Antibody immunosuppressive therapy in solid-organ transplant

Part I

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Currently, a wide variety of both polyclonal and monoclonal antibodies are being routinely utilized to prevent and treat solid organ rejection. More commonly, these agents are also administered in order to delay introduction of calcineurin inhibitors, especially in patients with already compromised renal function. While these antibody therapies dramatically reduced the incidence of acute rejection episodes and improved both short and long-term graft survival, they are also associated with an increased incidence of opportunistic infections and neoplastic complications. Therefore, effective patient management must necessarily balance these risks against the potential benefits of the therapy.

Introduction

Organ transplantation is a life saving procedure in patients with end-organ disease. While improvement in surgical techniques made transplantation possible in the 1960s,1 successful organ transplantation was not achieved until the discovery of immunosuppressive agents (ISAs) to prevent organ rejection, in particular azathioprine and then cyclosporine A (CsA) in the late 1970s.2

In the 1980s and 1990s, a large array of new immunosuppressant drugs increased the armamentarium of anti-rejection medications, providing excellent short and long-term graft and patient survivals (Table 1). Unfortunately, the first decade of the new millennium has been disappointing for transplant therapeutics—many agents have undergone or are undergoing clinical trials but none have received approval for clinical use. All immunosuppressant medications demonstrate substantial drug interactions and toxicities. Immunosuppressive protocols must be balanced to not only minimize graft rejection, but also avoid unwanted complications.

A commonly accepted protocol for immunosuppressive therapy includes:

(A) Induction Phase: during this phase a higher immunosuppressive load is given in the early stages of transplant, frequently including an induction-antibody therapy combined with a calcineurin inhibitor (CNI) drug, usually CsA or tacrolimus (FK 506). Both of these medications are considered to be cornerstones of immunosuppressive therapy. In addition to CNIs, a combination of corticosteroids and an antiproliferative agent such as mycophenolate mofetil (MMF) or azathioprine are also given.

(B) Maintenance Phase: this phase is based primarily on the use of CNIs alone if tolerated. Addition of MMF, azathioprine or sirolimus, a mammalian-target-of-rapamycin (mTOR) inhibitor, will primarily depend on the type of allograft and other inherent side effect profiles of ISAs.

(C) Anti-rejection Phase: during this phase, the graft suffers dysfunction due to immunological damage by the host. Prompt recognition and aggressive treatment are necessary to prolong graft function and survival.

This review will provide an overview of the currently available and promising ISAs, with a focus on antibodies used in solid organ transplantation. In the first part of this two-part review, we discuss those polyclonal and monoclonal antibodies that have been used for prevention and treatment of acute rejection, specifically in kidney, liver, lung and heart transplant patients.

Immune Response to Solid-Organ Allograft

The transplanted graft contains numerous antigens that are recognized as foreign by the host’s immune system. This graft-host interaction results in an allo-immune response (Fig. 1) that can be described by three phases: (1) Induction: this phase involves antigen recognition, T cell and B cell activation, differentiation and expansion; (2) Effector: during this phase direct allograft injury occurs; and (3) Resolution: during this phase the immune response to the allograft diminishes. Unfortunately, emergence of residual memory to donor antigens will occur. These anti-donor memory cells constitute a major obstacle to organ transplantation.

T cell immune responses are the prime target of most immunosuppressive drugs. T cell activation requires the delivery of distinct signals through several pathways including: the calcium-calcineurin pathway, the RAS-mitogen-activated protein (MAP) kinase pathway, and the nuclear factor-κB pathway. These pathways trigger the expression of many new molecules such as cluster designation (CD) 154, interleukin-2 (IL-2), IL-15, CD25 and...
other cytokines. IL-2 activates the mTOR pathway to provide the trigger for proliferation. The goal of all ISA therapies is to disrupt the host immune response against the allograft, primarily to inhibit allograft rejection, promote long-term allograft acceptance and minimize side effects.

