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Immunosuppression trends for solid organ transplantation have undergone a perceptible shift over the past decade. This period is of interest because it was during this time that the Food and Drug Administration (FDA) expanded the variety of medications to allow for alternatives in immunosuppressive management. An organ-by-organ review of SRTR data identifies several important trends. Antibody induction continues to be used for the majority of kidney (70%), simultaneous pancreas-kidney (SPK, 79%) pancreas after kidney (PAK, 74%), and intestine recipients (74%). It is used for under half of thoracic organ recipients and remains uncommon for liver transplant recipients (20%). The type of antibody preparation utilized has shifted from muromonab-CD3 and horse ATG to rabbit ATG and monoclonal anti-IL-2 receptor antagonists. Calcineurin inhibitors continue to be used for maintenance immunosuppression for most recipients, although there has been a shift from cyclosporine to tacrolimus. A clear transition is apparent in the choice of antimetabolite from azathioprine to mycophenolate mofetil. Although corticosteroids continue to be used as maintenance immunosuppression for most recipients prior to discharge, there is evidence that efforts of steroid avoidance protocols are having an impact across all organs, as slight decreases in their use have been observed.

Key words: Antirejection treatment, immunosuppression, induction therapy, maintenance immunosuppression, SRTR, transplantation

Introduction

This article focuses on trends that have evolved over the past 10 years in the immunosuppression of recipients of vascularized solid organ transplants. This period is of particular interest because it was during this decade that the variety of immunosuppressant medications approved by the Food and Drug Administration (FDA) expanded sufficiently to allow for clinically meaningful alternatives in immunosuppressive management. The mid-1980s and early 1990s offered few choices; patients could receive corticosteroids in combination with the calcineurin inhibitor cyclosporine and the antimetabolite azathioprine. The important clinical questions of that era revolved around the use of antibody induction and the proper dosing of these medications.

The first of the newer immunosuppressive agents, tacrolimus, and of the improved formulations of cyclosporine, cyclosporine for microemulsion, were approved in 1994. Over the next several years, the FDA licensed several important new maintenance immunosuppressants—mycophenolate mofetil (1995), sirolimus (1999) and mycophenolate sodium (2004)—as well as the new antibody preparations rabbit antithymocyte globulin (ATG) (1999), daclizumab (1999) and basiliximab (2000). The introduction of these agents substantially increased the number of options available for immunosuppression. While the OPTN/SRTR data do not capture all of the nuances of these newer combinations, they provide important information about trends in immunosuppressive practice.

Despite some strategic dissimilarity specific to the transplantation of different types of organs, there exist broad...
therapeutic patterns. Antibody induction continues to be prescribed for the majority of kidney, pancreas and intestine recipients, and for just under half of thoracic organ recipients; but its use remains uncommon in liver transplantation (Figure 1). However, there is an ongoing shift in the choice of antibody preparations being utilized from muromonab-CD3 (OKT3®, Orthobiotech, Bridgewater, NJ) and horse ATG (ATGAM®, Pharmacia & Upjohn, Kalama- zoo, MI) to rabbit ATG (Thymoglobulin®, SangStat Medical Corp., Fremont, CA) and the monoclonal anti-IL-2 receptor antagonists daclizumab (Zenapax®, Roche, Nutley, NJ) and basiliximab (Simulect®, Novartis, East Hanover, NJ). More recently, there has been growing interest in induction with the anti-CD52 monoclonal antibody alemtuzumab (Campath-1H®, ILEX Pharmaceuticals, San Antonio, TX). In 2003, 4% of kidney, 7% of simultaneous pancreas–kidney (SPK), 13% of pancreas after kidney (PAK), 35% of pancreas transplant alone (PTA), 9% of intestine and ≤1% of other organ recipients were treated with this agent. To avoid misinterpretation of various antibody preparations, we indicate both generic and brand names in Table 1, but we use those brand names that are commonly employed in clinical practice in the text and figures.

Maintenance immunosuppression is also undergoing gradual evolution. Although corticosteroids are prescribed for the overwhelming majority of patients, there is increasing interest across all solid organ transplant disciplines in the implementation of steroid avoidance and minimization protocols. Calcineurin inhibitors continue to be administered to most patients, but with the exception of cardiac transplantation and reflecting a progressive trend over the past 10 years, the majority of recipients treated with calcineurin inhibition now receive tacrolimus (Figure 2). Similarly, the use of azathioprine has been almost completely replaced by mycophenolate mofetil, which has become the most widely employed adjunctive immunosuppressive agent in solid organ transplantation (Figure 3). In addition, the roles and indications for immunosuppression with sirolimus in combination with other medications continue to evolve.

