft function in cadaveric renal transplantation: a report of the European Anti-ICAM-1 Renal Study Group. *Transplantation* 1999; 67: 729-736
 42. Souillou JP, Cantarovich O, Le Mauff B, Giral M, Robillard N, Hourmant M, et al. Randomized controlled trial of a monoclonal antibody against the interleukin-2 receptor (33B3.1) as compared with rabbit antithymocyte globulin for prophylaxis against rejection of renal allografts. *N Engl J Med* 1990; 322: 1175-1182.
 43. Kirkman RL, Shapiro ME, Carpenter CB, McKay DB, Milford EL, Ramos EL, et al. A randomized prospective trial of anti-Tac monoclonal antibody in human renal transplantation. *Transplantation* 1991; 51: 107-113.
 44. Vincenti F. Monoclonal antibody targeting of IL-2R complex. In: Sayegh MH, Remuzzi G, eds. *Current and Future Immunosuppressive Therapies Following Transplantation*. Netherlands, Kluwer Academic Publisher; 2001, p 235-248.
 45. Vincenti F. New monoclonal antibodies in renal transplantation. *Minerva Urol Nefrol* 2003; 55 (1): 57-66
 46. Crompton JA, Somerville T, Smith L, Corbett J, Nelson E, Holman J, Shihab FS. Lack of economic benefit with basiliximab induction in living related donor adult renal transplant recipients. *Pharmacotherapy* 2003; 23: 443-450
 47. Wiland AM, Fink JC, Weir MR, Philosophe B, Blahut S, Weir MR Jr, et al. Should living-unrelated renal transplant recipients receive antibody induction? Results of a clinical experience trial. *Transplantation* 2004; 77: 422-425
 48. Siwach V, Dhanda R, Aggarwal B, Singh B, Jain PK, Sarin PK. Early experience with simulect (basiliximab) induction in living donor renal allografting in India. *Transplant Proc* 2003; 35(1): 196-197
 49. Bunnapradist S, Takemoto SK. Multivariate analyses of antibody induction therapies. *Clin Transpl* 2003; 405-417
 50. Veroux P, Veroux M, Puliatti C, Macarone M, Cappello D, Caglia P, et al. Living kidney transplantation: a starting experience. *Transplant Proc* 2004; 36(3): 475-478
 51. Kizilisik AT, Ray JM, Nylander WA, Langone AJ, Helderman JH, Shaffer D. Living donor kidney transplantation in a Veterans Administration medical center. *Am J Surg* 2004; 188(5): 611-613
 52. Gloor JM, Lager DJ, Moore SB, Pineda AA, Fidler ME, Larson TS, et al. ABO-incompatible kidney transplantation using both A2 and non-A2 living donors. *Transplantation* 2003; 75(7): 971-977
 53. Langer RM, Hong DM, Katz SM, Van Buren CT. Basiliximab-sirolimus-prednisone induction regimen followed by delayed low dose cyclosporine in renal transplant recipients of living donors. *Transplant Proc* 2002; 34: 3162-3164
 54. Swiatecka-Urban A. Anti-interleukin-2 receptor antibodies for the prevention of rejection in pediatric renal transplant patients: current status. *Paediatr Drugs* 2003; 5: 699-716
 55. Acott PD, Crocker JF, Lee S. Simulect and HHV-6 in pediatric renal transplantation. *Transplant Proc* 2004; 36: 4835-4865
 56. Clark G, Walsh G, Deshpande P, Koffman G. Improved efficacy of basiliximab over antilymphocyte globulin induction therapy in paediatric renal transplantation. *Nephrol Dial Transplant* 2002; 17, 1304-1309
 57. Vidhun JR, Sarwal MM. Corticosteroid avoidance in pediatric renal transplantation: can it be achieved? *Paediatr Drugs* 2004; 6(5): 273-287