**Polyclonal Antibodies**

The first polyclonal antibodies were produced by injecting human lymphocytes into a horse, creating antilymphocyte serum (ALS). Since the immunoglobulin portion was responsible for the immunomodulatory effect, animal serum was further purified to isolate immune gamma globulin (IgG). This process produced new agents: Minnesota antilymphocyte globulin (MALG) and antithymocyte globulin (ATG) were both derived from horse sera. Due to a lack of the United States Food and Drug Administration (US-FDA) approval for use in humans, in spite of experimental use for over 22 years, MALG production ceased in 1994. A rabbit-derived antithymocyte globulin (RATG) product, previously produced and used by individual transplant centers as an investigational immunosuppressant, was approved in the U.S. in 1999 under the name Thymoglobulin (Genzyme, Cambridge, MA).

### Table 1. Polyclonal and monoclonal antibodies—sources and mechanisms of action

| Non-proprietary name | Trade name | Type       | Origin | Target                                      |
|----------------------|------------|------------|--------|---------------------------------------------|
| Antithymocyte Globulin | ATGAM      | Polyclonal | horse  | anti-CD2, CD3, CD4, CD8, CD11a, CD18, CD25, CD44, CD45, HLA-DR1 |
| Antithymocyte Globulin | Thymoglobulin | Polyclonal | rabbit |                                             |
| Muromonab-CD3\(^\d\) | OKT 3      | Monoclonal | mouse  | anti-CD3                                    |
| Basiliximab          | Simulect   | Monoclonal | recombinant, chimeric | anti-CD25 |
| Daclizumab\(^\d\)   | Zenapax    | Monoclonal | recombinant, humanized | anti-CD25 |
| Alemtuzumab          | Campath    | Monoclonal | recombinant, humanized | anti-CD52 |

\(^\d\)Withdrawn from global market in 2009; \(^\d\)withdrawn from US market in 2009.

**Figure 1.** The anti-allograft response.
in days (2–3 days for RATG, 1.5 to 12 days for ATG), RATG has an ability to cause persistent lymphopenia that extends beyond the drug's presence in the body, likely explaining its sustained immunosuppression. While neither agent holds the US-FDA approval for induction of immunosuppression in transplant patients, both agents have been used for this purpose, as well as the FDA-approved indications of treatment of acute cellular rejection.

Polyclonal antibodies—kidney transplants. By depleting T lymphocytes, induction therapy reduces the risk of early rejection and therefore improves long-term outcomes. In 1979, Wechter et al. initially noted that fourteen daily doses of ATG (along with azathioprine and corticosteroids) provided sufficient immunosuppression by delaying early acute rejection.

Approved earlier in Europe in 1984, RATG was not available in the U.S. until 1998. In a double blind study, Brennan et al. compared RATG and ATG in renal transplant recipients for induction. Patients were randomized to receive daily induction doses of 1.5 mg/kg of RATG (n = 48) or 15 mg/kg of ATG (n = 24) for at least 7 days. All patients received maintenance therapy with corticosteroids, an antiproliferative agent (azathioprine or MMF) and CsA (tacrolimus was permitted in patients who did not tolerate CsA). At 6 and 12 months, acute rejection rates were significantly lower among patients receiving RATG (RATG vs. ATG: 4% vs. 17%, p = 0.038 and 4% vs. 25%, p = 0.014, respectively). RATG-treated patients experienced more cytomegalovirus (CMV) infection episodes. According to United Network for Organ Sharing (UNOS) data, in the last decade more transplant centers have been administering RATG as an induction agent (Fig. 2). In spite of these advances, renal transplant patients still experience acute rejection episodes, which negatively affect long-term allograft function. Corticosteroids, antibody therapy, intensification of maintenance immunosuppression, or a combination of these are utilized in the treatment of rejection episodes. One meta-analysis found that antibody therapy (polyclonal and monoclonal) is more successful in treating a first rejection episode, as well as in preventing graft loss.