Importantly, the incidence of acute rejection has declined over the past decade. Treatments for acute rejection continue to include high-dose corticosteroid and antibody therapies. Practices of conversion of maintenance immunosuppressive regimens, principally between cyclosporine, tacrolimus and sirolimus, in association with antirejection therapy or in response to medication-related toxicities, are not fully reflected in the SRTR database.

The remainder of this article is devoted to organ-specific discussions, focusing on antibody induction, maintenance immunosuppression, the use of corticosteroids and the treatment of rejection. It provides a window into the dramatic changes that have occurred over the past 10 years on the part of practitioners within the transplant community.

Unless otherwise noted, statistics in this article are drawn from the reference tables in the 2004 OPTN/SRTR Annual Report. Two companion articles in this report, “Transplant

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<th>General names</th>
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<td>TOR inhibitors (or rapamycin)</td>
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Notes: For some immunosuppressants, the original data collection forms list brand names instead of generic names. Like the SRTR database, the figures in this article follow the terms on the data collection forms, though the text refers to the drugs by their generic names when there is a one-to-one correlation between the reported brand name and the generic name.
Kidney transplantation

**Trends in induction therapy in kidney transplantation**

Induction therapy refers to the temporary use of high doses of immunosuppressive medications in the early post-transplant period. Recipients treated with induction immunosuppression typically receive a brief course of antibody therapy that is intended to reduce or modify early immune system activity against the transplanted organ. During induction, some maintenance immunosuppressive medications, in particular the nephrotoxic calcineurin inhibitors, may be withheld for a variable number of days, usually until renal function stabilizes.

**Trends in maintenance immunosuppression therapy for the first year in kidney transplantation**

Because a substantial number of renal transplant recipients have received induction therapy with an anti-T-cell antibody in the perioperative period, some of the maintenance immunosuppressive medications, in particular nephrotoxic calcineurin inhibitors, are frequently withheld for a variable number of days post-transplant, usually until renal function stabilizes. The OPTN/SRTR data reflects this practice, since the percentage of patients receiving these agents...
increases during the first year post-transplant from that reported at discharge. The yearly trends in the administration of individual immunosuppressive agents seen following discharge are similar to those seen in the pre-discharge period. Within the category of calcineurin inhibitors, the trend toward more tacrolimus use and less cyclosporine maintenance continues. Among the antimetabolites, there is a notable preference for mycophenolate mofetil over azathioprine, the former accounting for 82% while the latter accounted for only 4% of recipients in 2002. After a rapid increase in the use of sirolimus from 3% in 1998 to 17% in 2000, the number of kidney transplant recipients on this drug has reached a plateau at 22% and 21% in 2001 and 2002, respectively. In 2002, 9% of patients were on steroid-free immunosuppressive regimens in the post-discharge period, reflecting the increased practice of attempting to spare recipients ongoing exposure to corticosteroid treatments.

**Trends in antirejection treatment in kidney transplantation**

In 2002, only 2185 (15%) out of 14 774 kidney transplant recipients required treatment for an acute rejection episode within 1 year of transplantation (Figure 6). This follows the decline from 18% in 2000 to 17% in 2001. Corticosteroids are still the mainstay of treatment for acute rejection, used alone or with antibodies in 78–80% of cases since 1998. The use of antilymphocyte antibodies for the treatment of rejection has also remained relatively stable at 36–39% since 1998. Within the antibody category, however, rabbit ATG has largely replaced the monoclonal anti-T-cell receptor antibody muromonab-CD3 as the principal antirejection treatment (Figure 7).

**Pancreas transplantation**

Induction, maintenance and antirejection immunosuppressive therapies for recipients of pancreas transplantation are rapidly evolving. The majority of pancreas transplant recipients in the early 1990s received muromonab-CD3 induction; corticosteroids, azathioprine and cyclosporine for maintenance immunosuppression; and corticosteroids or muromonab-CD3 as treatment for rejection. Reliance on these agents has decreased over the past 10 years. The use of muromonab-CD3 for induction has been supplanted by rabbit ATG, daclizumab and basiliximab. Similarly, while corticosteroids are still commonly employed in maintenance immunosuppression protocols, tacrolimus, mycophenolate mofetil and sirolimus have largely replaced cyclosporine and azathioprine. Finally, when antibodies have been employed within the past several years to treat rejection, the utilization of rabbit ATG (begun in 1998) has become similar to or surpassed that of muromonab-CD3.