 58. Duzova A, Buyan N, Bakkaloglu M, Dalgic A, Soylemezoglu O, Besbas N, Bakkaloglu A. Triple immunosuppression with or without basiliximab in pediatric renal transplantation: acute rejection rates at one year. *Transplant Proc* 2003; 35: 2878-2880
 59. Burke GW 3rd, Kaufman DB, Millis JM, Gaber AO, Johnson CP, Sutherland DE, et al. Prospective, randomized trial of the effect of antibody induction in simultaneous pancreas and kidney transplantation: three-year results. *Transplantation* 2004; 77(8): 1269-1275
 60. Gallay BJ, Perez RV, Ramsamooj R. Acute renal transplant injury and interaction between antithymocyte globulin and pooled human immunoglobulin. *Clin Transplant* 2004; 18: 327-331
 61. Wilson CH, Brook NR, Gok MA, Gupta AJ, Nicholson ML, Talbot D. Prospective randomised trial of the use of Daclizumab in renal transplantation using kidneys from non heart beating donors. *Ann Transplant* 2004; 9(2): 29-30
 62. Cecka JM. The UNOS Scientific Renal Transplant Registry. *Clin Transpl* 1999; 1-21
 63. Lucan M, Iacob G, Lucan C, Lapusan C, Munteanu A, Sirbu S. Ten years of cyclosporine use in renal transplantation: a single-center experience with 479 renal transplants. *Transplant Proc* 2004;

- 36(2 suppl): 177S-180S.
64. Bunnapradist S, Daswani A, Takemoto SK. Patterns of administration of antibody induction therapy and their associated outcomes. *Clin Transpl* 2002;: 351-358
 65. Heifets M, Saeed MI, Parikh MH, Sierka D, Kumar MS. Induction immunosuppression in kidney transplant recipients older than 60 years of age: Safety and efficacy of ATGAM, OKT3 and Simulect. *Drugs Aging* 2004; 21: 747-756
 66. Chapman TM, Keating GM. Basiliximab: a review of its use as induction therapy in renal transplantation. *Drugs* 2003; 63(24): 2803-2835
 67. Sanchez-Fructuoso AI, Prats D, Marques M, Ridao N, Conesa J, Garcia Mena M, et al. Daclizumab induction as an immunosuppressive regimen for renal transplant recipients from non-heart-beating donors. *Transplant Proc* 2003; 35(5): 1689-1690
 68. Kuypers DR, Evenepoel P, Maes B, Coosemans W, Pirenne J, Vanrenterghem Y. The use of an anti-CD25 monoclonal antibody and mycophenolate mofetil enables the use of a low-dose tacrolimus and early withdrawal of steroids in renal transplant recipients. *Clin Transplant* 2003; 17(3): 234-241
 69. Knight RJ, Kerman RH, Schoenberg L, Podder H, Van Buren CT, Katz S, Kahan BD. The selective use of basiliximab versus thymoglobulin in combination with sirolimus for cadaveric renal transplant recipients at low risk versus high risk for delayed graft function. *Transplantation* 2004; 78(6): 904-910
 70. Choy BY, Chan TM, Li FK, Lui SL, Lo WK, Yip T, et al. IL2-receptor antagonist (basiliximab) induction therapy is associated with lower morbidity and mortality in renal transplant recipients. *Transplant Proc* 2003; 35(1): 195
 71. Charpentier B, Rostaing L, Berthouix F, Lang P, Civati G, Touraine JL, et al. A three-arm study comparing immediate tacrolimus therapy with antithymocyte globulin induction therapy followed by tacrolimus or cyclosporine A in adult renal transplant recipients. *Transplantation* 2003; 75(6): 844-851
 72. Emparan C, Wolters H, Laukötter M, Dame C, Senninger N. Cost-effectiveness analysis of basiliximab induction and calcineurin-sparing protocols in "old to old" programs using Markov models. *Transplant Proc* 2003; 35(4): 1324-1325