Polyclonal antibodies—other solid organ transplants. Since liver allograft does not provoke the same kind of immune response as the kidney, induction is infrequently utilized in liver transplantation. According to UNOS data, in 2007, over 74% of liver transplants were performed without induction therapy. RATG was reportedly the most common induction agent and was primarily used to delay introduction of CNIs in patients with preexisting renal dysfunction. Early renal dysfunction has been linked to chronic kidney failure, which increases morbidity and mortality in liver transplant patients. Bajjoka and colleagues utilized daily RATG dosing in patients with preexisting kidney dysfunction to delay CNI introduction. Tacrolimus was initiated when serum creatinine fell below 1.3 mg/dL or after a maximum of five doses of RATG was given. These patients were compared to eighty patients initiated on tacrolimus therapy within 48 hours post-transplant, while both groups received three months of steroids and MMF. Although graft and patient survival were not different between the groups after twelve months, the RATG group did have a higher glomerular filtration rate (GFR). Moreover, 16% of patients in the RATG group who were dialysis-dependent prior to transplant had recovered renal function.

According to 2007 UNOS data, 53.9% of heart transplant patients received induction therapy, with RATG being the most commonly used agent (19.2%). Universal induction therapy has been shown to reduce rejection rates, but also predispose patients to a higher incidence of infectious complications and malignancies. In an attempt to identify patients who would benefit from...
induction therapy, Higgins et al. retrospectively reviewed outcomes of 5,897 heart transplant patients. Induction therapy was associated with survival benefits only in patients with the highest risk for rejection:

- black patients younger than 25 with 4 or more HLA mismatches.
- black patients younger than 40 with 4 or more HLA mismatches and dependency on a ventricular assist device (VAD) for more than 6 months.
- non-black patients younger than 35 with 4 or more HLA mismatches who have been VAD supported for more than 6 months.

Importantly, patients considered at a lower risk of rejection and received induction therapy, were found to have worse survival as a result of infectious and neoplastic complications.14

Lung transplant patients also benefit from induction therapy. In a 1999 prospective study, RATG was found to reduce rejection episodes when added to a triple immunosuppression regimen without affecting rates of bronchiolitis obliterans syndrome (BOS).15 Data supports that lung transplant patients receiving induction therapy have better graft survival compared to patients receiving no induction. A retrospective analysis of 3,970 lung transplant patients found that patients receiving induction with IL-2 receptor antagonist (IL-2RA) or RATG had better outcomes than patients without induction. This study also noted that IL-2RA induction yielded better graft survival in both single and double lung transplants, while RATG only showed benefits in patients receiving double lung transplant.16

Although just as efficacious as induction agents and anti-rejection drugs, safety profiles for RATG and ATG do cause concern with respect to short- and long-term outcomes. These agents are associated with a first-dose infusion reaction that generally causes fever, chills and rashes.17,18 Myelosuppression, thrombocytopenia and leukopenia are also observed with repeated doses but generally subside after lowering doses or discontinuing treatment.16,17 Although rare, serum sickness manifesting as high fever with arthralgia has been described in patients receiving both ATG and RATG.

Transplant patients receiving immunosuppression therapy were reported to have a higher incidence of opportunistic infections (viral, fungal and parasitic),19 polymavirus associated nephropathy (kidney transplant),20 recurrent hepatitis C virus (liver transplant)21 and malignancies. In renal transplant recipients, skin cancer and posttransplant lymphoproliferative disorder (PTLD) were found to be the most common malignancies.22 Bustami and colleagues analyzed the relationship between antibody therapy and malignancies in over 41,000 cadaveric renal allograft recipients and reported that induction therapy, regardless of the agent, increases PTLD incidence as well as de novo solid tumors. Furthermore, RATG therapy by itself increases the relative risk of PTLD (RR = 3.0) and de novo solid tumors (RR = 1.53) when compared to no induction.23

Monoclonal Antibodies

A series of monoclonal mAbs have been developed to prevent transplant rejection. The mechanisms of these mAbs are diverse, but all target specific CD proteins on the T or B cell surface. These include mAbs against CD3, CD25 and CD52.