**Trends in induction therapy in pancreas transplantation**

SPK recipients are more likely to receive induction immunosuppression (79%) than are PAK (74%) or PTA (79%) recipients. In 1994, muromonab-CD3 was the most common induction agent utilized in pancreas transplantation.
However, with FDA approval in the late 1990s of rabbit ATG and the anti-IL-2 monoclonal antibodies daclizumab and basiliximab, the use of muromonab-CD3 for pancreas transplantation induction began to decrease. By 2003, the administration of muromonab-CD3 for induction in SPK, PAK and PTA transplantation had fallen to less than 1%. In 2003, rabbit ATG was the most frequently utilized induction agent in SPK (49%), PAK (51%) and PTA (35%) recipients. However, daclizumab and basiliximab were received by a sizeable minority of SPK (8% and 16%), PAK (9% and 8%) and PTA (10% and 8%) recipients for induction therapy (Figure 8).

Trends in maintenance immunosuppression therapy prior to discharge in pancreas transplantation

Once among the key elements of maintenance protocols for pancreas transplantation, the use of cyclosporine and azathioprine has decreased dramatically over the past decade (Figure 9). In 1994, 88% of SPK, 76% of PAK and 57% of PTA recipients were given cyclosporine during their initial transplant hospitalization. By 2003, the use of cyclosporine had declined to 9%, 8% and 3% for recipients of SPK, PAK and PTA, respectively. The diminished utilization of cyclosporine was accompanied by an increasing reliance on tacrolimus for pancreas transplant immunosuppression. In 2003, 84% of SPK, 81% of PAK and 81% of PTA recipients received tacrolimus.

Even more striking changes have been seen in the use of azathioprine. In 1994, 99%, 91% and 100% of SPK, PAK and PTA recipients, respectively, received azathioprine following pancreas transplantation. In 2003, 1% or less of SPK, PAK or PTA recipients were administered azathioprine during their initial transplant hospitalization. Mycophenolate mofetil and, to a lesser extent, sirolimus have supplanted azathioprine for the initial maintenance therapy of pancreas transplant recipients. In 2003, 82% of SPK, 85% of PAK and 71% of PTA recipients received mycopheno-

late mofetil, and 20% of SPK, 15% of PAK and 21% of PTA recipients received sirolimus.

The majority of pancreas transplant recipients continue to be treated with corticosteroids as part of their maintenance immunosuppression. However, over the past 5 years, early maintenance corticosteroid use has declined for all three pancreas transplant procedures. In 2003, 84% of SPK, 81% of PAK and 62% of PTA recipients were treated with corticosteroids prior to discharge from their initial transplant hospitalization.

**Trends in maintenance immunosuppression therapy for the first year in pancreas transplantation**

Tacrolimus, mycophenolate mofetil and corticosteroids are currently the bulwarks of pancreas transplant maintenance immunosuppression during the first post-transplant year. During 2002, tacrolimus was used for 89%, 88% and 95%; mycophenolate mofetil for 80%, 77% and 71%; and corticosteroids for 89%, 93% and 90% of SPK, PAK and PTA recipients, respectively. In addition, 28% of SPK, 32% of PAK and 31% of PTA recipients received sirolimus.

In contrast to 1993, the use of cyclosporine and azathioprine has declined. In 2002, only 13% of SPK, 14% of PAK and 8% of PTA recipients were given cyclosporine maintenance therapy during the first post-transplant year, and fewer than 2% were treated with azathioprine. In 1993, nearly all pancreas transplant recipients received cyclosporine and azathioprine.

**Trends in antirejection treatment in pancreas transplantation**

The incidence of rejection in the first year after transplantation has declined in the past 10 years for SPK recipients (Figure 10). Corticosteroids remain the most commonly employed medications in the treatment of pancreas transplant rejection. However, their use in SPK recipients who have been treated for rejection has declined from 81% in


Immunosuppression, 1993-2003

Figure 10: Incidence of rejection during first year among simultaneous kidney–pancreas transplant recipients, 1993–2002. Source: 2004 OPTN/SRTR Annual Report, Table 8.6d.

Figure 11: Trends in antibody therapy for rejection episodes in first year following simultaneous kidney–pancreas transplantation, 1993–2002. Source: 2004 OPTN/SRTR Annual Report, Table 8.6d.

1993 to 76% in 2002. In contrast, corticosteroid treatment for rejection increased between 1993 and 2002 from 40% to 91% for PAK recipients, and from 28% to 82% for PTA recipients.

During the same interval, the use of antibody therapy has diminished. In 1993, 78% of SPK, 84% of PAK and 72% of PTA recipients who were treated for rejection were given antibodies. In 2002, these percentages decreased to 51%, 49% and 64%, respectively. The biggest decline was in the use of muromonab-CD3 following SPK transplantation (Figure 11). In 1993, 67% of SPK, 68% of PAK and 56% of PTA recipients who were treated for rejection were administered muromonab-CD3. In 2002, these percentages declined to 11%, 26% and 42%, respectively. Although rabbit ATG was not available for pancreas transplantation in the United States until 1998, it is now the most commonly employed antibody for the treatment of pancreas allograft rejection. In 2002, 34% of SPK, 30% of PAK and 33% of PTA recipients who were treated for rejection received rabbit ATG. Of those pancreas transplant recipients who were treated for rejection, 5% or less received daclizumab or basiliximab.

Liver transplantation

Trends in induction therapy in liver transplantation

Induction therapy is not part of the typical immunosuppressive regimen for most liver transplantation recipients (Figure 12). However, induction therapy is commonly employed in lieu of calcineurin inhibitors immediately after transplantation for those patients with marginal renal function to avoid the nephrotoxicity of tacrolimus and cyclosporine. The fraction of patients receiving induction therapy has increased incrementally since 1997 (when it was 7%), reaching 20% in 2003. The most important factor responsible for this trend is the increasing prevalence of renal failure and renal insufficiency in liver transplant recipients, due in large part to the importance of serum creatinine in the determination of the priority for liver transplantation using the Model for End-stage Liver Disease (MELD) score. Three agents make up 93% of induction therapy for liver transplantation. The most commonly administered agent is basiliximab (7% of all liver recipients), followed by rabbit ATG and daclizumab (6% each) (Figure 12). While the use of basiliximab and daclizumab has been relatively stable from 2002 to 2003, the percentage of patients receiving rabbit ATG increased by more than 50% from 2002 (4%) to 2003 (6%). The augmented utilization of rabbit ATG is possibly a result of recent data indicating successful liver transplantation with steroid-free immunosuppressive regimens using rabbit ATG (3). The use of induction therapy will likely continue to rise over the next few years because of the increasing incidence of renal insufficiency in liver transplant recipients.

Trends in maintenance immunosuppression therapy prior to discharge in liver transplantation

Three important trends are noted in immunosuppressive therapy employed prior to discharge in liver transplant recipients since 2002. First, the percentage of patients receiving corticosteroids prior to discharge decreased from 91% in 2002 to 82% in 2003. The continued trend of corticosteroid avoidance is due, in part, to the negative impact
of this agent on hepatitis C and the growing proportion of recipients infected with this virus (4). In addition, a small but increasing proportion of transplant centers have demonstrated that liver transplantation may be successfully performed in the absence of (or with minimization of) corticosteroid exposure (3,5–7). As a result, many liver transplant programs have reduced the dose and duration of corticosteroid administration to their patients. Second, tacrolimus remains the calcineurin inhibitor prescribed for most recipients (89%), with cyclosporine recently given to less than 10% of liver transplant recipients (Figure 13). Third, mycophenolate mofetil is the most commonly prescribed antimetabolite (administered to 54% of recipients), and the use of sirolimus during the immediate postoperative phase is minimal and has decreased (from 7% in 2002 to 4% in 2003). The decline in the administration of sirolimus (which had been increasing yearly since introduction in 1998) may reflect the influence on practice of the ‘black box’ warning of an increased risk of hepatic artery thrombosis that the FDA has issued for this agent (8). Because of concerns related to hepatic artery thrombosis, the use of sirolimus in the immediate perioperative period is likely to remain very small.

**Trends in maintenance immunosuppression therapy for the first year in liver transplantation**

The trends in immunosuppression administered during the first year following liver transplantation reflect the profile of immunosuppression at the time of discharge (Figure 13). Corticosteroid use decreased from 89% in 2001 to 87% in 2002. However, 87% is still higher than the percentage of patients given corticosteroids prior to discharge (82%), indicating that some patients not receiving corticosteroids at discharge are initiated on them during the first year. Many of these patients will have autoimmune liver disease and require corticosteroid therapy to control recurrences. Cyclosporine use decreased by 22%, dropping from 18% in 2002 to 14% in 2003. A higher percentage of patients is administered cyclosporine following discharge (14%) than is administered tacrolimus. Mycophenolate mofetil was given to 50% of recipients and continued its upward trend since its introduction in 1994. The use of sirolimus decreased from 17% in 2002 to 14% in 2003. As noted above, the decreased use of sirolimus appears related to concerns associated with the ‘black box’ warning issued by the FDA for this medication. However, the percentage of patients administered sirolimus following discharge (14%) is much higher than that administered sirolimus during the immediate perioperative period (4%). The increased use of sirolimus after discharge may reflect confidence in its safety as the post-transplant risk of hepatic artery thrombosis declines over time. The use of sirolimus during the first year following transplantation will likely continue to increase because of concerns regarding calcineurin inhibitor-related nephrotoxicity. In addition, transplant physicians are becoming more aggressive in weaning patients off calcineurin inhibitors during the chronic phase of immunosuppression to avoid the long-term nephrotoxic effects of these drugs (9).