Anti-CD3 mAbs. Orthoclone OKT3 (also known as Muromonab-CD3) is a murine IgG2a antibody that was first introduced in the setting of renal transplant induction therapy in the early 1980s, when it was shown to effectively treat acute allograft rejection.24,25 Its popularity continued to grow when it was unequivocally shown to significantly decrease the percentage of acute rejections of cadaveric transplants as compared to conventional high-dose steroid therapy.26 However, because of its numerous side-effects, better-tolerated alternatives and declining usage, OKT3 was recently removed from the market.

OKT3’s mechanism of action relies on specific interaction with the epsilon chain of the CD3 protein in association with the T cell receptor complex. This binding event transiently activates circulating T cells, resulting in the release of cytokines such as tumor necrosis factor, interferon gamma, and IL-2, IL-3, IL-6.27-28 Following this, opsonized T cells are unable to proliferate or differentiate and subsequently disappear from circulation through massive lysis.29

Although OKT3 experienced considerable success in reversing acute rejection episodes for a variety of solid organ transplants, especially in high-risk rejection patients,30 comparative studies with next-generation therapies generally provided alternatives with better empirical outcomes and reduced side-effects. In kidney transplants, OKT3 was most notably outperformed by ATG treatment, which demonstrated roughly equivalent short-term graft outcomes (89% ATG versus 81% OKT3 1-year graft survival rates) with fewer side-effects.31,32 More recently, a long-term associational study showed that patients treated with ATG had mean graft survival rates that were more than twice as long as those of OKT3-treated patients (9.5 versus 4.6 years, respectively).33 In heart transplants, a variety of anti-CD25 antibodies (murine, chimeric and humanized) have demonstrated equivalent cardiac allograft survival outcomes but without cytokine release-associated symptoms.34,35

Since the late 1980s, OKT3 administration in liver transplantation was largely confined to steroid-resistant acute rejections, with a long-term graft survival rate of approximately 50%.36-38 Its usage was specifically contraindicated in hepatitis C virus (HCV) infected patients because OKT3 treatment was associated with worse outcomes.39-41 Finally, in comparative OKT3 studies in lung transplant patients, RATG produced fewer side-effects, a lower incidence of BOS, and superior 5-year survival outcomes (52% RATG versus 34% OKT3).42,43 Additionally, both daclizumab and RATG have been shown to reduce drug-related side effects and infectious episodes, delay rejection and promote survival more effectively than OKT3.44

Despite OKT3’s early clinical success, its adverse effects proved to be consistently problematic. The first dose of OKT3 could cause short-term physiologic changes resembling a systemic
inflammatory response (secondary to cytokine release syndrome). This could manifest as high fever, hypotension, chills, nausea, vomiting, diarrhea, dyspnea and even pulmonary edema. More rarely, OKT3 treatment led to aseptic meningitis or intra- 
graft thrombosis. Separately, because OKT3 is a mouse monoclonal antibody, patients typically developed anti-idiotype and more importantly, anti-murine antibodies on the order of days, thus limiting its usefulness beyond a single round of treatment. A number of humanized OKT3 Fc variants have been developed to avoid this issue of antigenicity, but cytokine release syndrome remains a complication. Other adverse events described were probably due to excessive immunosuppression. These included increased rates of PTLD, fungal infections and CMV infections.