**Trends in antirejection treatment in liver transplantation**

The rate of antirejection treatment in 2002 (24%) is much lower than it was in 1993, when 50% of the patients were treated for rejection (Figure 14). The two most important reasons for the decreased rate in the treatment of rejection were (1) the introduction of several new immunosuppressive agents that may reduce the incidence of acute cellular rejection and (2) a decreased likelihood of treating mild rejection in the growing number of hepatitis C patients because of recognition of the deleterious effects of antirejection treatment on the progression of hepatitis C. In 2002, corticosteroids were used to treat acute cellular rejection during the first year following liver transplantation in 90% of cases, and antibody therapy was given to 18% of recipients, as compared to 17% during 2001. The three most commonly
administered antibody therapies were muromonab-CD3 (6%), rabbit ATG (6%) and basiliximab (4%), which collectively accounted for over 85% of all antirejection antibody therapies (Figure 15).

Figure 15: Trends in antibody therapy for rejection episodes in the first year following liver transplantation, 1993–2002. Source: 2004 OPTN/SRTR Annual Report, Table 9.6d.

Intestine transplantation

The number of intestine transplants performed in the United States is relatively small compared with other organs. In 2003, only 116 cases with data on immunosuppression were registered with the SRTR. Because of the small total number of cases, the significance of changes in the trends of immunosuppression may be difficult to assess.

Trends in induction therapy in intestine transplantation

Induction therapy was utilized in 74% of intestine transplants in 2003. Two agents accounted for 82% of induction therapy. The most commonly administered induction agent was rabbit ATG (46%), followed by daclizumab (16%). The most notable changes in the type of induction therapy were the use of rabbit ATG, which increased from 31% in 2002 to 46% in 2003, and a drop in the use of basiliximab, from 13% in 2002 to less than 2% in 2003.

Trends in maintenance immunosuppression therapy prior to discharge in intestine transplantation

Data on maintenance therapy prior to discharge were available on 103 intestine transplant recipients. Corticosteroids were given to 67% of the patients, which reflects a general downward trend in corticosteroid use in intestine transplantation. The percentage of intestine transplant recipients receiving corticosteroids decreased from 97% in 2000 to 80% in 2001 and 64% in 2002. Tacrolimus was administered to 93% of the patients, while cyclosporine was used for only 1% of the patients. Mycophenolate mofetil, the only antimetabolite used, was prescribed for only 9% of the patients.


Heart transplantation

Trends in induction therapy in heart transplantation

The use of induction therapy in heart transplantation has received a great deal of attention over the past decade. Driven primarily by approaches to other solid organ transplant patients, initial immunosuppression strategies often included an induction protocol but not, generally, with the same frequency observed with other organ transplants. Though few large-scale randomized clinical trials have been performed to test the efficacy of induction regimens immediately after heart transplant, some guidance has been developed, and these data are likely driving the changes noted today. Figure 16 details the specific trends in immunosuppression used for induction therapy from 1994 through 2003. In the mid-1990s, there was a decrease in the
percentage of recipients receiving induction therapy (from 36% in 1994 to 29% in 1998), but this trend has more recently been reversed, as 47% were given induction therapy in 2003. It has been speculated that recipient comorbidities often drive the decision to administer induction therapy to heart transplant recipients. Whereas induction therapy had primarily been employed as a strategy to decrease the incidence of early rejection following heart transplantation, induction therapy has more recently been used as a so-called ‘renal-sparing’ regimen that delays exposure to calcineurin inhibitors and, more specifically, cyclosporine. In the setting of pre-transplant renal insufficiency, some believe this approach will decrease the risk of developing renal failure early after heart transplant. With this observation in mind, several clear trends have emerged with respect to early post-transplant induction protocols for heart recipients. As Figure 16 demonstrates, muromonab-CD3 and equine ATG were the most commonly used induction agents in the latter half of the 1990s. Whereas 16% of patients receiving induction immunotherapy immediately post-transplant were treated with ATG in 1994, only 8% received this agent in 2003. Similarly, 20% receiving induction therapy in 1994 were given muromonab-CD3, but only 5% were prescribed this agent in 2003. As experience increased with the use of muromonab-CD3 for induction, concern was raised about acute pulmonary toxicity and about a seeming increase in post-transplant lymphoproliferative disease over the longer term. On the other hand, the administration of rabbit ATG increased substantially from 0% in 1998 to 13% in 2003. Similarly, the use of the anti-IL-2 receptor antibodies, daclizumab and basiliximab, has increased to 15% and 9%, respectively, both from 0% in 1997. These agents generally appear to be better tolerated. Clearly, the use of rabbit ATG or an anti-IL-2 receptor antibody is the strategy most often chosen today when induction therapy is prescribed.

**Trends in maintenance immunosuppression therapy prior to discharge in heart transplantation**

Although substantive changes in maintenance immunosuppression therapy prior to discharge from the hospital after heart transplantation can be seen between 1995 and 2000, no major changes in immunosuppressive schemes are noted from 2002 to 2003. Corticosteroids, antimetabolites, and calcineurin inhibitors remain the core therapies. In 2003, 93% of the patients were on corticosteroids, 90% on an antimetabolite and 100% on a calcineurin inhibitor, with more than 8% on other types of immunosuppression, such as sirolimus (8%) and cyclophosphamide (0.2%). However, there have been changes in immunosuppressive use within the major classifications.

**Calcineurin inhibitors:** Virtually all patients are receiving a calcineurin inhibitor in the early post-transplant period prior to hospital discharge (Figure 17). There has been a steady rise in the use of tacrolimus from 16% in 2000 to 41% in 2003. Though the majority of patients on a calcineurin inhibitor are still on cyclosporine, only 4% of the total population now receive the original formulation Sandimmune, with 43% receiving Neoral and 14% Gengraf. It is interesting to note the increase in proportion of patients on the generic cyclosporine compound Gengraf since 2000 when it first became available (2% in 2000 vs. 14% in 2003).

**Antimetabolites and sirolimus:** Mycophenolate mofetil use has increased over the past decade and it is now the antimetabolite most frequently prescribed prior to hospital discharge after heart transplantation. As noted in Figure 17, in 2003, 82% of patients were treated with this agent versus 4% in 1994. This should be compared with the 94% administration of azathioprine in 1994 versus about 10% in 2003. Sirolimus has, over the past 2 years, seen a steady rise in utilization as well (from 0% in 1997 to about 10% in 2002 and 8% in 2003). Other immunosuppressive agents, such as cyclophosphamide, are now rarely used and have never been employed with significant frequency.

**Corticosteroids:** Data suggest that there is almost universal belief that corticosteroids are an essential component of the immunosuppressive protocol prior to hospital discharge after heart transplantation. Little change has been noted in prescriptive practice over the past decade, with 93% of patients transplanted in 2003 receiving steroids.

**Trends in maintenance immunosuppression therapy for the first year in heart transplantation**

In 2002, corticosteroids, calcineurin inhibitors and the antimetabolite mycophenolate mofetil remained the most common maintenance agents within the first year after heart transplantation.

**Calcineurin inhibitors:** Matching observations made earlier regarding practice at the time of the initial post heart transplant discharge, the trend over the past decade has been for an increasing role for tacrolimus as the calcineurin...
inhibitor of choice. In 2002, about 50% of the patients were receiving this agent, compared with 43% in 2001. With regard to cyclosporine preparations, as noted with immunosuppression prior to hospital discharge, Gengraf use has increased to about 14%, with Neoral at approximately 43%, down from 68% in 2000.

**Antimetabolites and sirolimus:** The use of azathioprine continues to decrease substantially. Whereas in 1993, 95% of patients were treated with this agent, only 12% received azathioprine in 2002. Indeed, 80% of patients on an antimetabolite in 2002 were receiving mycophenolate mofetil. Also important is the apparent decrease in antimetabolite use over the past decade. Whereas in 1993, 96% of patients received an antimetabolite, in 2002 this fell to 87%. Some of this decline seems to be related to an increased use of sirolimus, which reached 14% in 2002, compared with 8% in 2001 and 5% in 2000.

**Corticosteroids:** Although the vast majority of heart transplant recipients are treated with corticosteroids as part of the maintenance immunosuppressive regimen during the first year post-transplant, this has declined over time, with 88% of patients receiving steroids in 2002 compared with 96% of patients in 1993. Some programs have focused on weaning heart transplant patients off steroids, but such patients represent a small minority.

**Trends in antirejection treatment in heart transplantation**
Over the past decade, the occurrence of episodes of rejection requiring augmentation of immunosuppressive therapy has shown only minor changes (41% in 1993 vs. 37% in 2002) (Figure 18). However, a striking trend has occurred over the past decade regarding therapeutic options for acute rejection. Corticosteroid utilization remains high, with 88% of patients receiving these agents as treatment for rejection in 1993 and 92% in 2002. However, as Figure 19 demonstrates, there is a continuing decrease in antibody administration for acute rejection. In 1993, 27% of patients received antibodies for acute rejection versus 18% in 2002. Of the antibodies used in 2002, rabbit ATG (6%), muromonab-CD3 (7%) and equine ATG (4%) made up the bulk of the treatments. Perhaps there has been a slight decrease in the use of anti-IL-2 receptor antibodies for the treatment of rejection, as only 2% of patients received these agents in 2002 versus almost 3% in 2001.