Anti-CD25 mAbs. The numerous complications of anti-CD3 treatments for acute allograft rejection incentivized the development of alternative means of immunosuppression. Activated T cells produce large amounts of IL-2, a major T cell growth factor. Two main antibodies—basiliximab and daclizumab—have been developed that selectively interact with the alpha subunit of the IL-2 receptor (CD25), thus competitively inhibiting IL-2 binding and subsequently preventing T cell expansion. In addition, both of these mAbs have been genetically modified by replacing murine amino acids with human sequences in order to prevent the induction of anti-idiotype and anti-murine antibodies. This has eliminated problems associated with antigenicity and short half-lives typical of murine mAbs.

Daclizumab—kidney transplants. Daclizumab, a humanized IgG1 mAb, was first introduced in 1998 when Vicenti et al. demonstrated its safety and efficacy in renal transplant patients in a prospective, placebo-controlled trial. Phase 3 clinical trial showed that daclizumab, compared to placebo on a background of triple therapy (CsA, azathioprine, corticosteroids) or double therapy (CsA, corticosteroids), had fewer biopsy-proven acute rejection (BPAR) episodes at a 1-year time point (43% vs. 28%, respectively). In addition, both of these mAbs have been genetically modified by replacing murine amino acids with human sequences in order to prevent the induction of anti-idiotype and anti-murine antibodies. This has eliminated problems associated with antigenicity and short half-lives typical of murine mAbs.

Daclizumab—other solid organ transplants. In addition to renal applications, daclizumab has been used in liver, heart, and to a lesser extent, lung transplants. In liver transplant patients, a two-dose regimen of daclizumab was shown to have immunosuppressive effects similar to that seen in renal transplant patients. Subsequently, adding daclizumab to conventional tacrolimus plus MMF therapy was shown to reduce acute rejection episodes in several studies. More recently, several studies have shown that corticosteroids can safely be eliminated from daclizumab double therapy regimes (usually MMF and tacrolimus) while preserving outcomes. In heart transplant patients, five-dose daclizumab induction was shown, in a small pilot study, to significantly reduce the frequency of acute rejection episodes compared to conventional immunosuppression (18% vs. 63%, respectively). This result was validated in a 434-subject study by Hershberger et al. (rejection rate of 41.3% standard immunosuppression vs. 25.5% daclizumab regimen). Two-dose daclizumab therapy has been shown to be at least as effective as conventional five-dose in heart transplant patients. Finally, in lung transplant patients, two controlled studies have shown that daclizumab slightly outperforms RATG therapy (one-year survival 96% vs. 88%, respectively). Although daclizumab has been widely used for more than a decade, it was discontinued in the US in September 2009 due to the availability of more popular alternatives and decreasing demand.

Basiliximab—kidney transplants. Nashan et al. published results of a randomized prospective trial with basiliximab induction (a 20 mg dose on day 0 and 4 post-transplant) compared to placebo on a double therapy background (CsA and steroids) in 1997. The 6-month incidence of BPAR was lower in the basiliximab group (29.8% basiliximab vs. 44% placebo), as was the incidence of antibody-requiring steroid-resistant first rejection episodes (10% vs. 23.1%). Additionally, there was no evidence of cytokine release syndrome, nor was there any significant difference in rates of infection or PTLD. This result was independently verified in other phase 3 trials at a number of other institutes, with both deceased donor and living donor transplants as well as in the setting of triple therapy (CsA, azathioprine and prednisone; 6-month acute rejection rate 20.8% basiliximab vs. 34.9% placebo). In pediatric transplant patients, early evidence argued that basiliximab with triple therapy drastically improved GFR (98 mL/min basiliximab vs. 75 mL/min placebo) and reduced BPAR (7.1% vs. 26.1%). However, Offner et al.
subsequently showed a non-significant difference in BPAR. As with daclizumab, a number of studies have examined different dosing and supplementary immunosuppressive regimes. Matl et al. used one dose of basiliximab (40 mg administered on the day after surgery) and showed slightly improved BPAR rates (17.0% vs. 19.6%) and lower acute rejection incidence (20% vs. 22.5%) compared to the conventional two-dose course, with no increase in morbidity. In 2006, Baquero et al. arrived at a similar outcome, further emphasizing the cost-saving implications of a single dose. Other research has focused on eliminating steroids or CNIs from immunosuppressive regimes in the context of basiliximab induction. CNI-free or CNI-sparing regimes have been shown by several studies to be extremely well-tolerated without compromising acute rejection outcomes. Because both basiliximab and RATG have been widely used in renal transplant patients, a number of studies have compared their outcomes in a variety of settings. In a small pilot study in 2001, Mariat et al. demonstrated that at one-year follow up, renal transplant patients treated with basiliximab had a significantly higher BPAR rate than those treated with RATG (50% vs. 19%). Larger prospective studies, however, have shown a less pronounced clinical difference between the two therapies. Lebranchu et al. randomized 100 patients to two-dose basiliximab with CsA or RATG with delayed CsA, all on a background of MMF and steroids. Both BPAR rates (8% in both), patient survival (98% RATG vs. 94% basiliximab), and graft survival rates (100% RATG vs. 96% basiliximab) were comparable in both groups.