Treatment of rejection within the first year of transplantation thus remains primarily based on corticosteroids, with the most notable changes being a gradual decline in the use of antibody therapy over time.

**Lung transplantation**

**Trends in induction therapy in lung transplantation**
Overall, there has been a continuing increase in the utilization of induction therapies for lung transplant recipients. In 1994, 25% of the patients received antibody induction immediately after transplantation, compared with 44% in 2003. More specifically, the use of equine ATG has declined from 23% in 1995 to about 5% in 2003, and the use of muromonab-CD3 has declined from about 6% in 1994 to 1.1% in 2003. There was some utilization of rabbit ATG, following its approval by the FDA; however, its use was only 3% in 2003, compared with almost 8% in 2002. In contrast, significant increases have been noted in the utilization of the anti-IL-2 receptor antibodies daclizumab and basiliximab (Figure 20). Thus, the overall increase since 1998 in the utilization of lung transplant induction protocols principally reflects the use of anti-IL-2 receptor antibodies.

**Trends in maintenance immunosuppression therapy prior to discharge in lung transplantation**
Paralleling heart transplantation over the past decade, major changes in maintenance immunosuppression immediately following lung transplantation were noted after the introduction of tacrolimus and mycophenolate mofetil in
Sirolimus is rarely prescribed early after lung transplantation. In 2001, 4% of patients received this agent, whereas in 2002 only 2% and in 2003 only 1% of patients were taking this compound as part of their immunosuppressive regimen. Cyclophosphamide continues to be used rarely for lung transplant recipients.

**Corticosteroids:** Corticosteroids are still a mainstay of immunosuppressive therapy following lung transplantation. In 2003, 95% of patients were on corticosteroids. This is similar to the heart transplant experience.

**Trends in maintenance immunosuppression therapy for the first year in lung transplantation**

In 2002, the most common maintenance regimens used within the first year following lung transplantation included corticosteroids (97%), tacrolimus (76%) or cyclosporine (35%) and an antimetabolite (89%), such as azathioprine (44%) or mycophenolate mofetil (54%). Sirolimus use increased to 14% in 2002, up from 11% in 2001.

**Calcineurin inhibitors:** Calcineurin inhibitors remain the basis of maintenance immunosuppression in patients during the first year following lung transplantation. In contrast to heart transplant recipients, however, there has been a more dramatic increase in the percentage of lung transplant patients receiving tacrolimus: from 47% in 1999 to 76% in 2002. For patients receiving cyclosporine, Neoral utilization has fallen from a high of 59% in 1998 to 76% in 2002; the utilization of alternative cyclosporine formulations in 2002 has not been common in these patients (3% Sandimmune and 7% Gengraf).

**Antimetabolites and sirolimus:** Though antimetabolite use overall is still frequent for lung transplant recipients during the first post-transplant year, the proportion of patients on mycophenolate mofetil versus azathioprine continues to change. In 2001, 49% of patients were on azathioprine, while in 2002, 44% of patients were on this agent and 54% on mycophenolate mofetil. Interestingly, the percentage of lung recipients on sirolimus within 1-year post-transplant (14%) was similar to that for heart transplant recipients (also 14%). However, the utilization of sirolimus at 1-year post-transplant (14%) should also be compared with its use prior to hospital discharge (1%). In comparison, 8% of patients were on sirolimus prior to discharge after heart transplant. The differences in early utilization of sirolimus are likely related to observations suggesting an increased risk of airway anastomotic dehiscence when sirolimus is employed as part of the protocol immediately after surgery.

**Corticosteroids:** As with heart transplant recipients, the vast majority of lung transplant recipients received corticosteroids as part of their immunosuppressive maintenance therapy during the first postoperative year. This has changed little over the past decade.
Trends in antirejection treatment in lung transplantation
There has been little change in the incidence of rejection within the first year following lung transplantation since 1996 (Figure 22). In the treatment for rejection within the first year after lung transplantation, corticosteroids continued to be the agents primarily used. In 2002, 95% of recipients receiving antirejection treatments had steroids administered as part of the treatment protocol. Overall, antibodies were used as the main class of agent for steroid-resistant rejection during the past decade. Since 1997, there has been a slight increase in the utilization of rabbit ATG (5% in 2002) and anti-IL-2 receptor antibodies, of which daclizumab was used for 5% of the patients and basiliximab for 0.2% of the patients in 2002 (Figure 23).