**Basiliximab: other solid organ transplants.** In 2002, several studies demonstrated that two-dose basiliximab induction in liver transplant patients was well-tolerated and effective in reducing BPAR rates (35.1% basiliximab vs. 43.5% placebo at six-month follow up), although to a lesser extent in HCV-positive cohorts. Lin et al. further demonstrated that by allowing for delayed tacrolimus administration, basiliximab induction preserved renal function better than conventional therapy (renal insufficiency incidence of 26% vs. 67% at three-month follow up). To minimize toxicity, steroid-withdrawal protocols have been actively tested in conjunction with basiliximab usage. In the setting of HCV-seropositive individuals, Filippini et al. demonstrated lower BPAR rates with normal steroid supplementation (24.3% basiliximab plus steroids vs. 39.4% basiliximab minus steroids), but better patient survival without (84.3% without steroids vs. 61.0% with steroids). In this and other studies, short-term HCV recurrence has been less prevalent in treatment arms that are steroid-free.

In heart transplant patients, basiliximab has a mixed record. Although Mehr et al. demonstrated only a non-significant increase in time to first BPAR with basiliximab induction relative to controls (73.7 vs. 40.6 days at six-month follow up), Rosenberg et al. showed that basiliximab could safely allow for delayed CsA administration and thereby minimize renal toxicity post-heart transplant. Comparative studies with anti-thymocyte globulins are controversial—Mattei et al. showed decreased rates of infection and similar efficacy with basiliximab relative to RATG, but two other groups have shown that RATG is superior to basiliximab in both biopsy scores and freedom from rejection (65% basiliximab vs. 83% RATG).

Finally, in lung transplant patients, there is only one small comparative study that evaluates basiliximab induction. In high-risk recipients, 15 patients receiving basiliximab plus triple therapy demonstrated lower rates of acute and chronic rejection compared to 13 controls receiving triple therapy alone (13.3% vs. 38.5% acute and 20% vs. 38% chronic rejection incidence).

**Anti-CD52 mAbs.** A third class of mAbs, anti-CD52 mAbs, are used to prevent acute graft rejection. CD52 is a membrane glycoprotein with unknown function that is expressed on T and B lymphocytes, macrophages, monocytes, eosinophils and along the male reproductive tract. It is especially highly-expressed on lymphocytes (up to 5% of surface antigens), explaining the powerful immunodepleting effect of anti-CD52 antibodies.

**Campath-IH: kidney transplants.** Campath-IH (also known as alemtuzumab) is the humanized form of a murine anti-CD52 mAb (Campath-1G). Campath-1G was used extensively to repress rejection of bone marrow grafts, but in the setting of solid organ transplants, the antigenicity and dosing limitations proved restrictive. In 1999, Campath-IH trials showed that the humanized IgG2b variant, with low-dose CsA monotherapy, successfully reversed acute rejection episodes in renal transplant patients without the concomitant anti-idiotypic response and single dosing limitations (94% functioning grafts at a mean follow-up of 21 months). Subsequently, Campath-IH was shown to be effective and safe for steroid-resistant rejection, provided the regimen was limited to two doses of 30 mg (95% patient survival, 73.5% graft survival at 453 day mean follow-up). Additionally, a treatment regimen of alemtuzumab induction with sirolimus monotherapy exhibited remarkable three-year outcomes (96% graft survival and 100% patient survival), although a high rate of early rejection episodes was observed (28%).

Comparative studies have been relatively limited—Kaufman et al. conducted a non-random, single-center retrospective study comparing basiliximab to alemtuzumab on a background of double therapy (MMF and tacrolimus). The alemtuzumab group had a lower rate of rejection episodes at three months (4.1% alemtuzumab vs. 11.6% basiliximab), but both arms demonstrated equivalent 1-year rejection rates. Tan et al. compared RATG (24 patients) to alemtuzumab (166 patients) on a background of low-dose tacrolimus monotherapy. At 401-day follow up, alemtuzumab-treated patients had significantly lower rates of acute rejection (8.4% alemtuzumab vs. 29.2% RATG) with no difference in CMV infections or PTLD.

Only recently have there been randomized trials comparing alemtuzumab to conventional treatment regimes emerged. Thomas et al. compared RATG treatment (along with triple therapy of tacrolimus, MMF and steroids) against single-dose alemtuzumab induction (with tacrolimus monotherapy) in 21 high-risk immunological patients. Both yielded similar one-year graft survival results (87.5% RATG vs. 85.7% alemtuzumab) with similar infection rates. In 2008, Munoz et al. randomized 14 kidney transplant patients to alemtuzumab with CsA or triple therapy (CsA, azathiprine, steroids). At three-year follow up, the alemtuzumab group had more acute rejection episodes than the control
group (67% vs. 20%), with similar rates of infection in both. The third and largest randomized controlled trial was conducted by Margreiter et al. in 2008. A total of 131 kidney transplant patients were randomized to alemtuzumab with delayed tacrolimus or triple therapy (tacrolimus, MMF, steroids). At one-year follow up, the alemtuzumab arm demonstrated slightly improved BPAR rates (20% alemtuzumab vs. 32% control) and graft survival (96% vs. 90%), but the incidence of CMV infections was also higher. This series of controversial data illustrates the need for larger, long-term studies comparing alemtuzumab to mainstream immunosuppression regimes.

**Campath-1H: other solid organ transplants.** Campath-1H has not been extensively tested in solid organ transplants besides the kidney. Tzakis et al. used alemtuzumab induction and low-dose tacrolimus therapy in 40 adult liver graft recipients and compared outcomes to a 50-patient control group on conventional tacrolimus and steroids. The incidence of acute rejection in the study group was slightly lower at one-year follow up (46% vs. 55%) with significantly longer median time to rejection (2.7 vs. 0.34 months). Additionally, alemtuzumab-treated patients required less steroid maintenance and experienced less renal toxicity. In lung transplant patients experiencing refractory acute rejection or BOS, Reams et al. administered alemtuzumab and showed that histological rejection scores in RAR patients improved, as did freedom from BOS at two-year follow up. Both of these preliminary studies show that alemtuzumab may have beneficial applications in non-renal organ transplant patients.

**Conclusion**

Because of their remarkable outcomes, antibody therapies have become a staple of induction and acute rejection therapy in solid organ transplant patients. Empirically, these treatments have been more extensively tested in kidney transplant patients than in those with liver, heart or lung transplants. Still, any given antibody protocol should be implemented with calculated, evidence-based considerations of the potential risks and complications involved. As trials continue, antibody induction trends are likely to continue evolving, especially with the influx of new and exciting therapies. These antibodies in the pipeline will be discussed in the forthcoming second part of this review.

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