Heart–lung transplantation
Trends in induction therapy in heart–lung transplantation
It is difficult to comment definitively about immunosuppressive protocols in patients undergoing combined heart–lung transplantation because few such procedures are now performed. In 2003, only 29 en bloc heart–lung transplants were performed. With the success of single lung, double lung, and lung segment transplantation, sometimes combined with repair of the primary cardiac lesions that obviate the need for heart transplantation, the demand for combined heart–lung transplant procedures has decreased. Thus, over the past decade, no clear-cut trends in induction immunosuppressive therapy for these procedures can be identified. In 2003, about half of the patients received induction therapy, with a variety of approaches being used. Basiliximab was utilized for 19% of patients, daclizumab for about 7%, rabbit ATG in 11% and muromonab-CD3 and equine ATG each in 4% of the patients.

Trends in maintenance immunosuppression therapy prior to discharge in heart–lung transplantation
Utilization of immunosuppressive therapies in heart–lung transplant recipients parallels the observations made in both isolated heart and lung transplant cases.

Calcineurin inhibitors: Virtually all patients after heart–lung transplantation received a calcineurin inhibitor. More like isolated heart recipients, the percentage receiving tacrolimus versus cyclosporine is closer to half. In 2003, 53% of heart–lung transplant recipients received tacrolimus. Neoral and Gengraf were the most commonly used cyclosporine formulations, as they were both used in 21% of heart–lung transplants prior to discharge.

Antimetabolites and sirolimus: Antimetabolite usage is still quite common among heart–lung transplant recipients (79% in 2003), with azathioprine used in 47% of cases and mycophenolate mofetil in 32% of cases in 2003. Clear-cut trends in prescription of these two agents cannot be identified, as the proportions have risen and fallen over the past several years. Interestingly, sirolimus use has been reported in 5% of combined heart–lung transplant recipients in 2003, compared to 0% from 1994 to 2002.

Corticosteroids: Corticosteroids remain an integral component of the immunosuppressive regimens for heart–lung transplant recipients at the time of discharge, with 90% of patients receiving these agents in 2003.

Trends in maintenance immunosuppression therapy for the first year in heart–lung transplantation
Calcineurin inhibitors: Calcineurin inhibitors are the basis of immunosuppressive therapy in heart–lung transplant recipients, and this has been the case over the past decade. However, as with other organs, tacrolimus has been more frequently utilized during the past several years. Indeed, within the first post-transplant year, tacrolimus usage increased from 52% in 1999 to 65% in 2002. Among heart–lung transplant recipients, when cyclosporine was used, Neoral was the most common formulation prescribed and was used for 50% of the patients receiving cyclosporine.
Antimetabolites and sirolimus: Again, as with heart and lung transplantation, antimetabolites are frequently used as part of the immunosuppressive protocol and were used for 95% of heart–lung recipients in 2002. Azathioprine was used for 55% of recipients and mycophenolate mofetil for 55%. The use of sirolimus during the first operative year varied over the past few years from 0% in 2001 to 5% in 2002, with a peak of 10% in 2000.

Corticosteroids: As with the other thoracic organ transplant recipients, corticosteroids play an extremely important role after heart–lung transplantation. Indeed, all patients in 2002 were receiving corticosteroids during the first post-transplant year.

In 2002, though the observations are few, as with heart and lung transplants, the most common maintenance therapy for heart–lung recipients within the first year included corticosteroids, tacrolimus and mycophenolate mofetil.

Trends in antirejection treatment in heart–lung transplantation

Only 8 of the 32 heart–lung transplant recipients received treatment for acute rejection in 2002. All of these patients received steroid therapy, with no antibody use, similar to what occurred in 2001.

Summary

There has been noticeable evolution in the selection of immunosuppressive agents in solid organ transplantation over the past 10 years. An ongoing shift is seen in the types of antibody preparation being utilized as induction therapy, from muromonab-CD3 and horse ATGAM to rabbit ATG and the monoclonal anti-IL-2 receptor antagonists daclizumab and basiliximab. Furthermore, while calcineurin inhibitors continue to be used for maintenance immunosuppression in most patients, there has been a movement in the preference of calcineurin inhibitor used from cyclosporine to tacrolimus. An even more noticeable transition is seen in the choice of antimetabolite from azathioprine to mycophenolate mofetil; the latter is currently the most commonly administered immunosuppressive agent in solid organ transplantation. Despite the impact of steroid avoidance and near-avoidance protocols, corticosteroids continue to be widely employed in discharge maintenance immunosuppression in most solid organ transplant recipients. The incidence of acute rejection is decreasing. Steroids and antibody therapies are employed for treatment of acute rejection. It is probable that future studies will continue to demonstrate a significant impact of the newer medications on immunosuppressive practices.

References